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ASSESSMENT OF NON-INVASIVE TESTS IN HBEAG-NEGATIVE CHRONIC HEPATITIS B

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ABSTRACT

Overview: In this study, individuals with Recurrent hepatitis B with HBeAg-negative have their liver fibrosis and inflammation assessed using non-invasive diagnostic assays for accuracy and clinical value. In order to ascertain how well these techniques differentiate between HBeAg-negative CHB and dormant carriers of the hepatitis B surface antigen it contrasts them with conventional liver biopsies. The study also investigates how these tests might be used to track the effectiveness of antiviral therapy. Blood-based indices were evaluated, including the APRI ratio, the fibrosis-iv index, the neutrophil-to-lymphocyte (N/L) ratio, and the alanine aminotransferase-to-aspartate aminotransferase (AAR) ratio. Results highlight the potential of non-invasive methods as reliable alternatives to liver biopsy, paving the way for improved management of CHB. Two participant groups were established according to the METAVIR grading scheme. Each participant underwent measurements of several clinical indices, including the fibrosis-4 index, the (N/L) ratio, the alanine aminotransferase to AAR ratio, and APRI ratio." The mean platelet volume (MPV), AAR, FIB-4, APRI, N/L ratio, and platelet count had AUROC values of 0.581, 0.558, 0.502, 0.505, 0.506, and 0.460, respectively. To determine if fibrosis was substantial or progressed, platelet counts were employed (METAVIR ≥2). APRI, FIB-4, N/L ratio, MPV, AAR, for detecting severe fibrosis (METAVIR = 2), and platelet count exhibited corresponding AUROCs of 0.473, 0.451, 0.484, 0.503, 0.525, and 0.605. Clinical evaluations for each participant included determining several indices: the fibrosis-4 (FIB-4) index, the ratio of (N/L), the ratio of APRI to AAR, and the ratio of aspartate aminotransferase to platelets (APRI)." According to our research, severe fibrosis has only been partially detected via non-invasive diagnostic methods like APRI and FIB-4. Due to its unreliability, liver biopsies cannot currently be used in place of these assays. They are only applicable to Individuals who do not make excellent liver biopsies

KEYWORDS: Non-invasive test, HBeAg-negative CHB, APRI, FIB-4, liver biopsy.

INTRODUCTIONA major global health issue, chronic hepatitis B affects about two hundred fourty million people who have been long-term carriers of the hepatitis B virus. Liver cirrhosis and fibrosis are serious adverse effects of this illness that may lead to cancer or liver failure. CHB is classified into two subtypes, one of which contains the HBeAg and the other does not (1,2). There are over two hundred ninety six million people infected with chronic hepatitis B globally, making it a major health burden. Chronic liver fibrosis and inflammation are hallmarks of HBeAg-negative CHB, which calls for antiviral treatment. while inactive carriers typically have minimal liver damage and do not require immediate treatment (3, 4). Depending based the degree of liver damage and the quantity of viral replication, this subtype can be further classified into two groups. People who do not have severe liver necroinflammation and are inactive HBsAg carriers fall into the first groupIndividuals with substantial fibrosis and HBeAg-negative, moderate liver inflammation, and normal or raised Alanine Aminotransferase (ALT) values are included in the second group (5,6). Patients with active HBeAg-negative CHB require therapy to avoid the development of cirrhosis and its related consequences, whereas those with the inactive hepatitis B carrier status do not require treatment. Therefore, it is essential to differentiate between these two types of the illness in order to choose the best management and treatment plan (4, 5). Preventing chB issues requires early detection and treatment. The standard for staging

liver fibrosis is acknowledged to be the liver biopsy. The potential for sample errors, the potential for different observers to interpret the histology, and the associated risks of complications and mortality are only a few of the drawbacks of this invasive procedure. Scientists are presently searching for non-invasive, reliable, and different methods for tracking the development of liver disease due to these constraints. However, none of these serum-based diagnostics are accurate enough. There is also ongoing debate over how well these non-invasive tests reflect developments in antiviral drugs. Currently, there is a dearth of comprehensive research on this topic, and the findings of various studies range greatly.

MATERIAL AND METHODS

The outcomes served as the benchmark for assessing the accuracy of non-invasive testing. ROC curves, which especially target patients with co-infections like HIV and hepatitis C, were used to calculate the area under the curve (AUC) for each test. The AUC results offer a solid assessment of the efficacy of non-invasive techniques for predicting fibrosis in these individuals, amply demonstrating the tests' sensitivity and specificity, liver transplant recipients, autoimmune liver illnesses, liver cancer, metabolic liver disorders, and those who drank more than 20 grams of alcohol daily were excluded. Several participant characteristics, such as mean platelet volume (MPV), age, gender, aspartate aminotransferase (AST), neutrophil and lymphocyte counts HBV DNA levels and alanine aminotransferase (ALT) were measured. The FIB-4 index, APRI index, ALT/AST ratio (AAR), and NL ratio were all computed using established formulas. A 17-gauge needle was used to take liver samples under ultrasound guidance. After that, the samples were embedded in paraffin and kept in formalin. We set a criterion that required at least 15 mm of liver tissue that included at least six portal tracts in order to ensure the accuracy of our histological investigation. Using the METAVIR scoring system, we methodically assessed the liver's fibrosis and inflammation levels. We were able to distinguish between individuals with Significant/Advanced fibrosis (METAVIR scores of 2-4) and those with No/Mild fibrosis (METAVIR scores of 0-1) because to this thorough methodology.

For statistical analysis, IBM SPSS Statistics version 22.0, was used. Standard deviation (SD) ± mean was used to summarize the data. Categorical data were assessed using the Chi-Square test, while continuous variables were examined using the Student's t-test or paired samples t-test. By predicting fibrosis using the area under the receiver operating characteristic curve (AUROC), the diagnostic performance of non-invasive techniques was evaluated. P-values below 0.05 were considered statistically significant. The study complied with ethical guidelines and obtained the required authorization from the appropriate authorities.

RESULTS

159 people participated in the study, 85 of those were men (53.5%), and 74 of were women (46.5%). Each participant's biochemical, histological, and demographic information is shown in Table 1. The groups with advanced or substantial fibrosis and those with little or moderate fibrosis did not vary statistically significantly ($p > 0.05$) in terms of age, gender, or other biochemical and hematological characteristics.

On the other hand, across the two groups, the p-values for AAR, MPV, platelet counts, and NL ratio were comparable, coming in at 0.237, 0.754, 0.360, and 0.622, respectively (Table 2). ROC curve analysis revealed that 0.226 was the ideal APRI cut-off value for identifying significant/advanced fibrosis. This resulted in 62.3% sensitivity, 49.1% specificity, 37.9% PPV, and 72.2% NPV (AUROC: 0.581), as shown in Table 3, Figure 1A. At a threshold value of 0.240, the AUROC for APRI in identifying severe fibrosis (METAVIR = 2) was determined to be 0.473 (Table 4, Figure 1B).

According to Table 3, Figure 1A, the FIB-4 index likewise had a 0.558 AUROC and a threshold value of 1.012, which translated into a PPV of 38.8% and an NPV of 71.1% indicated substantial/advanced fibrosis, along with a 50.0% sensitivity and a specificity of 61.0%. FIB-4's AUROC was 0.451, with a cut-off value of 0.822 for predicting significant fibrosis (METAVIR = 2) (Table 4, Figure 1B).

With matching AUROC values of 0.502, 0.505, 0.506, and 0.460, the N/L ratio, MPV, AAR, and platelet count were predictive of substantial or advanced fibrosis (Table 3, Figure 1A). These indicators had AUROC scores of 0.484, 0.503, 0.525, and 0.605 to detect substantial fibrosis (METAVIR = 2) (Table 4, Figure 1B). The distribution of FIB-4 and APRI levels across fibrosis phases is shown in Figure 2A-B.

Lamivudine was administered to two patients, tenofovir disoproxil fumarate to two, and entecavir to 80APRI and FIB-4 scores decreased following therapy as compared to their pre-treatment values, although these decreases ($p = 0.210$ and $p = 0.516$, respectively) fell short of statistical significance. MPV, AAR, N/L ratio, and platelet count did not

change significantly before or after therapy; their respective p-values were 0.094, 0.423, 0.431, and 0.134. HBV DNA concentrations did not change. however, dramatically dropped following treatment (p = 0.016) (Table 5).

DISCUSSION

The findings underscore the clinical value of non-invasive tests in managing HBeAg-negative CHB. Among the indices evaluated, the FIB-4 index and APRI emerged as the most reliable markers for liver fibrosis. The N/L ratio showed promise as an inflammation marker but requires further validation. These diagnostic instruments provide a more cost-effective and secure substitute for liver biopsies and aid in the early diagnosis and tracking of treatment results. APRI and FIB-4 worked together to provide exceptional diagnostic accuracy, suggesting a synergistic effect. This approach could significantly reduce reliance on invasive procedures, particularly in resource-limited settings. However, integrating non-invasive tests into routine clinical practice requires standardization of cut-off values and further multicentric validation studies. Before starting successful antiviral medication, it is critical to differentiate between individuals with inactive HBsAg carriers and those with HBeAg-negative CHB. While liver biopsy remains the gold standard for accurately diagnosing hepatic fibrosis, its invasive nature carries inherent risks, including complications and even mortality. Therefore, the development of non-invasive methods for assessing liver disease has become imperative for safer diagnosis and patient care, including imaging techniques and mathematical models that use both direct and indirect blood indicators. APRI and FIB-4 are helpful markers of

Age	**46.86±12.13**
Gender (Female / male)	74 (46.5%) / 85 (53.5%)
Histological Activity Index A0 / A1 / A2	109 (68.6%) / 49(30.8%) / 1 (0.6%)
Fibrosis F0 / F1 / F2 / F3 / F4	29 (18.2%) / 77(48.4%) / 28 (17.6%) / 15(9.4%) / 10(6.3%)
HBVDNA (copies/mL)	7941442.06±71236351.39
Alanine aminotransferase (IU/L)	44.12±137.40
Aspartate aminotransferase (IU/L)	28.37±27.80
Platelets (10^9/L)	2135.09±58.99
Mean platelet volume (fL)	9.25±1.32
Lymphocyte (10^9/L)	4.14±1.40
Neutrophil (10^9/L)	2.40±1.33

Table 1: Baseline characteristics of the study group

	No/Mild Fibrosis (No:106)	**Significant/Advance Fibrosis (No: 53)**	**P**
Age	47.04±12.15	46.50±12.21	0.793
Gender Female/Male	50 (47.2%) / 56 (52.8%)	24 (45.3%) / 29 (54.7%)	0.822
AST (IU/L)	24.90±17.67	35.30±40.54	0.079
ALT (IU/L)	46.78±166.40	38.81±37.49	0.731
MPV (fL)	9.23±1.30	9.30±1.36	0.754
Platelet (10^9/L)	235.97±54.83	226.87±66.29	0.360
Neutrophil/Lymphocyte	2.01±0.97	2.10±1.46	0.622
AAR	0.91±0.32	0.99±.057	0.237
APRI	0.27±0.19	0.50±0.81	0.007
FIB-4	0.95±0.48	1.45±2.03	0.019
HBV-DNA 10^6 (copies/mL)	1.47±6.03	21.38±124.43	0.101

ALT: Alanine aminotransferase, AST: Aspartate aminotransferase MPV: Mean platelet volume, AAR: ALT/AST Ratio, APRI: Aspartate aminotransferase to platelet ratio index, FIB-4: Fibrosis-4.

Table 2: Comparison of the demographics, laboratory and non-invasive markers of the patients with No/Mild fibrosis and Significant/Advance fibrosis

	Cut-off	AUROC	Sensitivity	Specificity	PPV	NPV
MPV	9.050	0.505	60.3	48.1	37	70
Platelet	219.500	0.460	54.7	38.6	30.8	63.1
Neutrophil/Lymphocyte	1.713	0.502	64.1	49.1	38.6	73.2
AAR	0.883	0.506	49.1	50.0	33.3	66.3
APRI	0.226	0.581	62.3	49.1	37.9	72.2
FIB-4	1.012	0.558	50.0	61.0	38.8	71.1

ALT: Alanine aminotransferase, AST: Aspartate aminotransferase MPV: Mean platelet volume, AAR: ALT/AST Ratio, APRI: Aspartate aminotransferase to platelet ratio index, FIB-4: Fibrosis-4.

Table 3: Performance of non-invasive tests to distinguish No/Mild fibrosis from Significant/Advance fibrosis

	Cut-off	AUROC	Sensitivity	Specificity	PPV	NPV
MPV	9.050	0.503	64.3	48.1	24.7	83.6
Platelet	233.500	0.605	60.7	51.9	25.0	83.3
Neutrophil/Lymphocyte	1.724	0.484	57.1	49.1	22.9	81.3
AAR	0.885	0.525	50.0	57.1	20.9	79.1
APRI	0.240	0.473	48.1	52.8	20.6	80.0
FIB-4	0.822	0.451	50	45.7	19.7	77.4

ALT: Alanine aminotransferase, AST: Aspartate aminotransferase MPV: Mean platelet volume, AAR: ALT/AST Ratio, APRI: Aspartate aminotransferase to platelet ratio index, FIB-4: Fibrosis-4.

Table 4: Performance of non-invasive tests to distinguish No/Mild fibrosis from Significant Fibrosis

	Before Antiviral Therapy	Post Antiviral Therapy	P
AST (IU/L)	28.27±27.94	17.89±1.43	0.430
ALT (IU/L)	44.29±137.82	31.64±31.80	0.265
MPV (fL)	9.30±1.30	9.43±1.10	0.094
Platelet (10^9/L)	232.31±59.81	2.35±58.99	0.423
Neutrophil/Lymphocyte	2.02±1.13	2.29±2.17	0.134
AAR	0.94±0.42	0.98±0.48	0.431
APRI	0.35±0.51	0.30±0.23	0.210
FIB-4	1.12±1.28	1.07±0.71	0.516
HBVDNA 10^6(copies/mL)	2.34±9.71	0.22±2.47	0.016

ALT: Alanine aminotransferase, AST: Aspartate aminotransferase MPV: Mean platelet volume, AAR: ALT/AST Ratio, APRI: Aspartate aminotransferase to platelet ratio index, FIB-4: Fibrosis-4.

Table 5: Comparison of the laboratory and non-invasive markers of the patients before and after treatment

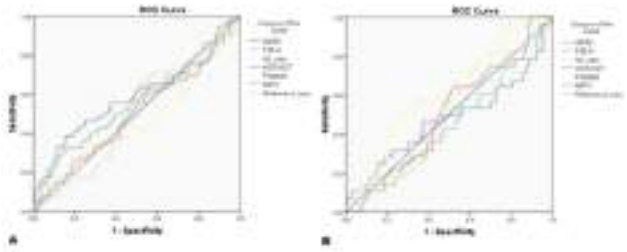

Fig. 1: A- ROC curves of non-invasive test to distinguish No/Mild fibrosis from Significant/Advance fibrosis. B- ROC curves of non-invasive test to distinguish No/Mild fibrosis from Significant fibrosis

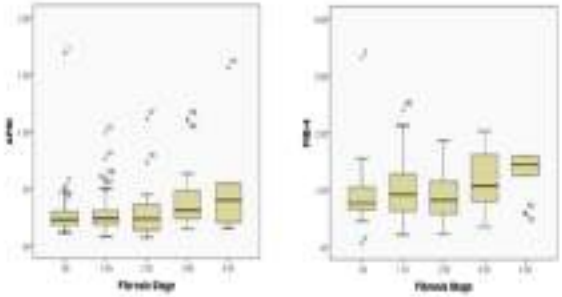

Fig.e 2: A- APRI levels according to the stage of fibrosis.
B- FIB-4 levels according to the stage of fibrosis.

liver fibrosis, particularly in people with an HCV diagnosis, Given that the Wang et al. and Wu et al. cohorts had a higher prevalence of patients with severe cirrhosis and fibrosis, etc. This greater representation may have overestimated the perceived accuracy of non-invasive exams.

The slightly better results for APRI in their study could be due to differences in study populations. Despite some support for APRI, it is not the best option and has limited use for identifying severe fibrosis in CHB patients, as indicated by a supporting meta-analysis. Most research indicates that The accuracy of APRI in identifying fibrosis in individuals with congenital heart block is quite modest, even though the WHO and APASL endorse it as a useful non-invasive method. The main goals of antiviral treatment in CHB are to reduce fibrosis, suppress the virus, and prevent liver cancer and cirrhosis. Resolving liver inflammation is essential for liver regeneration, where new hepatocytes replace fibrotic tissue. Effective viral suppression is crucial in this process for chronic viral hepatitis. Several trials have shown that antiviral therapies effective against HBV significantly aid fibrosis regression. Notably, fibrosis can be completely reversible with the right antiviral treatment, especially if identified early. The level of fibrosis that warrants antiviral treatment is known as the "significant fibrosis level" and corresponds to METAVIR 2. Distinguishing this level from no or moderate fibrosis is a critical challenge. Consequently, these results might create the impression that these tests are overly effective at diagnosing problems. Many studies evaluating non-invasive testing often omit comparisons between individuals with minimal or moderate fibrosis and those with substantial fibrosis (METAVIR 2). In contrast, our study examined how well non-invasive diagnostics could differentiate between individuals with METAVIR 0/1 and those with METAVIR 2. APRI and FIB-4 did not demonstrate sufficient ability to distinguish between no or moderate fibrosis and substantial fibrosis. The relationship between antiviral therapies and non-invasive diagnostic techniques is underexplored, and their effectiveness in monitoring antiviral treatment has shown varied outcomes. In their study, Tenggara et al. reported a significant decline in APRI scores one year after starting antiviral therapy, closely matching the transient elastography (TE) measurement of a significant reduction in liver stiffness. They suggested that APRI would be a useful tool for monitoring antiviral therapy. However, Stasi et al. found notable histological improvements in liver biopsy samples obtained after antiviral therapy, with a correlation between lower FORNS scores and reduced liver stiffness on TE. In our research, APRI and FIB-4 scores did not significantly decline after antiviral treatment. Since our patients did not undergo post-treatment liver biopsies, further conclusions were limited by the data available.

CONCLUSION

Future studies should focus on refining these methods and validating their utility across diverse populations. The accuracy of diagnosis and patient outcomes can be further enhanced by combining many non-invasive techniques. The results of this investigation indicate that non-intrusive diagnostic approaches such as APRI and FIB-4 are not effective in distinguishing between significant and severe/advanced fibrosis versus moderate or absent fibrosis in individuals who suffer from HBeAg-negative chronic hepatitis B. People who are mild fibrosis who do not require antiviral treatment may face unnecessary healthcare expenditures and potential side effects from medications if these tests are not modified.

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MORTALITY OUTCOMES ASSOCIATED WITH INVASIVE ASPERGILLOSIS

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ABSTRACT

Prognostic variables for invasive aspergillosis (IA) are poorly recognised, despite the disease's high mortality rate. The majority of studies on clinical implications of Aspergillus species infections have focused on patients with opportunistic infection that primarily affects cancer patients and immunocompromised individuals who have prolonged neutropenia. This study was carried out prospectively in a tertiary care hospital in Navi Mumbai, India, between January 2014 and December 2015. Standard microbiological protocols were followed in the collection and processing of samples from a total of 1785 patients. Out of the 251 patients that tested positive for Aspergillus, 8 individuals (3.19%) died as a result of their infections; males were 5 (62.50%), and females were 3 (37.5%). Maximum age group for those over 50, or 5 (62.5%), is followed by those between the ages of 31 and 40, or 1 (12.5%), and 41 and 50, or 2 (25%). Five (62.5%) and three (37.5%) deaths were attributable to Aspergillus fumigatus and Aspergillus niger, respectively.The highest number of causes of mortality in cases of Aspergillosis was found to be Allergic Broncopulmonary Aspergillosis (ABPA), which accounted for 2 cases. This was followed by Chronic Pulmonary Aspergillosis, Invasive Aspergillosis in Solid Organ Transplant, HIV, Tuberculosis, Diabetes, and Lung Cancer, which each accounted for 1 case. The study assessed the variations in therapy, comorbidities, and demographics between the in-hospital mortality and survival groups. Additionally, multivariate analysis was done to find mortality risk factors. The current study displays the mortality trend for patients with IA during a two-year span. Acute renal failure, bone marrow transplantation, intubation, advanced age, male gender, and patients were on steroid use was identified as death risk factors.

KEYWORDS: Invasive aspergillosis, Allergic Broncopulmonary Aspergillosis, HIV, Aspergillus Fumigatus.

INTRODUCTION

The prevalent invasive fungal infection known as invasive aspergillosis (IA) mainly affects patients with compromised immune systems. Severe pneumonia and respiratory failure are common the outcomes of the majority of IA cases that affect the lungs (1, 2). IA is becoming more common every year (3), diabetes mellitus, chronic obstructive pulmonary disease, end-stage renal disease, and long-term steroid use are the factors for IA (4). In addition to improved diagnostic tools and antifungal therapies, identifying predictors of death may aid in identifying individuals with high mortality rates who could benefit from more aggressive therapy, resulting in patients outcome (5).

Study found that steroid use was associated with low survival of patients (6). There was no significant relationship established between patients which were on steroid and morale in invasive pulmonary aspergillosis (7). The latter authors identified respiratory failure, diabetes, and prolonged hospitalisation as independent predictors of poor prognosis. A study on ICU patients with invasive aspergillosis and discovered that older age, bone marrow transplantation, mechanical ventilation, and renal replacement therapy were found responsible for poor outcome (1).

A study conducted on the epidemiology of invasive mould infections in 5 countries of Asia, concluding that disseminated disease, rheumatic disease were predictive of mortality (8). However, some data suggest that Aspergillus species might induce invasive illness in patients in different settings, including intensive care units (9-13).

Clinical diagnosis of invasive aspergillosis is quite difficult, because standard diagnostic definitions have only been developed and validated for cancer patients

(14). IA is thought to be a rare disease among critically sick patients (15-17).

Patients acquired invasive aspergillosis; the mortality rate for these patients was 60% (18). In another study, researchers discovered that 7% of people with IA had a 91% mortality rate. Surprisingly, invasive fungal infection was not a risk factor for 70% of these patients (19). Furthermore, IA is frequently misdiagnosed and connected to poor outcomes in critical care patients, where it can affect many organs and lead to a broad disease (20).

Samples taken from non-sterile body locations, such as trachea and bronchi, in that case the diagnosis of invasive aspergillosis is frequently assumed (21). Because Aspergillus species are so common, it is important to exercise caution when presuming that fungus collected from these samples have a pathogenic function. Aspergillus isolated from respiratory tract samples in immunocompromised patients has been extensively researched (22,23).

A positive Aspergillus culture may be more clinically relevant if other risk factors, such as chronic lung or liver illness or general weakness, are present (20). Nonetheless, patients with acute respiratory failure or critical illness are frequently unable to undergo invasive diagnostic procedures which are required to confirm the diagnosis of Aspergillus infection (24-26). Non-invasive diagnostic assays such as galactomannan measures necessitating future research in intensive care patients (10, 27).

Therefore, the aim of this study was to obtain data on mortality associated with invasive aspergillosis in patients attending a tertiary care hospital in Navi Mumbai.

MATERIALS AND METHODS

Patients and settings: This prospective study was carried out for two years, from January 2014 to December 2015, at the Department of Microbiology, MGM Medical College, Kamothe, Navi Mumbai, India. A total of 251 patients were enrolled, and samples were collected and processed using conventional microbiological procedures. Clinical suspicion of IA prior to ICU admission was an exclusion criterion.

Sample collection: Clinical samples such as sputum, Bronchoalveolar lavage (BAL), paranasal sinuses aspirates, eye swab, ear swab, blood, and pus from suspected cases of aspergillosis in different patients were collected in a sterile container.

Identification of Aspergillus species was done using standard methods (28)

RESULT

The current investigation was started in response to an invasive aspergillosis-related fatality. 251 (14.06%) of the 1785 samples that were tested for Aspergillus species proved positive for the fungus. and eight of those fatalities were linked to invasive aspergillosis. The highest number of deaths from invasive aspergillosis, 5 (62.5%) in males and 3 (37.5%) in females, was shown to be gender-specific. Age-wise distribution, there was a maximum of 5 (62.5%) in the age group 50 years and above, 2 (25%) in the age group 41 to 50 years, and 1 (12.5%) in the age group 31 to 40 years.

Aspergillus fumigatus, accounting for 5 (62.5%) of the total Aspergillus species identified in mortality, followed by Aspergillus niger, accounting for 3 (37.5%). (Table 4)

The type of Aspergillus species recorded in mortality were maximum due to Aspergillus fumigatus i.e. 5 (62.5%) and followed by Aspergillus niger i.e. 3 (37.5%). (Table 4)

The analysis of causes of death in invasive aspergillosis cases was recorded maximum due to allergic bronchopulmonary aspergillosis (ABPA) i.e. 2 (25%) followed by chronic pulmonary aspergillosis, invasive aspergillosis in Solid organ transplant, HIV, Tuberculosis, Diabetes and Lung cancer i.e. 1(12.5%) each. (Table 5)

Fungal and Bacterial growth in various clinical samples. Out of total 1785 samples 251 showed Aspergillus species, 19 (8%) samples showed only Aspergillus species growth, 196 (78%) samples showed mixed bacterial and Aspergillus growth and 36 (14%) samples showed Aspergillus and Candida mixed growth. (Table 6 and Fig.1)

Overall Aspergillus co-infection with other fungus and bacteria were Aspergillus isolated (251), Bacterial isolate (n=194) and other fungal isolates (n=36).

Aspergillus co-infection with other fungus and bacteria were recorded in sputum samples i.e. 104. Aspergillus species isolated was Aspergillus niger 61 (58.65%), Aspergillus fumigatus 24 (23.08%), Aspergillus flavus 12 (11.54%), Aspergillus brasiliensis 5 (4.81%) and Aspergillus terrus 2 (1.92%). Bacterial isolates was recorded Streptococcus pneumoniae 39 (37.50%), Pseudomonas aeruginosa 14 (13.46%), Klebsiella pneumoniae 11 (10.58%), Acinetobacter species 9 (8.65%), Streptococcus pyogenes 7 (6.73%), Staphylococcus aureus 6 (5.77%), Escherichia coli 5 (4.81%), Enterobater species 4 (3.85%), Coagulase negative staphylococcus (CoNS) 4 (3.85%), GNNF 3

(2.88%), Enterococcus species 2 (1.92%). Other fungal isolates were Candida albicans 15 (83.33%) and Penicillium species 3 (16.67%).

Aspergillus co-infection with other fungus and bacteria were recorded in nasal and paranasal sinuses samples i.e. 52. Aspergillus species isolated was Aspergillus niger 32 (61.54%), Aspergillus fumigatus 13 (25%), Aspergillus flavus 5 (9.62%) and Aspergillus brasiliensis 2 (3.85%). Bacterial isolates was recorded Streptococcus pneumoniae 15 (41.67%), Klebsiella pneumoniae 6 (16.67%), Acinetobacter species 6 (16.67%), Streptococcus pyogenes 5 (13.89%), Staphylococcus aureus 4 (11.11%) Other fungal isolates was Candida species5 (100%)

Aspergillus co-infection with other fungus and bacteria were recorded in pus samples i.e. 51. Aspergillus species isolated was Aspergillus niger 31 (60.78%), Aspergillus fumigatus 13 (25.49%), Aspergillus flavus 5 (9.80%), Aspergillus brasiliensis 1 (1.96%) and Aspergillus terrus 1 (1.96%). Bacterial isolates was recorded Staphylococcus aureus 16 (47.06%), Escherichia coli 8 (23.53%), Acinetobacter species 6 (17.65%), Pseudomonas aeruginosa 4 (11.76%). Other fungal isolates was Candida species 6 (100%)

Aspergillus co-infection with other fungus and bacteria were recorded in Ear swab samples i.e. 11. Aspergillus species isolated was Aspergillus niger 5 (45.45%), Aspergillus fumigatus 3 (27.27%), Aspergillus flavus 2 (18.18%)and Aspergillus brasiliensis 1 (9.09%). Bacterial isolates was recorded Staphylococcus 3 (50%) and Escherichia coli 3 (50%). Other fungal isolates was Penicillium species 2 (100%).

Aspergillus co-infection with other fungus and bacteria were recorded in Bronchoalveolar lavage (BAL) samples i.e. 13. Aspergillus species isolated was Aspergillus niger 6 (46.15%), Aspergillus fumigatus 4 (30.77%) and Aspergillus flavus 3 (23.08%). Bacterial isolates was recorded Streptococcus pneumoniae 3 (42.86%), Klebsiella pneumoniae 2 (28.57%), Streptococcus pyogenes 1 (14.29%), Staphylococcus aureus 1 (14.29%). Other fungal isolates was Candida species2 (100%)

Aspergillus co-infection with other fungus and bacteria were recorded in Eye swab samples i.e. 10. Aspergillus species isolated was Aspergillus niger 4 (40%), Aspergillus fumigatus 3 (30%), Aspergillus flavus 3 (30%). Bacterial isolates was recorded Staphylococcus aureus 1 (50%) and CoNS 1 (50%), however no other fungal were isolated.

Aspergillus co-infection with other fungus and bacteria were recorded in blood samples i.e. 4. Aspergillus species isolated was Aspergillus niger 2 (50%) and Aspergillus fumigatus 2 (50%) Bacterial isolates was recorded Staphylococcus aureus 1 (50%) and Escherichia coli 1 (50%). Other fungal isolates was Candida species1 (100%).

Aspergillus co-infection with other fungus and bacteria were recorded in urine samples i.e. 6. Aspergillus species isolated was Aspergillus niger 1 (16.66%) and Aspergillus flavus 5 (83.34%). Bacterial isolates was recorded Escherichia coli 2 (75%) and Staphylococcus aureus 1 (25%). Other fungal isolates was Candida species 2 (100%) (Table 8).

DISCUSSION

The saprophytic, thermotolerant fungus Aspergillus species are common in the environment and air. About 20 of the 185 species in the genus Aspergillus are capable of infecting humans. Even though hundreds of Aspergillus spores are inhaled by humans every day, problems are uncommon. (28)

Aspergillus infections are more likely to occur in people who already have lung diseases like asthma, COPD, or cancer. Corticosteroids, immune suppressants, and common antibiotics are used. Invasive aspergillosis, keratitis, and other lung lesions are caused by Aspergillus species. Aspergillus infection rates are influenced by factors such as improved survival from other illnesses, pollution-induced lung disorders, and longer lifespans. (29).

Of the 251 patients whose samples in our study contained Aspegillus species, 8 deaths were ascribed to invasive aspergillosis. (Table 1).

Males had the highest mortality rate from invasive aspergillosis (56.2%), while females had the highest mortality rate (37.5%). (Table 2)

The age-wise distribution was highest in the group 50 and older, which was 5 (62.5%), followed by 2 in the age group 41 to 50, which was 2 (25%) and 1 in the age group 31 to 40, which was 12.5%. (Table 3)

The type of Aspergillus species recorded in mortality were maximum due to Aspergillus fumigatus i.e. 5 (62.5%) and followed by Aspergillus niger i.e. 3 (37.5%). (Table 4)

The analysis of causes of death in invasive aspergillosis cases was recorded maximum due to allergic bronchopulmonary aspergillosis (ABPA) i.e. 2 (25%) followed by Chronic Pulmonary Aspergillosis, Invasive Aspergillosis in Solid organ transplant, HIV, Tuberculosis, Diabetes and Lung cancer i.e. 1(12.5%) each. (Table 5)

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Aspergillus co-infection with other fungus and bacteria were recorded in nasal and paranasal sinuses samples i.e. 52. Aspergillus species isolated was Aspergillus niger 32 (61.54%), Aspergillus fumigatus 13 (25%), Aspergillus flavus 5 (9.62%) and Aspergillus brasiliensis 2 (3.85%). Bacterial isolates was recorded Streptococcus pneumoniae 15 (41.67%), Klebsiella pneumoniae 6 (16.67%), Acinetobacter species 6 (16.67%), Streptococcus pyogenes 5 (13.89%), Staphylococcus aureus 4 (11.11%) Other fungal isolates was Candida species5 (100%)

Aspergillus co-infection with other fungus and bacteria were recorded in pus samples i.e. 51. Aspergillus species isolated was Aspergillus niger 31 (60.78%), Aspergillus fumigatus 13 (25.49%), Aspergillus flavus 5 (9.80%), Aspergillus brasiliensis 1 (1.96%) and Aspergillus terrus 1 (1.96%). Bacterial isolates was recorded Staphylococcus aureus 16 (47.06%), Escherichia coli 8 (23.53%), Acinetobacter species 6 (17.65%), Pseudomonas aeruginosa 4 (11.76%). Other fungal isolates was Candida species 6 (100%)

Aspergillus co-infection with other fungus and bacteria were recorded in Ear swab samples i.e. 11. Aspergillus species isolated was Aspergillus niger 5 (45.45%), Aspergillus fumigatus 3 (27.27%), Aspergillus flavus 2 (18.18%)and Aspergillus brasiliensis 1 (9.09%). Bacterial isolates was recorded Staphylococcus 3 (50%) and Escherichia coli 3 (50%). Other fungal isolates was Penicillium species 2 (100%).

Aspergillus co-infection with other fungus and bacteria were recorded in Bronchoalveolar lavage (BAL) samples i.e. 13. Aspergillus species isolated was Aspergillus niger 6 (46.15%), Aspergillus fumigatus 4 (30.77%) and Aspergillus flavus 3 (23.08%). Bacterial isolates was recorded Streptococcus pneumoniae 3 (42.86%), Klebsiella pneumoniae 2 (28.57%), Streptococcus pyogenes 1 (14.29%), Staphylococcus aureus 1 (14.29%). Other fungal isolates was Candida species2 (100%)

Aspergillus co-infection with other fungus and bacteria were recorded in Eye swab samples i.e. 10. Aspergillus species isolated was Aspergillus niger 4 (40%), Aspergillus fumigatus 3 (30%), Aspergillus flavus 3 (30%). Bacterial isolates was recorded Staphylococcus aureus 1 (50%) and CoNS 1 (50%), however no other fungal were isolated.

Aspergillus co-infection with other fungus and bacteria were recorded in blood samples i.e. 4. Aspergillus species isolated was Aspergillus niger 2 (50%) and Aspergillus fumigatus 2 (50%) Bacterial isolates was recorded Staphylococcus aureus 1 (50%) and Escherichia coli 1 (50%). Other fungal isolates was Candida species1 (100%).

Aspergillus co-infection with other fungus and bacteria were recorded in urine samples i.e. 6. Aspergillus species isolated was Aspergillus niger 1 (16.66%) and Aspergillus flavus 5 (83.34%). Bacterial isolates was recorded Escherichia coli 2 (75%) and Staphylococcus aureus 1 (25%). Other fungal isolates was Candida species 2 (100%) (Table 8).

The epidemiology of Influenza Acute (IPA) is unknown and affected by case mix, environmental factors, and diagnostic techniques. Geographic region influences IPA rates, but European studies show comparable rates (10%) to Asia (11%). Lack of knowledge in other regions could contribute to low rates. (30-33).

Chronic lung disease, such as asthma or COPD, increases the risk of developing IPA because of impaired respiratory function and increased corticosteroid use. A study discovered multiple comorbidities, higher mortality, longer hospital stays, and higher costs among invasive aspergillosis patients

Species wise	Total death	Percentages
Aspergillus Fumigatus	**5**	**62.5%**
Aspergillus niger	3	37.5%
Aspergillus flavus	0	0%
Aspergillus brasiliensis	0	0%
Aspergillus terrus	0	0%
Total	8	100%

Table 1: Showing type of Aspergillosis

Number of death	Complications and Causes of death
2	**Allergic Bronchopulmonary Aspergillosis (ABPA)**
1	Chronic Pulmonary Aspergillosis
1	Invasive Aspergillosis in Solid organ transplant
1	HIV
1	Tuberculosis
1	Diabetes
1	Lung cancer

Table 2: Analysis of causes of death in Aspergillosis cases.

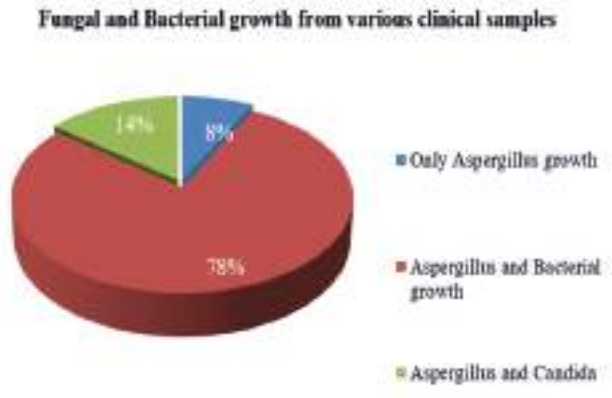

Fig.1: Fungal and Bacterial growth from various Clinical Samples

Parameter	Value
No. of isolates	251
No. of patients	1785
Sample origin	
Sputum	104/251 (41.43%)
Nasal and Paranal Sinuses	52/251 (20.72%)
Pus	51/251 (20.32%)
Ear swab	11/251 (4.38%)
Bronchoalveolar lavage fluid	13/251 (5.18%)
Eye swab	10/251 (3.98%)
Blood	04/251 (1.59%)
Urine	06/251 (2.39%)
Clinical diagnoses	
Invasive pulmonary aspergillosis	85/1785 (4.76%)
Chronic pulmonary aspergillosis except simple aspergilloma	59/1785 (3.31%)
Simple aspergilloma	41/1785 (2.30%)
Allergic bronchopulmonary aspergillosis	34/1785 (1.90%)
Colonization	32/1785 (1.79%)

Table 4: Clinical Correlation of Patients and Isolates

Total No. of samples	Total Aspergillus	Only Aspergillus growth	Aspergillus and Bacterial growth	Aspergillus and Candida
1785	251	19	196	36

Table 3: Showing Fungal and Bacterial growth in various Clinical Samples.

Sr. No.	Nature of samples	Aspergillus isolated (251)	Bacterial Isolate (n=194)	Other fungal isolates (n=36)
1	Sputum (n=104)	Aspergillus niger 61 (58.65%)	Streptococcus pneumoniae 39 (37.50%)	Candida albicans 15 (83.33%)
		Aspergillus fumigatus 24 (23.08%)	Pseudomonas aeruginosa 14 (13.46%)	Penicillium species 3 (16.67%)
		Aspergillus flavus 12 (11.54%)	Klebsiella pneumoniae 11 (10.58%)	
		Aspergillus brasiliensis 5 (4.81%)	Acinetobacter species 9 (8.65%)	
		Aspergillus terrus 2 (1.92%)	Streptococcus pyogenes 7 (6.73%)	
			Staphylococcus aureus 6 (5.77%)	
			Escherichia coli 5 (4.81%),	
			Enterobater sp. 4 (3.85%)	
			CoNS 4 (3.85%)	
			GNNF 3 (2.88%)	
			Enterococcus sp. 2 (1.92%)	
2	Nasal and Paranasal sinuses (n=52)	Aspergillus niger 32 (61.54%)	Streptococcus pneumoniae 15 (41.67%)	Candida species 5 (100%)
		Aspergillus fumigatus 13 (25%)	Klebsiella pneumoniae 6 (16.67%)	
		Aspergillus flavus 5 (9.62%)	Acinetobacter species 6 (16.67%)	
		Aspergillus brasiliensis 2 (3.85%)	Streptococcus pyogenes 5 (13.89%)	
			Staphylococcus aureus 4 (11.11%)	
3	Pus (n=51)	Aspergillus niger 31 (60.78%)	Staphylococcus aureus 16 (47.06%)	Candida species 6 (100%)
		Aspergillus fumigatus 13 (25.49%)	Escherichia coli 8 (23.53%)	
		Aspergillus flavus 5 (9.80%)	Acinetobacter species 6 (17.65%)	
		Aspergillus brasiliensis 1 (1.96%)	Pseudomonas aeruginosa 4 (11.76%)	
		Aspergillus terrus 1 (1.96%)		
4	Ear swab (n=11)	Aspergillus niger 5 (45.45%)	Staphylococcus 3 (50%)	Penicillium species 2 (100%)
		Aspergillus fumigatus 3 (27.27%)	Escherichia coli 3 (50%)	
		Aspergillus flavus 2 (18.18%)		
		Aspergillus brasiliensis 1 (9.09%)		
5	BAL (n=13)	Aspergillus niger 6 (46.15%)	Streptococcuspneumoniae 3 (42.86%)	Candida species2 (100%)
		Aspergillus fumigatus 4 (30.77%)	Klebsiella pneumoniae 2 (28.57%)	
		Aspergillus flavus 3 (23.08%)	Streptococcus pyogenes 1 (14.29%)	
			Staphylococcus aureus 1 (14.29%)	
6	Eye swab (n=10)	Aspergillus niger 4 (40%)	Staphylococcus aureus 1 (50%)	-
		Aspergillus fumigatus 3 (30%)	CoNS 1 (50%)	
		Aspergillus flavus 3 (30%)		
7	Blood (n=4)	Aspergillus niger 2 (50%)	Staphylococcus aureus 1 (50%)	Candida albicans 1 (100%)
		Aspergillus fumigatus 2 (50%)	Escherichia coli 1 (50%)	
8	Urine (n=6)	Aspergillus niger 1 (16.66%)	Escherichia coli 2 (75%)	Candida albicans 2 (100%)
		Aspergillus flavus 5 (83.34%)	Staphylococcus aureus 1 (25%)	
	Total (n=251)	251 (100%)	194 (100%)	36 (100%)

Table 5: Aspergillus Co-infection with other Fungus and Bacteria.

with aspergillosis. The most common host factor associated with IA was previous corticosteroid use for autoimmune disease. (34-37).

CONCLUSION

This study shows trends in mortality in IA patients over a 2-year period. Male gender, allergic bronchopulmonary aspergillosis, chronic pulmonary aspergillosis, invasive aspergillosis in solid organ transplant, HIV, tuberculosis, diabetes and lung cancer were identified as risk factors for death. Compared with Aspergillus-colonized patients, IA patients were more likely to have sepsis or respiratory failure on admission, and more often had underlying medical conditions such as immunocompromised states.

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Original Article

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ROLE OF HRCT IN EVALUATION OF PATHOLOGIES OF TEMPORAL BONE AND ITS SURGICAL INTERVENTION

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ABSTRACT

Background: Advanced medical imaging techniques like CT and HRCT help diagnose pathologies in the temporal bone, providing detailed visualization and insights into pathological conditions, particularly soft tissue density eg. cholesteatoma, which is difficult to diagnose through clinical examination alone. Aims and Objectives: The study aims to identify temporal bone changes in chronic suppurative otitis media patients using HRCT, correlate surgical intervention with HRCT findings, and confirm diagnosis through intraoperative findings. Methods: Total 100 patients with temporal bone pathologies. The patients were aged 10-60 years and provided clinical data. They underwent a Siemens Somatom AS 128 Slice multi-slice CT scan, revealing ear ossicle erosion, dural plate erosion, mastoid sclerosis, and scutum erosion. Surgical procedures were scheduled based on HRCT findings. The study compared HRCT and intraoperative findings to determine their correlation, using IBM SPSS 23rd version software and Chi-square test. Results: The study analyzed 100 patients with ossicular abnormalities, with incus erosion being the most common. Other common conditions included scutum, malleus, and stapes erosion. Sinus plate erosion was rare, while mastoid sclerosis was common but not as prevalent. Soft tissue/fluid attenuation was prevalent during intraoperative procedures, with the epitympanum having the highest prevalence at 98%, indicating density-related abnormalities. Conclusions: The data offers crucial insights into ossicular and mastoid health conditions, aiding clinicians in comprehensive assessments, accurate diagnoses, and effective treatment strategies, ultimately improving patient care and outcomes in otolaryngology.

KEYWORDS: High resolution computed tomography, Cholesteatoma, Temporal bone lesions, Otomastoiditis, Malignant otitis externa.

INTRODUCTION

The temporal bone is crucial for protecting hearing and balance organs. Its proximity to vital structures like the middle ear cleft and mastoid air cells presents complex challenges in evaluating and diagnosing pathologies within this region (1). Pathologies can range from congenital anomalies to acquired conditions, affecting the temporal bone or adjacent soft tissue structures (2-3). Clinical examination alone is often insufficient to determine prevalence, complications, and risk of recurrence. Advanced medical imaging techniques, such as Computed Tomography (CT) and High-Resolution Computed Tomography (HRCT), play a crucial role in addressing these challenges. CT scans have long been the standard imaging modality for assessing temporal bone pathologies (4).

High-Resolution CT (HRCT) is a powerful imaging technology that provides detailed visualization of temporal bone and its surrounding structures, providing valuable insights into the location, extent, and nature of pathological conditions (5-6). It is particularly useful in assessing soft tissue density eg. cholesteatoma, a condition that can be challenging to diagnose through clinical examination alone. HRCT complements traditional clinical evaluations and helps clinicians make informed decisions regarding patient care, especially in cases where surgical intervention is warranted. Its high-resolution thin-section CT scanning capabilities reveal subtle details of even smaller pathologies, aiding in the formulation of operative strategies based on exact estimation of underlying pathology. By assessing the entire middle ear and neighboring structures, HRCT enhances the precision of surgical interventions (7-8). High-resolution computed tomography (HRCT) is crucial for evaluating temporal bone pathologies, providing

detailed visualization of complex anatomy. It aids in diagnosing conditions like soft tissue density eg cholesteatoma, otosclerosis, and temporal bone fractures, aiding in surgical planning. HRCT's surgical implications include improved patient outcomes, minimally invasive procedures, and enhanced efficacy and safety in delicate surgeries like mastoidectomy and stapedectomy. This research study aims to investigate the significant role of HRCT in evaluating temporal bone pathologies and its correlation with surgical intervention outcomes, contributing to the ongoing improvement of patient care and medical decision-making within the challenging domain of temporal bone pathologies.

AIM AND OBJECTIVES

The study aims to describe temporal bone changes in chronic suppurative otitis media patients using HRCT, correlate surgical intervention and HRCT findings, and obtain a confirmatory diagnosis through intraoperative findings in patients presenting with temporal bone pathologies.

MATERIAL AND METHODS

A prospective study was conducted at the ENT Department of the Integral Institute of Medical Sciences and Research in Lucknow, India, involving 100 patients with clinical suspicion of temporal bone pathologies. The patients were aged 10-60 years, both genders, and willing to provide informed consent for HRCT evaluation and potential surgical intervention. Patients outside the specified age range, unwillingness to provide consent, contraindications, and pre-existing conditions were excluded from the study.

All patients provided comprehensive clinical data, including name, age, gender, and medical history, focusing on symptoms related to temporal bone pathologies. Patients underwent HRCT scans of the temporal bone and adjacent structures using a Siemens Somatom AS 128 Slice multi-slice CT scanner. The scans assessed the entire middle ear and neighboring structures, including ossicles, tegmen, sinus plate, and dural structures. Results showed ear ossicle erosion, dural plate erosion, mastoid sclerosis, and scutum erosion, as well as soft tissue/fluid density.

Surgical Procedures:

Patients with alopecia, incus, stapes, dural plate, mastoid sclerosis, scutum, and soft tissue/fluid density collection in the middle ear cavity were scheduled for surgical interventions based on HRCT findings, following standard procedures at the Department of Ear, Nose, and Throat (ENT).

Intraoperative Findings:

Surgical procedures involved meticulous documentation of intraoperative findings, including pathologies encountered, variations from HRCT results, and any unexpected conditions or complications.

The study compared HRCT and intraoperative findings to determine their correlation. Data was analyzed using IBM SPSS 23rd version software, and descriptive statistics were used to summarize patient characteristics and pathology types. Surgical success rates and other outcomes were assessed. The Chi-square test was used to analyze the co-relation between groups.

RESULTS

Total 100 patients, with 36% falling into age groups 10-20 and 21-30 years old, 13% in age groups 31-40 and 41-50 years old, and 5% in age groups 51-60 years old. Out of the 100 patients, 41% were male, while 59% were female. The mean age was 27.45 years, with a median age of 23 years, and the age range was 10 years to 58 years (Table 1).

Intraoperative and HRCT Conditions of Cases

The study reveals that incus erosion is the most common ossicular abnormality, accounting for 89% of cases. Other common ossicular conditions include scutum erosion, malleus erosion, and stapes erosion. Sinus plate erosion is rare, while mastoid sclerosis is common but not as prevalent. These statistics provide insights into the distribution and prevalence of intraoperative conditions related to ossicular and mastoid health, aiding in clinical assessment and management strategies. The data shows that scutum erosion is the most common condition observed in High-Resolution Computed Tomography (HRCT) scans, accounting for 88% of cases. Incus erosion followed closely with 79 cases, accounting for 79% of the total cases. Malleus erosion was reported in 71 cases, followed by stapes erosion in 68%. Sinus plate erosion was relatively rare, with only 2 cases reported. Mastoid sclerosis was observed in 73 cases, accounting for 73% of the cases examined. These findings provide valuable insights into the frequency and distribution of ossicular and mastoid-related abnormalities detected through HRCT imaging (Table 2).

Co-relation between Intraoperative and HRCT conditions between different variables

The comparison between intraoperative and HRCT data reveals interesting insights into the prevalence of various conditions related to ossicular and mastoid health. On HRCT- Scutum erosion shows a slight increase in the HRCT dataset, with 88 cases (88%)

compared to 87 cases (87%) in the intraoperative data. Conversely, malleus erosion is more commonly observed during intraoperative assessments, with 88 cases (88%), whereas the HRCT data report 71 cases (71%). Incus erosion follows a similar trend, being more prevalent in intraoperative findings (89 cases, 89%) compared to HRCT scans (79 cases, 79%). Stapes erosion is slightly more common in HRCT scans, with 68 cases (68%) versus 62 cases (62%) in intraoperative data. Sinus plate erosion appears to be rare in both datasets, with 9 cases (9%) intraoperatively and only 2 cases (2%) in HRCT scans. Mastoid sclerosis, on the other hand, is reported in 67 cases (67%) intraoperatively and 73 cases (73%) in HRCT scans. These variations suggest nuanced differences in diagnostic sensitivity or criteria between intraoperative assessments and HRCT imaging, underscoring the importance of utilizing multiple diagnostic modalities for comprehensive evaluation and management of these conditions (Table 3).

Soft tissue/fluid attenuation Intraoperative and HRCT Variables

The data shows that soft tissue/fluid attenuation is prevalent during intraoperative procedures in the epitympanum, with 96% of cases exhibiting this feature, while in the mesotympanum, it is moderately frequent, with 54% of cases showing this. The study reveals a high prevalence of soft tissue/fluid attenuation in the Epitympanum, with 98 cases reported, accounting for 98% of the analyzed cases. In the Mesotympanum, 45 cases were reported, indicating a moderate prevalence compared to the Epitympanum. In the Hypotympanum, 59 cases were observed, indicating a relatively high prevalence in the lower part of the tympanic cavity. The data suggests that soft tissue/fluid attenuation is prevalent in these areas (Table 4).

Correlations between soft tissue/fluid attenuation Intraoperative and soft tissue/fluid attenuation HRCT

The data shows the prevalence of soft tissue/fluid attenuation in tympanic regions, specifically the epitympanum, mesotympanum, and hypotympanum, during HRCT scans and intraoperative assessments. The epitympanum has the highest prevalence at 98%, indicating density-related abnormalities. The mesotympanum has a moderate frequency at 45%, while the hypotympanum has a high prevalence of 59%. During intraoperative procedures, the epitympanum shows a high prevalence at 96%, while the mesotympanum maintains a moderate prevalence at 54% (Table 5).

Gender	N (n=100)	%
Male	41	41.0%
Female	59	59.0%
Age Intervals		
10-20 years	36	36.0%
21-30 years	36	36.0%
31-40 years	13	13.0%
41-50 years	10	10.0%
51-60 years	5	5.0%
Mean age (Mean±SD)	27.45±10.81	

Table 1: Distribution of Demographic Profile

Class of Intraoperative conditions	N	%
Scutum Erosion	87	87.0%
Malleus Erosion	88	88.0%
Incus Erosion	89	89.0%
Stapes erosion	62	62.0%
Sinus Plate Erosion	9	9.0%
Mastoid Sclerosis	67	67.0%
Class of HRCT Conditions		
Scutum Erosion	88	88.0%
Malleus Erosion	71	71.0%
Incus Erosion	79	79.0%
Stapes Erosion	68	68.0%
Sinus Plate Erosion	2	2.0%
Mastoid sclerosis	73	73.0%

Table 2: Intraoperative and Class of HRCT Conditions of Cases

Variables	Scutum Erosion	Malleus Erosion	Incus Erosion	Stapes Erosion	Sinus Plate Erosion	Mastoid Sclerosis
Intraoperative	87	88	89	62	9	67
HRCT	88	71	79	68	2	73

Table 3: Co-relation between Intraoperative and HRCT Conditions between different Variables

Class of soft tissue/ fluid attenuation Intraoperative variables	Number	%
Epitympanum	96	96%
Mesotympanum	54	54%
Hypotympanum	35	35%
Class of soft tissue/ fluid attenuation HRCT variables	Number	%
Epitympanum	98	98%
Mesotympanum	45	45%
Hypotympanum	59	59%

Table 4: Soft tissue/fluid attenuation Intraoperative and HRCT variables

The study reveals that incus erosion is the most prevalent, accounting for 89% of ossicular abnormalities. Stapes erosion is less frequent at 62%, while sinus plate erosion is rare at 9%. Mastoid sclerosis is the most common at 67%. These statistics provide insights into the distribution and prevalence of intraoperative conditions related to ossicular and mastoid health, aiding in clinical assessment and management strategies. The use of High-Resolution CT (HRCT) scans has been shown to detect various pathologies, including scutum erosion, mastoid sclerosis, and tympanic membrane abnormalities. The sensitivity and specificity of HRCT in detecting these conditions are over 90%, with the overall accuracy being above 90% for most pathologies except for identifying erosion in the malleus, incus, and stapes.(10) Mastoid sclerosis is the most common finding on HRCT, observed in all 40 cases (100%). In a

Class	Epitympanum	Mesotympanum	Hypotympanum
Soft tissue/fluid attenuation HRCT	98	45	59
Soft tissue/fluid attenuation intraoperative	96	54	35

Table 5: Correlations between Soft Tissue/fluid attenuation Intraoperative and Soft tissue/fluid attenuation HRCT

DISCUSSION

Total 100 patients with a mean age of 27.45 years, with a wide age distribution. The median age is 23 years, indicating a diverse demographic. 36% of patients fall within the 10-20 and 21-30 age groups, with a significant proportion of younger individuals. The 31-40 and 41-50 age groups represent 13% and 10%, respectively. The majority of patients are female, with 59%, compared to 41% male. This gender disparity may impact healthcare considerations and research perspectives. Studies by Thukral et al. (2015), Kapoor et al. (2023), Bharat (2024), and Husain et al. (2020) provide a comprehensive overview of temporal bone pathologies, their demographic characteristics, and clinical presentations (9-12). Thukral et al. found a diverse age range, with ear discharge being the most common presenting symptom (9). Kapoor et al. found a mean age of 32.35 years, with a higher representation of females (10). Bharat's study highlighted infections as the primary cause of temporal bone pathologies (53.75%), followed by trauma, tumors, and congenital anomalies.(11) Husain et al. found a prevalence of younger patients, especially below 35 years, in the 15-24 and 25-34 years age brackets (12). These studies highlight the multifaceted nature of temporal bone disorders.

study by Kataria T et al., scutum erosion was detected in 18 cases on pre-operative HRCT, with intraoperative findings confirming erosion in only one case (13). In a study by Mandal et al., the most common findings included non-dependent soft tissue mass (60%), scutum erosion (45%), and ossicular involvement (53.33%). Less frequent findings included labyrinthine fistula, sigmoid sinus plate abnormalities, mastoid cortex erosion, tegmen erosion, and mastoiditis with sub-periosteal abscess. These findings provide valuable insights into the prevalence of different temporal bone abnormalities detected through HRCT imaging in the study population (14).

The data shows a high prevalence of soft tissue/fluid attenuation in the Epitympanum, Mesotympanum, and Hypotympanum, with 98 cases reported in the Epitympanum, 45 cases in the Mesotympanum, and 59 cases in the Hypotympanum, indicating a significant occurrence in the lower part of the tympanic cavity. This indicates a moderate prevalence of soft tissue/fluid attenuation in these areas. The study by Thukral et al. found soft tissue density in the epitympanum in 23 patients, with 20 having unsafe chronic suppurative otitis media (9). Additionally, 16% of patients had soft tissue density involving other

areas. Abdulmonaem et al. (2015) found 94.3% of cases had radiological features typical for cholesteatoma, including location in the epitympanum and mastoid antrum, along with bony erosion (15). Hiral Happani et al. (2018) found the epitympanum as the most commonly involved site (16).

The data shows the prevalence of soft tissue/fluid attenuation in the epitympanum, mesotympanum, and hypotympanum during HRCT scans and intraoperative assessments. The epitympanum has the highest prevalence at 98%, indicating density-related abnormalities. The mesotympanum has a moderate frequency at 45%, while the hypotympanum has a high prevalence of 59%. Intraoperatively, the epitympanum has a high prevalence at 96%, while the mesotympanum has a moderate prevalence at 54%. The epitympanum/prussak's space is the most commonly involved site in diseased temporal bones, with soft tissue density observed in 95.2% of cases. The aditus ad antrum and mesotympanum are also involved in 80.9% of cases. Soft tissue density is present in the mastoid antrum and air cells in 73% of cases and in the hypotympanum in 31.7% of cases (17). In a Jacob et al HRCT study, soft tissue density was found in the epitympanum in 73.3% of patients with chronic suppurative otitis media (CSOM) with cholesteatoma, followed by the mesotympanum in 56.6% and the aditus ad antrum in 53.3%. Understanding the distribution and prevalence of soft tissue/fluid attenuation in different tympanic regions is crucial for accurate diagnosis and management of ear disorders, especially those involving CSOM and cholesteatoma. HRCT remains a valuable tool in assessing these conditions and guiding clinical decisions and treatment strategies for patients with temporal bone abnormalities (18).

The study's 100-patient sample size may not accurately represent the broader population due to potential biases in patient selection, such as recruitment from a specific healthcare facility or demographic group.

CONCLUSIONS

The data provides valuable insights into the prevalence, distribution, and correlation of conditions affecting ossicular and mastoid health. These insights, supported by statistical analysis, aid clinicians in conducting comprehensive assessments, formulating accurate diagnoses, and developing effective treatment strategies for patients with these conditions. Understanding these abnormalities and their diagnostic methods can improve patient care and outcomes in otolaryngology.

HRCT	:	High Resolution Computed Tomography
CSOM	:	Chronic Suppurative otitis Media
CA	:	Cochlear Aqueduct
CC	:	Carotid Canal
EAC	:	External Auditory Canal
ET	:	Eustachian Tube
I	:	Incus
M	:	Malleus
MA	:	Mastoid Antrum
OW	:	Oval Window
SSC	:	Superior Semicircular canal
TM	:	Tympanic Membrane
V	:	Vestibule

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Original Article

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PANCREATO PROTECTIVE AND ANTI-INFLAMMATORY EFFECTS OF *PTEROCORPUS MARSUPIUM* ON RAT PANCREATIC ISLETS IN STREPTOZOTOCIN-NICOTINAMIDE INDUCED DIABETES MODEL

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ABSTRACT

Background: Type 2 Diabetic complications are one of the most common problems in the society. Increased glucose causes human pancreatic beta cells to produce cytokines, which impede insulin production and cause apoptosis and reduced cell proliferation. The secreted proinflammatory cytokine can cause local pancreatic-islet inflammation (insulitis) resulting in the gradual depletion of β cells that produce insulin. Here we evaluated the protective and anti-inflammatory effects of *Pterocarpus marsupium* on pancreatic islets in diabetes rats. Methods: Rats were given streptozotocin-nicotinamide (STZ-NA) intraperitoneally (i.p.) to induce diabetes. Five groups of animals were created, including normal control (NC), disease control (DC), two groups treated with 250 & 500 mg/kg of *P.marsupium* (PM250 & PM500) and a group by standard drug glibenclamide (500 µg/kg) (Glib500). After 120 days of treatment, the blood was collected from tail vain and estimation of insulin in plasma, IL-6, and IL-10 was ELISA-determined. HbA1c and fasting blood sugar levels were calculated by glucometer and nephelometry, respectively. Morphology of the rat pancreas and islet was evaluated by H&E staining. Results: Insulin levels and inflammatory cytokines DC had significantly greater levels of IL-6 and IL-10 ($p<0.004$).. The IL-6 levels in the PM250 & PM500 and Glib500 groups significantly decreased ($p<0.05$), but the alterations in insulin and IL-10 levels were negligible. When compared to NC, diabetic controls had as substantially higher glucose and HbA1c levels ($p < 0.05$). Test groups PM250 & PM500 and Glib500 showed significant decrease in glucose & HbA1c. Pancreatic acinar cell damage, cell atrophy and destruction of beta cells in DC was observed under microscope. There was a clear improvement in pancreatic beta cell regeneration, decreased congestion and edema in test groups. Conclusion: According to our research, P. marsupium may be a game-changer for reducing inflammation and islet damage in type 2 diabetes, as it exhibited anti-inflammatory activity and a significant improvement in beta cell regeneration of pancreatic islets in diabetes rats.

KEYWORDS: Pterocarpus marsupium, Diabetes mellitus, Inflammation, Pancreatic beta cells, Streptozotocin-Nicotinamide.

INTRODUCTION

A substantial rise in blood sugar levels brought on by a partial or whole lack of insulin action or secretion is the hallmark of diabetes mellitus, a chronic metabolic disease. According to the WHO Diabetes Global Report 2021, diabetes directly caused one point five million deaths in 2019 and affects 42. 2 crore persons globally, elevated blood glucose levels also contributed to 3.7 million deaths, which were caused by a variety of diseases and organ failures (1). From a pathogenic perspective, insulin resistance and the widespread death of beta cells in the pancreas (due to the production of autoantibodies) are the causes of diabetes mellitus of t1 and t2, respectively (2). Both t 1 and t 2 diabetes have been shown to have inflammation is probably a major factor in the destruction or functioning of the pancreatic islets. By improving glucose utilization and altering oxidative phosphorylation, increased free fatty acids (FFAs) and hyperglycemia may sustain inflammation. Studies reveal that the pro-inflammatory characteristics of macrophages found in or invading adipose tissues and

islets are influenced by these aberrant metabolic processes. Furthermore, by producing more interleukin-1 and interleukin-6, two active inflammatory cytokines, oxidative stress brought on by hyperglycemia and lipotoxicity might trigger an inflammatory response. By encouraging the overproduction of extra cytokines and chemokines, which in turn draw in more macrophages, interleukins exacerbate inflammation. Increased inflammation can cause insulin resistance, beta-cell malfunction, and eventually cell apoptosis (8).

Insulin replacement treatment and oral hypoglycemic medications, such as inhibitors of sodium-glucose co-transporter type 2 (SGLT-2), sulfonylureas, metformin, acarbose, and inhibitors of Both t1 and t2 diabetes are treated with dipeptidyl peptidase 4 (DPP-4). Even though there are several anti-diabetic drugs available, their use is frequently restricted because of their high cost and potential for long-term negative effects. As a result, research is still being done to find safe and effective therapy alternatives.

Numerous medicinal plant species contain alkaloids, which have been investigated as possible alternatives to medications that reduce inflammation and diabetes. Numerous previous studies have shown the advantages Using plant extracts and their byproducts in diabetes care. The Leguminosae family includes the tall tree Pterocarpus marsupium Roxb, also called Bijasar or Vijayasar. It is frequently seen in Sri Lanka western, eastern, and southern regions and in India. For many years, Ayurveda has utilized the bark, heartwood, leaves, and flowers of the P. marsupium tree for therapeutic reasons. In the past, studies have shown that P. marsupium heartwood has positive benefits on inflammatory diseases and diabetes. Additionally, research has demonstrated that the tree's flavonoid and phenolic component concentration confers antihyperlipidemic and antioxidant qualities. Furthermore, P. marsupium heartwood is used for its astringent and antihelmintic qualities as well as to treat leprosy, bronchitis, asthma, diarrhea, and skin conditions. Therefore, in albino Wistar rats that had been given STZ-NA diabetes, We sought to evaluate the pancreatic regeneration and anti-inflammatory qualities of P. marsupium, a natural extract.

MATERIALS AND METHODS

Animals: A total of 100±5g male albino Wistar rats were supplied by the Central Animal House of Mangaluru's Kasturba Medical College. The rats were kept in a controlled environment with a 12-hour light and dark cycle (16) and were given full access to water and normal rat food.

Plant collection: Dr. Nagalakshamma from the Botany Department at Santosius College in Mangaluru, Karnataka, confirmed the identity of the P. marsupium heartwood, which was obtained from Alva's herbal pharmacy in Moodbidri, Karnataka (voucher number: The Wood/2006/745/62).

To prepare the plant extract, 30g of powdered P. marsupium heartwood, dry and coarse was cooked for 15 minutes at 50˚C in 16 parts (480ml) of water. A rotary vacuum flash evaporator was used to evaporate the filtrate for seven hours at 75˚C after the resultant mixture had been filtered through muslin cloth. A semi-solid extract was obtained by collecting the leftover residue from the round-bottom flask and drying it with a heating mantle for three hours. After that, this extract was kept for later research at -4˚C in a refrigerator.

Chemicals: Cipla Pvt Ltd in Mumbai, India, provided the glibenclamide, while Himedia Drug Company in India provided the nicotinamide and streptozotocin.

Ethical approval: Prior to commencement, the study required approval from the Institutional Animal Ethics Committee (IAEC) of Kasturba Medical College, Manipal University, Karnataka, India (Certification No. 14062013).

Diabetes induction: 15 minutes prior to the administration of STZ at a dosage of 50 mg/kg dissolved in 0.1M citrate buffer (pH 4.5), the rats were given intraperitoneal injections of 25 mg/kg nicotinamide dissolved in normal saline (17). Rats were chosen from the general population, and only after their blood glucose levels exceeded 250 mg/dL were they placed in the appropriate groups.

Experimental Design:

The study included 30 rats in total, 24 of which had diabetes and 6 of which were normal. Five groups of six rats each were created from the rats. On the seventh day following the STZ-NA injection, oral therapy with plant extract and Glibenclamide started. This course of therapy lasted for sixteen weeks.

Group I: Saline-treated normal controls (Control)

Group II: Diabetic untreated group (Model)

Group III: Glibenclamide 500µg/kg BW (Glib500)-treated diabetic rats

Group IV: P. marsupium 250 mg/kg BW (PM250)-treated diabetic rats

Group V: P. marsupium 500 mg/kg BW (PM500)-treated diabetic rats

Estimation of Glycemic profile: A glucometer was used to measure blood glucose, and nephelometry was used to measure HbA1c. Insulin was quantitated in

serum collected at the end of the study period, by Sandwich ELISA technique using anti-rat insulin antibodies from Genexbio pvt.ltd. Delhi, India as per the instructions given by the manufacturer.

Estimation of Interleukins: Il-6 and Il-10 of serum and kidney were estimated using Rat IL-6 & IL-10 ELISA kits which were bought from RayBiotech pvt ltd. USA. by using ELX 800 ELISA reader.

Histological assessment of pancreas: Following the procedure outlined by Feldman et al., 2014, the pancreas was prepared for histological analysis after being removed from anesthetized rats (18). In a nutshell, tissue was placed in paraffin wax after being treated with 10% formalin. The blocks were divided into 4µm thick slices using a rotary microtome. Hematoxylin and Eosin was used to stain these sections after they had been deparaffinized. To evaluate and rank the histo-architectural distortions for each experimental group, sections were examined under a microscope. Histomicrographs of typical sections were produced.

Statistical analysis:

For every batch of six animals, the data was shown as Mean ± S.D. The means of the groups were compared using Tukey's post hoc test following a one-way ANOVA. The statistical software SPSS version 16 was used for the analysis. A p-value was considered significant if it fell below 0.05.

RESULTS

Group	RBG (mg/dL)	HbA1C (%)	Insulin (ng/ml)
Control	119.17±8.65	4.11±0.26	12.75 ± 2.65
Model	469.67±20.04a	7.33±0.25a	26.82 ± 2.24a
Glibenclamide 500µg/kg (Glib500)	148.41±8.74b	4.73±0.36b	15.97 ± 1.38b
P.Marsupium 250mg/kg (PM250)	171.17±18.69 b	5.24±0.12b	16.6 ± 4.82b
P.Marsupium 500mg/kg (PM500)	169.83±15.43 b	5.50±0.48b	20.28 ± 3.37b

Table 1: Random Blood Glucose, HbA1c and Insulin in various groups

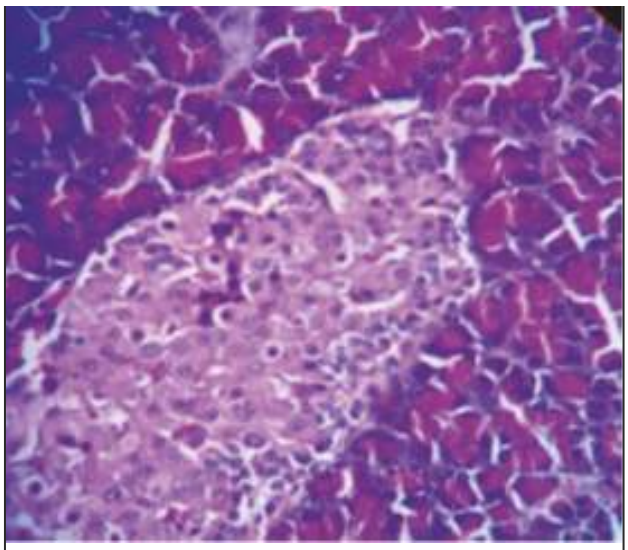
Mean ± SD is employed to denote values (n = 6 per group). P < 0.01 represents a significant difference compared to the sickness control group. P < 0.05 denotes the comparison between Control and Model.b- P < 0.05 (Model vs. PM or Glibenclamide).

Group	In Serum		In Kidney	
	IL-6 (pg/ml)	**IL-10 (pg/ml)**	**IL-6 (pg/ml)**	**IL-10 (pg/ml)**
Control	**20.43 ± 5.83**	**20.97 ± 8.62**	**74.70±33.60**	**1981.44±84.4**
Model	**115.70 ±13.65[a]**	**111.61 ± 31.43[a]**	**149.16±21.06[a]**	**3182.1±60.73[a]**
Glibenclamide 500µg/kg (Glib500)	**47.98 ± 7.29[b]**	**189.81 ± 21.29[b]**	**65.90±13.9[b]**	**1791.6±41.9[b]**
P.Marsupium 250mg/kg (PM250)	**54.58 ± 7.06[b]**	**101.11 ± 28.78**	**89.01±3.26[b]**	**2805.5±59**
P.Marsupium 500mg/kg (PM500)	**49.18 ± 9.02[b]**	**96.50 ± 10.43**	**117.87±25.3[b]**	**3017.0±65.2**

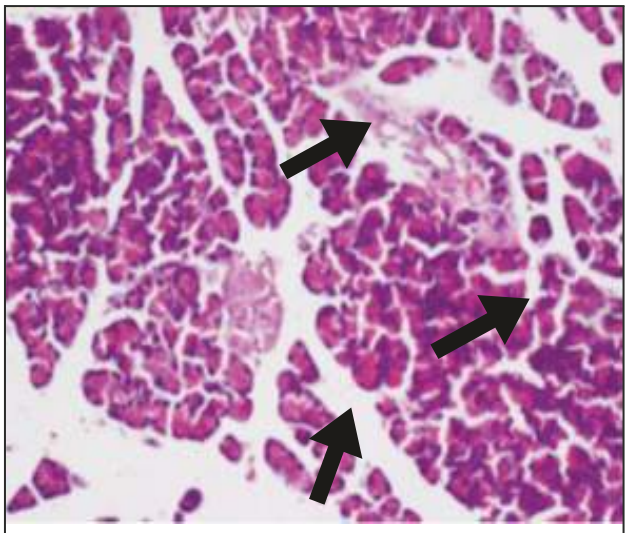
Table 2: IL-6 and IL-10 levels in Serum and Kidney in various groups

Values are expressed as mean ± SD (n = 6 per group). A significant difference from the ill control group is shown by a P < 0.01 value. P (Control vs. Model) < 0.05.

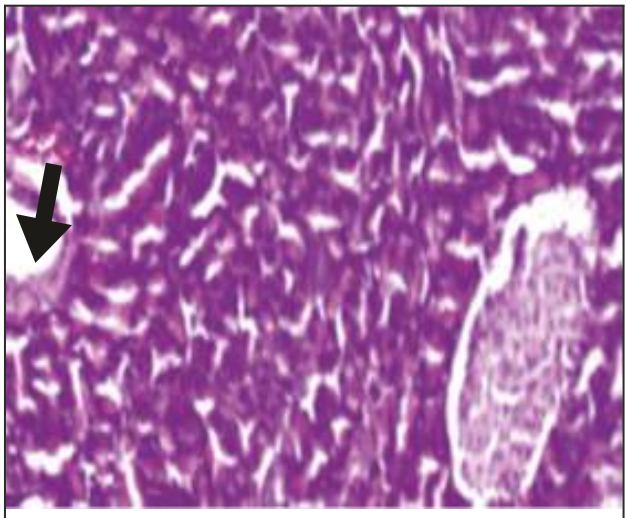
b- P < 0.05 (Model vs. PM or Glibenclamide).



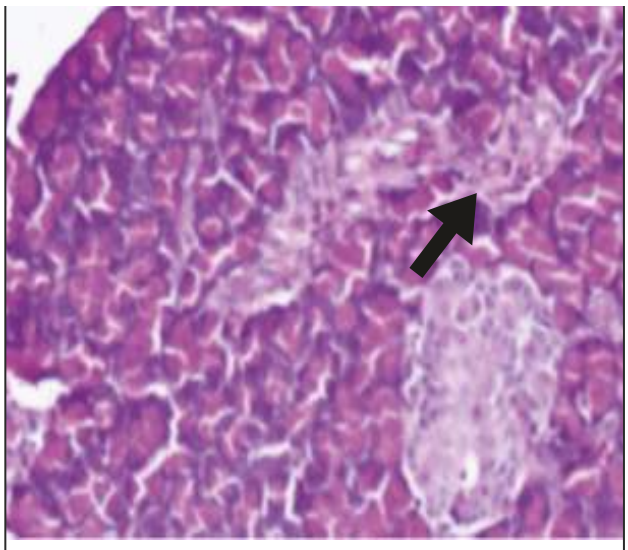
A. Normal control rat pancreas



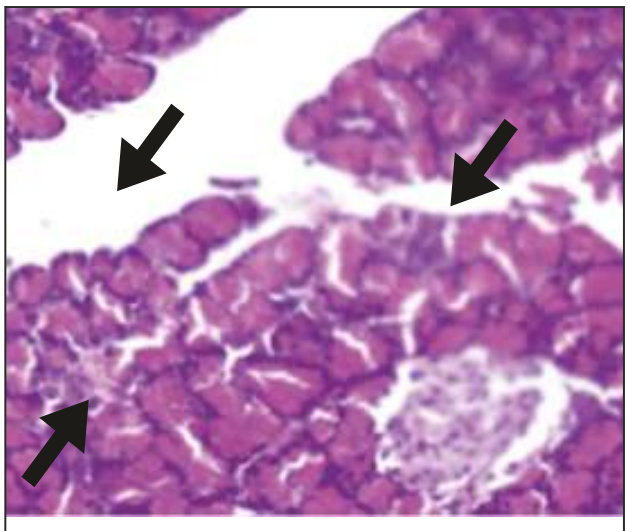
B. Diabetic control rat pancreas



C. Glibenclamide 500mcg treated rat pancreas



D. P.Marsupium 250mg treated rat pancreas



D. P.Marsupium 250mg treated rat pancreas

Fig. 1: Histopathology of Pancreas of various groups

Histopathology pictures of Pancreas of various groups:

The images (magnification ×200) show six animals each experimental group. a. Pancreatic lobules were arranged into tiny lobules, and islet cells were seen strewn among acinar cells. The control group had normal pancreatic anatomy, including normal exocrine gland and acinar cells. Compared to the nearby acinar cells, the islets appeared to be less defined. b. The exocrine and endocrine glands of diabetic rats showed pathological alterations. Small vacuoles and swollen acinar cells were observed in almost all the parts of pancreas and the epithelium was compressed (indicated by black arrow). Model group rats showed almost complete destruction of Islet β-cells. c. Diabetic

rats treated with Glibenclamide exhibited some changes in the general architecture. Acinar damage, cell atrophy and vacuolation was observed in most of the exocrine part (indicated by green arrow). Additionally, wider intralobular (shown by the blue arrow) and interlobular (shown by the red arrow) ducts were seen. d. After receiving PM250, diabetic rats showed almost normal islet cell structure. A distinct demarcation between the exocrine and endocrine sections was seen, and there was acinar cell atrophy and destruction that was somewhat less severe. g. PM500-treated diabetic rats showed that their islets cells had recovered. It was also discovered that the vacuoles in the acinar cells' basal region were smaller.

DISCUSSION

In this investigation, diabetic rats treated with PM showed a distinct glucose response suggestive of normal glycemic kinetics, as indicated by RBG levels (below 175 mg/dL) and HbA1c levels (below 5.5%), in contrast to disease control, which showed noticeably higher values under comparable conditions. The substantial increase in insulin and decrease in blood glucose levels relative to healthy individuals were suggestive of PM's promotion of insulin release and glucose utilization. Epicatechin, an isolated component from PM, has been shown in previous studies to encourage the pancreatic beta-cells' production of insulin and to produce a dose-dependent rise in cAMP levels. Additionally, it has been proposed that PM converts pro-insulin into insulin while increasing the concentration of cAMP in the Langerhans islets in vitro. The standard approach to diabetes mellitus management and treatment with P. marsupium wood is somewhat supported by these preliminary findings, in addition to supporting a previous report on the insulin secretogague impact of P. marsupium (20). Histopathology of model group pancreas showed inflammation and reduction in endocrine part and treatment with PM increased the β-cells density and reduced the lymphocyte infiltration. This impressive finding shows that, in addition to the antidiabetic effect, β-cell regeneration is also possible with PM extract. Recent animal studies suggested that β-cell regeneration (Neogenesis) is possible with certain hormones, including as gastrin and glucagon-like peptide (GLP-1), prevent cell death and encourage the growth and development of β-cells. Many companies are now developing and testing the GLP-1 analogues in this regard in T1DM and T2DM patients (21). Hence plausible mechanism for β-cell neogenesis in the present study could be due to upholding the actions of above hormones by the plant extract.

Although hyperglycemia and insulin resistance/ insensitivity are the central pathologies in diabetes, it is now widely accepted that almost all the complications of diabetes share an inflammatory basis. This has been particularly appreciated in coronary artery disease and nephropathy. It is specified that pro-inflammatory cytokine, IL-6 is one of the earliest cytokines which is upregulated in many infectious conditions. TNF-α and IL-6 in diabetes, increases ROS production and causes activation of Ikkβ. Insulin function is compromised by the phosphorylation of Ser307 IRS-1, which results from Ikkβ activation (22). Furthermore, IL-6 overexpression increased β-cell inflammation (23). In a similar vein, the illness model group in this study had higher serum and kidney levels of the cytokine IL-6. In a number of renal illness models, mesangial proliferation, tubular atrophy, and interstitial infiltration are all directly correlated with kidney IL-6 expression, which further advances the course of the disease (24, 25). In comparison to the model group, the PM therapy group's serum and kidney IL-6 levels were noticeably lower. Our results are corroborated by earlier research showing that anti-IL-6 treatment or the usage of plants with anti-inflammatory qualities lowers blood levels of pro-inflammatory cytokines, improving the sensitivity of insulin and glucose metabolism (26). On the other hand, the model and PM groups' blood and kidneys had IL-10, an anti-inflammatory cytokine, was present in much greater amounts than in the control groups. The rise in IL-10 levels in the model group might be due to T helper cells' higher transforming growth factor-beta (TGF-β) production in reaction to IL-6 (27). Interestingly, IL-10 is believed to inhibit IL-6 production; earlier research has shown that IL-10 therapy can completely cure insulin resistance caused by IL-6. (28). The PM and Glib500 treated groups showed significantly higher levels of IL-10 in their blood and kidney homogenate, which is in line with previous research. IL-10's protective actions might be linked to the restoration of insulin signaling and muscle fatty acyl-CoA levels (29). Liver and skeletal muscle insulin resistance was caused by acute IL-6 injection in vivo; however, IL-10 co-treatment prevented both lipid-induced and IL-6-induced insulin resistance (28). Thus, the inhibitory activity of IL-10 is acknowledged as a possible explanation for the reduced IL-6 levels seen in the treated groups.

CONCLUSION

Using a diabetic model made using STZ-NA, the current study measured blood and kidney levels of IL-6 and IL-10 and looked at pancreatic histology to investigate the anti-inflammatory and pancreatic healing effects of the aqueous extract of PM.

Following PM treatment, beta cell regeneration increased, congestion, edema, and necrosis decreased, and the tissues' levels of IL-6 and IL-10 decreased. The herbal extract's therapeutic and supplemental potential in the treatment of diabetes and its associated conditions is supported by these findings.

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Original Article

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SPECTRUM OF THYROID LESIONS ON FNAC IN A TERTIARY CARE CENTRE OF NORTHERN INDIA

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ABSTRACT

In surgical practice, thyroid abnormalities are frequently encountered, and Fine Needle Aspiration Cytology (FNAC) is frequently employed as the preliminary diagnostic test. By classifying thyroid lesions as inflammatory, benign, or malignant, FNAC helps doctors decide which treatments-such as surgery or medicine-are best for their patients. This study attempted to determine the diagnostic accuracy in patients with thyroid gland swelling, as well as the morphology of thyroid lesions by FNAC and their distribution by age and sex. A one-year retrospective study was carried out in a tertiary care center's Department of Pathology from July 2022 to June 2023. Using a data collection tool, the age, gender, and diagnosis of 152 patients who had Fine Needle Aspiration procedures were identified from their medical records.138 (90.7%) of the 152 patients were men, and 14 (9.3%) were women. The average age was 39.78 ± 12.6. Lesion types comprised 92.7% non-neoplastic lesions and 7.3% malignant lesions. Goiter accounted for 62.5% of all non-neoplastic lesions. The majority of patients (29.6%) experienced hypothyroidism symptoms in addition to thyroid gland hypertrophy. Additionally, there was one case of papillary carcinoma (0.6%). Twenty-third-century individuals exhibited the majority of thyroid lesions (26.3%). In the fourth and fifth decades of life, goiter would manifest. In the third decade, Hashimoto's and lymphocytic thyroiditis were most frequently observed. With an AUC of 0.93, FNAC further revealed high accuracy in evaluating lesions, with true positive cases being 89%, specificity of 98%, PPV of 97%, and NPV of 95%. The study emphasize the need for evacuation of palpable thyroid lesions by FNAC as it can prove to be indispensable tool for early diagnosis of malignancy.

KEYWORDS: FNAC, Goiter, Benign Thyroid lesions, Cytology, Thyroiditis.

INTRODUCTION

A total of 4-12% people report with palpable thyroid enlargements, and many more have impalpable nodules. Thyroid lesions are a common occurrence.(1) People following goitrogenic diets are more likely to have these nodules. An accurate diagnosis is crucial for preventing invasive procedures and guaranteeing the right course of therapy. (2)

Thyroid lesions encompass a wide spectrum of disorders, from such as goitre and thyroiditis to malignancies, including papillary, follicular and anaplastic carcinomas. Globally, the prevalence of thyroid diseases is on the rise, and in India, the incidence is particularly high due to factors such as deficiency of iodine, environmental influences and genetic predispositions. Approximately 42 million people in India are affected by thyroid disorders, with women being more susceptible. (2,3)

The common thyroid lesions in India include multinodular goiter, Hashimoto's thyroiditis, and various neoplasms. Although benign conditions like colloid goiter are more frequent, distinguishing them from malignant thyroid nodules can be challenging due to overlapping clinical and radiological features. In this context, FNAC plays an important role in the diagnostic process. (2)

FNAC is globally favoured for its affordability, low complication rates, and high diagnostic accuracy, FNAC is used to classify lesions into inflammatory, benign, or malignant categories, helping clinicians determine the next steps in treatment. (4)

The accuracy of diagnosing through FNAC is compared to histopathology, the gold standard for confirming thyroid lesions following surgical

excision. While FNAC provides an initial diagnosis, histopathology offers more detailed structural information. Studies show FNAC's diagnostic accuracy ranges from 85% to 95%, depending on factors like the pathologist's expertise and the sample quality. FNAC's ability to detect malignancies early allows for timely surgical intervention, making it a pivotal tool.(5,6)

Aim of this study is to evaluate the morphology of thyroid lesions by FNAC in patients with swelling of thyroid gland and to determine the distribution of thyroid lesions according to age and sex.

MATERIAL AND METHOD

Study Design

This was a retrospective study in nature, based on the medical records of patients who sought treatment at a Northern Indian tertiary care center's Department of Pathology between July 2022 and June 2023 for palpable thyroid enlargement.

Study participants

152 patients who have undergone FNAC for thyroid lesion at our centre over the study period.

Data Collection

Medical record of 152 patients were taken ,their age, gender and diagnosis were collected using a data gathering tool. Lesions of FNAC were noted and classified as benign and malignant. Lesions were classified on the basis of Bethesda Classification. Distribution on the basis of age and gender was also done. The histopathology reports of these patients were obtained from the records and were compared with diagnostic accuracies of FNAC.

STATISTICAL ANALYSIS

Data collection was done and SPSS software (IBM) version 24.0 was used for analysis. The results were presented in the form of frequency and percentage. Chi-square was done. A P value of <0.05 was considered significant. Receptor operator Curve was constructed for FNAC accuracy as compared to histopathology report and area under the curve, sensitivity, specificity, NPV and PPV was estimated analyzing the final histopathology report.

RESULTS

Patients were of the average age - 39.77± 12.6 years. The range of ages was 17–69. A total of 138 (90.7%) of the 152 patients,were women & 14 (9.3%) were men (Fig 1) The remaining lesions (7.3%, 11) were cancerous, while 92.7% (141) were non-neoplastic. Goitre was the most frequent non neoplastic lesion (53, 34.8%). FA (10, 6.6%) was the most common neoplastic lesion. (Table 1) Most of the lesions on FNAC were Bethesda grade 2 (92.2%) (Table 2)

The majority of patients presented with an enlarged thyroid gland and had features of hypothyroidism (29.6%) followed by thyroid tenderness in 23% patients. 1 patient also had features of hyperthyroidism. (Fig. 2)

The age group in which the thyroid lesions were most commonly seen was 30-40 years (26.3%) followed 20-30 years (25%) and 40-50 (23.6%). The common age-group for colloid goitre was 40-50 years. Nodular goitre, Hashimoto thyroiditis and lymphocytic thyroiditis was 20-30 years. Follicular Adenoma was seen mostly in patients of fifth and sixth decade. In patients of 10-20 age group , colloid goitre and thyroiditis were the lesions observed. In men colloid goitre (50%) was the commonest observed thyroid abnormality followed by nodular goiter (35.7%) and cyctic nodule in 14.2% (Table 3)

FNAC showed a high sensitivity of 89%,while its specificity of 98% highlighted its strength in accurately excluding true negatives. The test's PPV of 97% implied that majority of individuals who tested positive truly had the condition, and its negative predictive value (NPV) of 95% indicated that most individuals who tested negative were indeed free from the condition. With an overall diagnostic accuracy of 90.6%, FNAC reliably classified a large portion of cases correctly. The ROC curve, showed area under the curve of 0.93, confirmed FNAC's excellent ability to distinguish between positive and negative cases, further supporting its robustness as a diagnostic tool. These results suggested that FNAC was highly effective in diagnosing the condition, making it a reliable method for both detecting and ruling out cases with minimal errors. (Table 4)

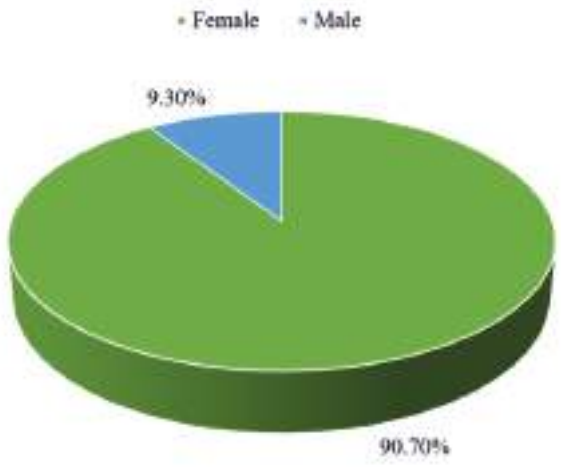


Fig. 1: Distribution of study participants on the basis of Gender

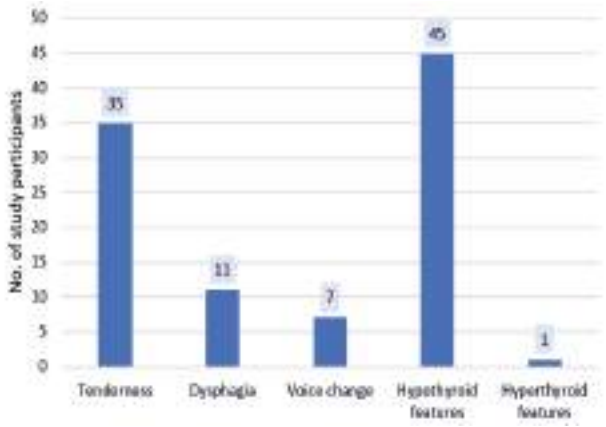


Fig. 2- Clinical Features of the study participants

Lesions on FNAC (N=152)	N (%)
Nodular Goitre	42 (27.7%)
Colloid Goitre	53 (34.8%)
Hashimoto Thyroiditis	13 (8.6%)
Lymphocytic Thyroiditis	18 (11.8%)
Cystic Nodule	10 (6.6%)
Follicular Adenoma	10 (6.6%)
Papillary Carcinoma	1 (0.6%)
Adenomatoid Goitre	5 (3.3%)

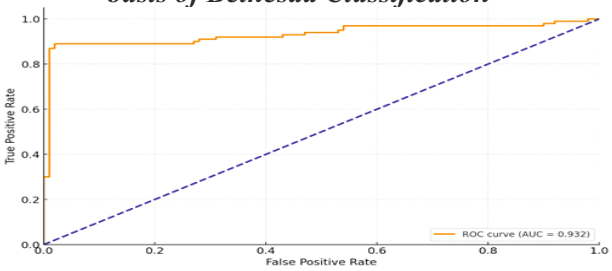
Table 1: Distribution of Study Participants on the

FNAC	Values
Sensitivity	89%
Specificity	98%
Positive predictive value	97%
Negative Predictive value	95%
Diagnostic Accuracy	90.6%

Table 4: Diagnostic Accuracy of FNAC in Evaluating Thyroid Nodules

Bethesda Classification	N (%)
1	0
2	141 (92.7%)
3	0
4	10 (6.6%)
5	0
6	1 (0.7%)

Table 2: Distribution of FNAC findings on the basis of Bethesda Classification



Lesions on FNAC	Age Category						Gender	
	10-20	20-30	30-40	40-50	50-60	>60	Male	Female
Nodular Goitre (42)	0	14 (36.8%)	12 (30%)	10 (27.7%)	4 (16.6%)	2 (25%)	5 (35.7%)	37 (26.8%)
Colloid Goitre (53)	2 (33.3%)	6 (15.7%)	10 (25%)	19 (52.7%)	12 (50%)	4 (50%)	7 (50%)	46 (33.3%)
Hashimoto Thyroiditis (13)	2 (33.3%)	7 (18.4%)	4 (8.3%)	0	0	0	0	13 (9.4%)
Lymphocytic Thyroiditis (18)	2 (33.3%)	8 (21.0%)	6 (15%)	2 (5.5%)	0	0	0	18 (13.04%)
Cystic Nodule (10)	0	0	6 (15%)	4 (11.1%)	0	0	2 (14.2%)	8 (5.7%)
Follicular Adenoma (10)	0	0	0	0	8(33.3%)	2 (25%)	0	10 (7.2%)
Papillary Carcinoma (1)	0	1 (2.6%)	0	0	0	0	0	1 (0.7%)
Adenomatoid Goitre (5)	0	2 (5.2%)	2 (5%)	1 (2.7%)	0	0	0	5 (3.6%)
Total (152)	6	38	40	36	24	8	14	138
P value	**0.036**						**0.002**	

Table 3: Distribution of Study Participants on the Basis of Age, Gender and Thyroid Lesions on FNAC

DISCUSSION

In clinical practice, it is essential to accurately differentiate the few number of thyroid malignancies from the benign lesions in order to definitively schedule the necessary operation and provide pertinent patient counseling. (6) Regarded as the most precise and economical method, FNAC is a standard diagnostic technique used to identify thyroid abnormalities. (8)

It was noted that females were more affected with a F to M ratio being 9.5:1. Study by Akshatha N etal., (9) in 101 cases where the M:F ratio was 1:7.41 (Females = 89 , Males = 12). Handa U et al. (10) and Bahaj AS et al. (11) also reported a comparable observation, showing a distinct female predominance. The distribution of age within the study population was also analyzed. Manzoor F et al., (12) also observed 3.65 times more females than males with thyroid lesion in their study. Manzoor F et al. (12), who observed the highest prevalence in the 20-29 age group-which was the second most prevalent age group in our analysis after the 30-40 age group-consistently corroborated our findings. Similarly, in the 30- to 40-year-old age group, Oberoi JS et al. (7) reported a significant prevalence of thyroid lesions (28.75%).

Thyroiditis manifested clinically in a variety of ways in the patients. Tenderness was detected in 23% of the cases, pressure symptoms such dysphagia and voice abnormalities in 2.6% and 7.2% of the cases, respectively. Symptoms of hypothyroidism were present in 29.6% of cases, while hyperthyroidism features were observed in only one case (0.99%). Similar presentations were documented in other Indian studies as well (7, 9, 10).

Benign lesions were 92.7% and 7.3% were malignant lesions. In a study by Esmaili HA et al., (1) there were 1054 (64.3%) benign, 128 (7.8%) malignant. Other studies showed varied percentages of cancerous and non cancerous lesions due to the difference in incidence of these lesions in their country, however benign lesions were almost 2/3rd of the total lesions observed. (7,9,10,11,13)

Thyroiditis was the second most common non-neoplastic lesion seen in Indian investigations, after goiter. The most common neoplastic lesion found was follicular adenoma (7, 9, 10, 13, 14). There was only one instance of papillary carcinoma documented, although other South Asian investigations found that the disease affected 4% to 9% of cases (7, 13–16).

Compared to other studies, our FNAC findings were generally superior. Bahaj et al. reported lower sensitivity (79.8%), PPV (74.77%), NPV (84.91%), and diagnostic accuracy (81.2%), suggesting their FNAC results were less reliable. (11) Sengupta et al. reported slightly higher results in some areas, with sensitivity 90%, specificity 100%, and accuracy 98.3%, but our study showed more balanced performance across all metrics like our study findings.(17) Roy etal. (18), Gupta etal.(19), Kessler etal.(20) also reported lower diagnostic values than our study, particularly in sensitivity and PPV, confirming that our FNAC results were more effective at accurately identifying and managing thyroid nodules.Overall, our study confirms FNAC as a highly reliable tool for diagnosing thyroid lesions, with more consistent and balanced performance compared to other studies.

As this study was retrospective in nature , complete clinical information of patients were unavailable for a few cases. Retrospective studies are inherently limited by their design, relying on chart reviews that were not originally intended for research purposes, which may result in incomplete data collection.

CONCLUSION

Thyroid lesions slowed definite female preponderance, with maximum number of cases occurring in patients of 30 to 40 years age. The lesion that was most frequently seen was Colloid Goiter. Most of the neoplastic lesions were diagnosed in the fifth and sixth decade and all were in females. The study emphasizes the need for evaluation of palpable lesions of thyroid by FNAC as it can prove to be indispensable tool for early diagnosis of malignancy. Our study demonstrates, FNAC is a reliable diagnostic tool for evaluating lesions of thyroid, with an overall diagnostic accuracy of 90.6%.

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Original Article

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EVALUATION OF CAROTID ARTERIAL SYSTEM IN STROKE PATIENTS USING COLOUR DOPPLER SONOGRAPHY IN A TERTIARY CARE INSTITUTE

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ABSTRACT

Stroke ranks among the world's major causes of mortality and disability, often linked to carotid artery atherosclerosis. Non-invasive imaging techniques such as colour Doppler sonography provide valuable insights into the carotid arterial system. To assess the carotid artery system in stroke patients with colour Doppler sonography, with an emphasis on carotid stenosis, plaque morphology, and intima-media thickness (IMT). This observational research included 50 stroke patients from a tertiary care hospital. Colour Doppler sonography was performed to measure IMT, Assess the degree of carotid stenosis and categorise the structure of the plaque. Majority of carotid arteries had <50% stenosis. Older age linked to greater stenosis and IMT. Color Doppler imaging is effective for screening carotid artery disease. Colour Doppler sonography is an effective tool for non-invasive evaluation of carotid arterial system, aiding in early detection and management of carotid artery disease.

KEYWORDS: Carotid Arterial System, Stroke, Colour Doppler Sonography, Carotid Stenosis, Plaque Morphology.

INTRODUCTIONStroke represents a major global health issue, resulting in considerable illness and death. Ischemic strokes make up about 80–85% of all strokes, and carotid artery stenosis is an important contributing risk factor (1). Narrowing of the carotid arteries, primarily because of atherosclerosis, can lead to diminished cerebral blood flow and increase likelihood of thromboembolic events (2). Accurate and prompt assessment of the carotid arteries is crucial for effective management. and prevention of stroke.Colour Doppler sonography has emerged as a reliable, non-invasive imaging technique for assessing carotid artery stenosis. It offers real-time visualization of blood flow and vessel wall abnormalities, making it a valuable tool in the clinical evaluation of stroke patients (3). Among the primary causes of death and morbidity is stroke. 80–85% of fall strokes are due to ischemic infarcts. One of the primary risk factors for ischemic stroke, which accounts for 5–10% of cases, is carotid atherosclerosis (4).It has been demonstrated that carotid endarterectomy significantly lowers the risk of stroke in patients with substantial stenosis, or 70% or higher.

Plaque composition is thought to play a significant role in symptom determination. Thus, a trustworthy, ideally non-invasive technique to describe the content and structure of the plaque would be helpful in identifying patients who are more susceptible to plaque disruption and in identifying the factors that contribute to the formation of unstable atherosclerotic lesions. A variety of sonographic techniques have been utilized for over ten years to examine carotid arteries in patients with cerebrovascular illness.

This study aims to assess the carotid arterial system using colour Doppler sonography in stroke patients admitted to a tertiary care hospital.

AIMS AND OBJECTIVES

The objective of this study is to evaluate carotid arterial system using colour Doppler sonography in stroke patients. The specific objectives include:

- Evaluating the prevalence of carotid artery stenosis in patients with stroke.
- Analyzing the affiliation between carotid artery stenosis and patient demographics such as age and gender.
- Evaluating the efficacy of colour Doppler sonography in detecting carotid artery abnormalities.

REVIEW OF LITERATURE

Carotid artery disease has been widely studied due to its significant role in cerebrovascular events. Carotid sonography has been demonstrated as an effective tool in detecting stenosis and assessing stroke risk (5). Research has demonstrated that the existence of plaques in the carotid arteries, particularly those causing significant luminal narrowing, has been linked to a higher risk of stroke (6).

Development of colour Doppler sonography has enhanced the ability to evaluate both the structural and hemodynamic aspects of the carotid arteries. It allows for the measurement of intima-media thickness (IMT) and the detection of turbulent flow, both of which are indicators of atherosclerotic disease (7). Previous research has highlighted the utility of this imaging modality in routine stroke care, emphasizing its role in both diagnosis and follow-up (8).

MATERIAL AND METHODS

Study Design

This cross-sectional investigation was carried out at the Department of Radiodiagnosis, IIMS&R, Lucknow. The institutional review board granted ethical approval.

STUDY POPULATION

The study involved the enrolment of a total of (50) patients who had been diagnosed with stroke. The inclusion criteria was patients with confirmed ischemic stroke, while exclusion criteria included patients with a history of carotid surgery or incomplete medical records.

DATA COLLECTION

All patients underwent a detailed clinical examination followed by colour Doppler sonography of the carotid arteries. The sonographic evaluation was performed using (Aloka Hitachi F 31 Ultrasound and Doppler machine), and images were analyzed for the presence of stenosis, plaque morphology, and IMT.

STATISTICAL ANALYSIS

(SPSS version 24.0 (IBM Corp, Armonk, NY, USA)) used to analyse the data. The sonographic results and patient data were compiled using descriptive statistics. Using logistic regression analysis and chi-square testing, the prevalence of carotid artery stenosis was determined along with its correlation with demographic characteristics.

Observations and Results

- **Demographics**: 50 patients (72% male, 28% female), mainly 60-69 years.
- **Plaque Detection**: 71 out of 100 arteries had plaques.
- Types: 39.43% hypoechoic, 21.13% hyperechoic, 39.43% calcified.
- Surface: 15.49% irregular, 84.5% smooth.
- **Plaque Morphology**: Irregular plaques were mostly calcified (72.72%). Smooth plaques: 43.33% homogeneously hypoechoic, 33.33% calcified.
- **Stenosis Severity**: 73.2% <50%, 12.7% 50-59%, 5.6% 60-69%. More prevalent on the left (52.1%). Males more likely to have <50% stenosis ($p < 0.01$).
- **Hemodynamics**: Higher stenosis associated with increased ICA velocities.
- **IMT**: 48% had IMT >0.80mm; 29.16% under 60 years, 70.84% over 60 years.

STATISTICAL ANALYSIS

We found statistically significant association among carotid artery stenosis and male gender ($p < 0.05$). Additionally, age was found to be a significant predictor of stenosis severity ($p < 0.01$).

OBSERVATIONS AND RESULTS

Gender	No. of Patients	Percent
Female	14	28.00%
Male	36	72.00%
Total	50	100.00%

Table 1: Gender Distribution

Age (Years)	No. of cases	Percentage
30-39	1	2.00%
40-49	3	6.00%
50-59	10	20.00%
60-69	18	36.00%
70-79	13	26.00%
80–89	4	8.00%
90–99	1	2.00%
Total	50	100.00%

Table 2: Age Distribution

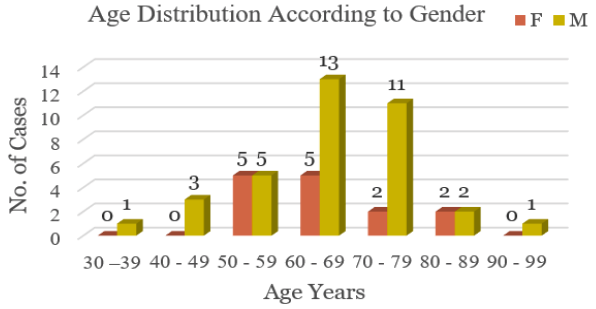

Fig. 1: Age Distribution of the Patients According to Gender

Plaque surface	Calcified	Heterogeneously hyperechoic	Heterogeneously hypoechoic	Homogenously hyperechoic	Homogenously hypoechoic	Not seen	%
Irregular	8	2	1	0	0	0	11.0%
Not seen	0	0	0	0	0	29	29.0%
Smooth	20	7	1	6	26	0	60.0%
Total	28	9	2	6	26	29	100.0%
%	28.0%	9.0%	2.0%	6.0%	26.0%	29.0%	

Table 3: Plaque Characteristics

Side	Carotid bulb	Carotid bulb extending to ECA	Carotid bulb extending to ICA	CCA	CCA Extendig to carotid bulb	Distal CCA	Distal CCA Extendig to ICA	ICA	Mid CCA	Mid CCA extending to ICA	Proximal ICA	%
Left	18	1	5	2	1	1	2	2	1	1	3	52.2
Right	13	0	5	1	0	1	3	6	0	0	5	47.9
Total	31	1	10	3	1	2	5	8	1	1	8	100
%	43.7	1.4	14.1	4.2	1.4	2.8	7	11.3	1.4	1.4	11.3	

Table 4: Plaque Location

% Area stenosis (Rt)	No. of Carotid Vessels (n=34)	Rt ICA PSV(cm/s)		Rt ICA EDV(cm/s)		Rt ICA PSV/Rt CCA PSV	
		Mean	SD	Mean	SD	Mean	SD
<50	23	89.87	13.96	33.5128	3.7966	1.0769	0.2497
50-59	6	146.17	46.88	35.1667	5.1929	1.9333	0.4179
60-69	2	216.50	12.02	70	14.1421	2.5	0.2828
70-79	1	285.00	0.00	110	0.00	4.1	0.00
80-89	1	300.00	0.00	105	0.00	4.5	0.00
90-100	1	280.00	0.00	103	0.00	4.1	0.00

Table 5: Duplex Criteria in Relation with Directly Observed Stenosis (Right Side)

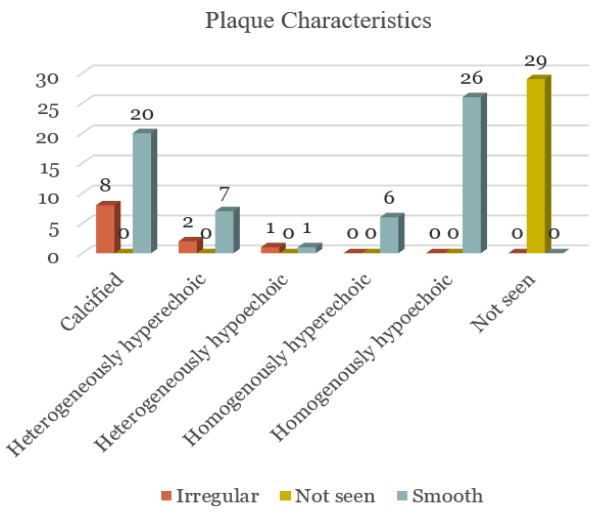

Fig. 2: Plaque Characteristics

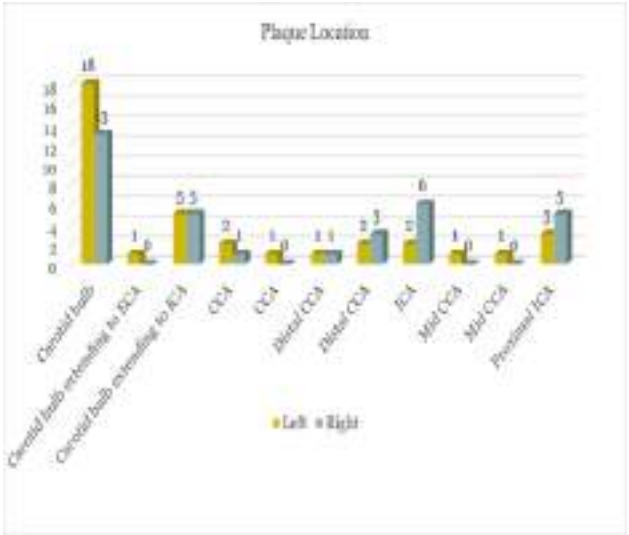

Fig. 3: Plaque Location

% Area stenosis (Lt)	No. of Carotid Vessels (n=71)	Lt ICAPSV(cm/s)		Lt ICAEDV(cm/s)		Lt ICA PSV/Lt CCA PSV	
		Mean	SD	Mean	SD	Mean	SD
<50	52	88.48	9.89	33.17	3.06	1.07	0.22
50-59	9	138.67	52.55	40.33	4.16	1.57	0.72
60-69	4	212.50	10.61	58.00	31.11	2.70	0.42
70-79	3	159.00	86.27	33.50	4.95	1.52	1.39
80-89	2	285.00	0.00	110.00	0.00	4.10	0.00

Table 6: Duplex Criteria in Relation with Directly Observed Stenosis (Left Side)

IMT	Gender	No .of Cases	Mean	SD	P value
Left CCA IMT (mm)	F	14	0.81	0.13	0.0315
	M	36	0.94	0.30	
Right CCA IMT (mm)	F	14	0.76	0.13	0.0109
	M	36	0.98	0.44	

Table 7: Mean IMT Relation with Gender

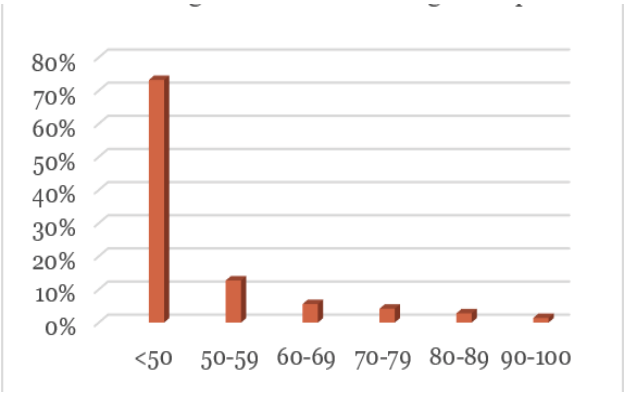

Fig. 4: Percentage area Sstenosis.

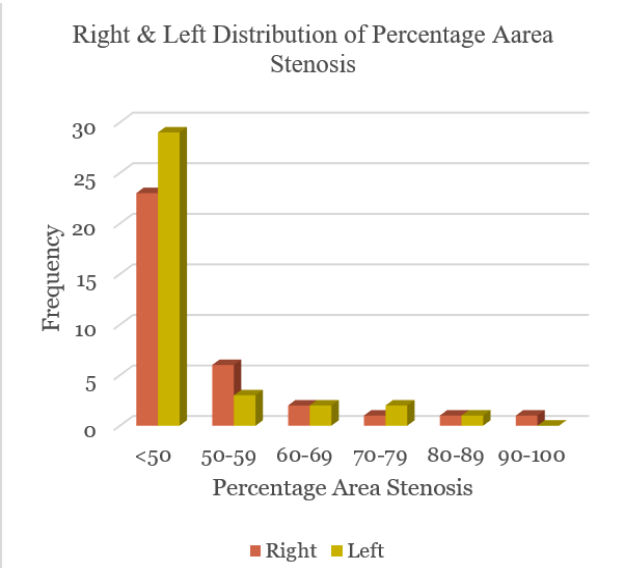

Fig. 5: Distribution of Percentage Area Stenosis in Various Age Groups

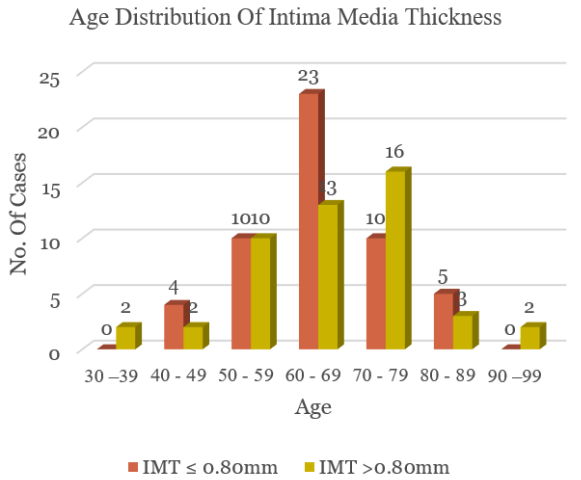

Fig. 6:Age Distribution of Intima Media Thickness

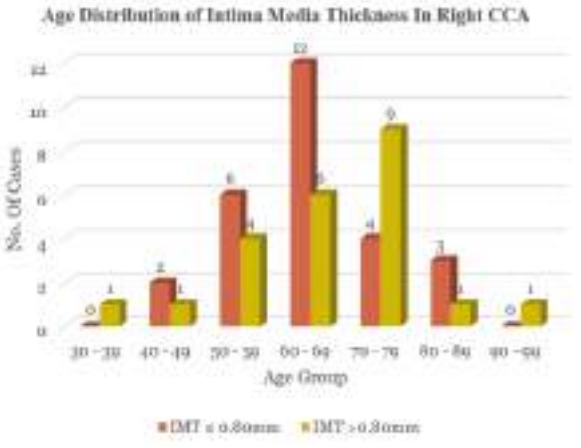

Fig. 7: Age Distribution of Intima Media Thickness in Right CCA

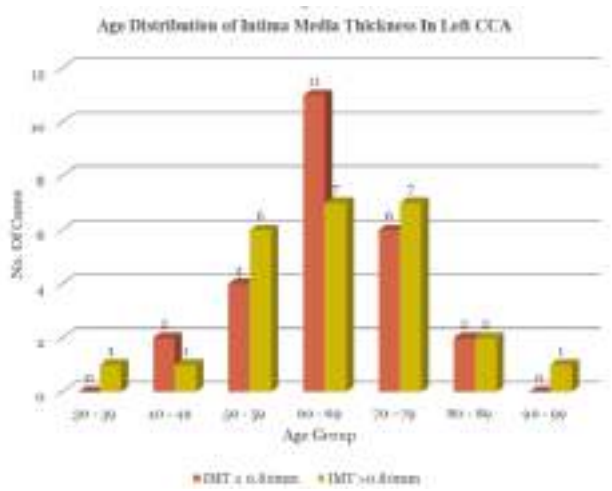

Fig. 8: Age Distribution of Intima Media Thickness in Left CCA

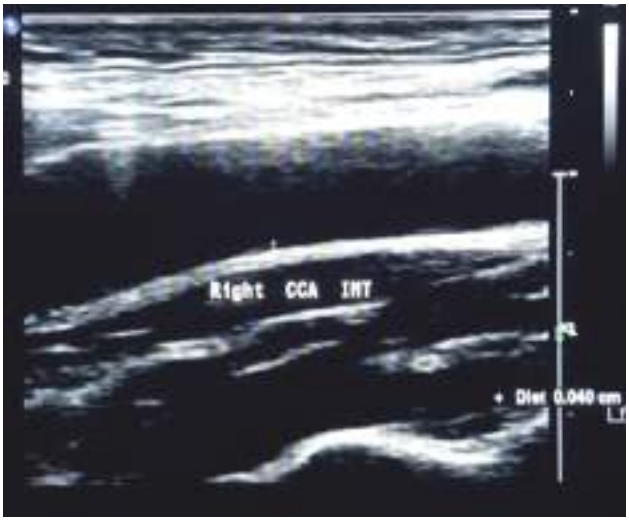

Fig. 9: Gray Scale Longitudinal image Showing normal IMT of right CCA

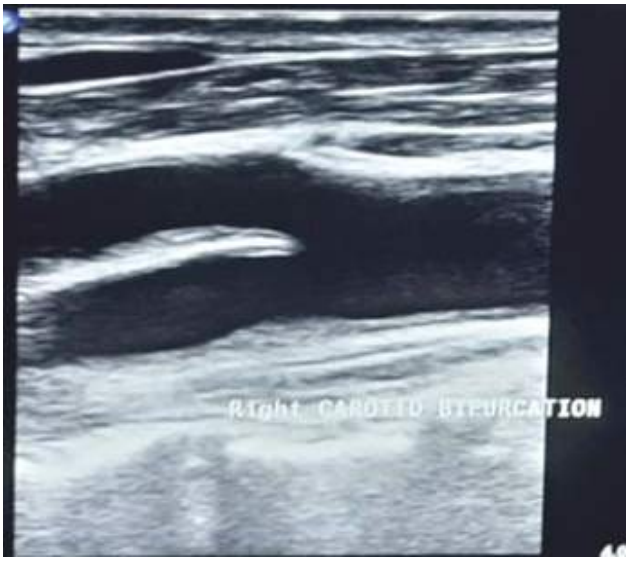

Fig. 10 : Gray Scale Longitudinal Image - Normal Bifurcation of Right Carotid Artery

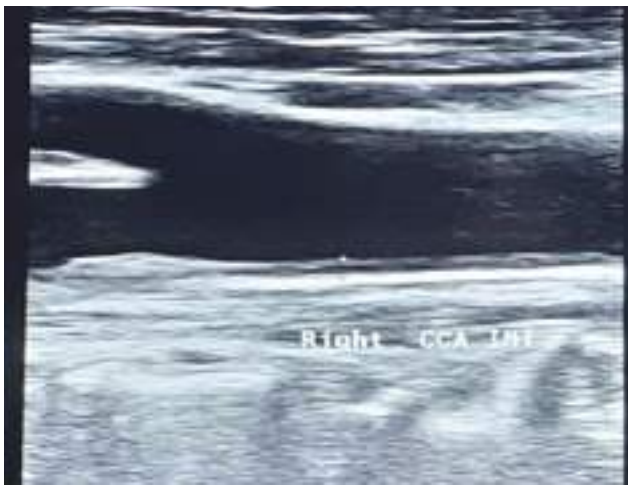

Fig. 11: Gray scale longitudinal image - thickened IMT in right CCA

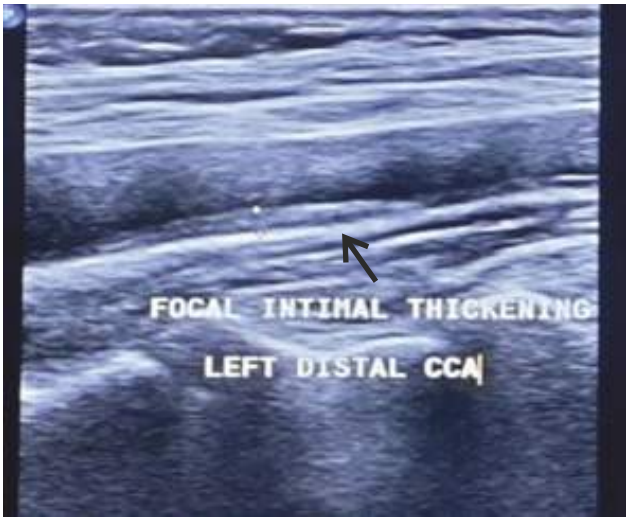

Fig. 12:Gray scale longitudinal image showing focal intimal thickening in left distal CCA

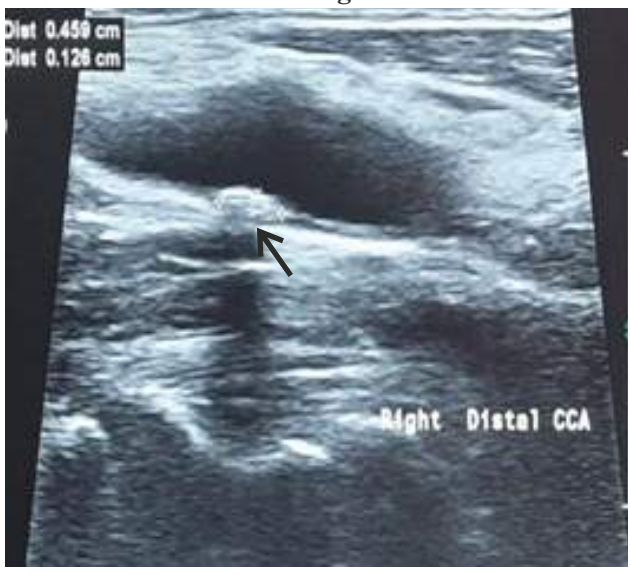

Fig. 13: Gray longitudinal image - hypoechoic plaque with irregular margin in right distal CCA

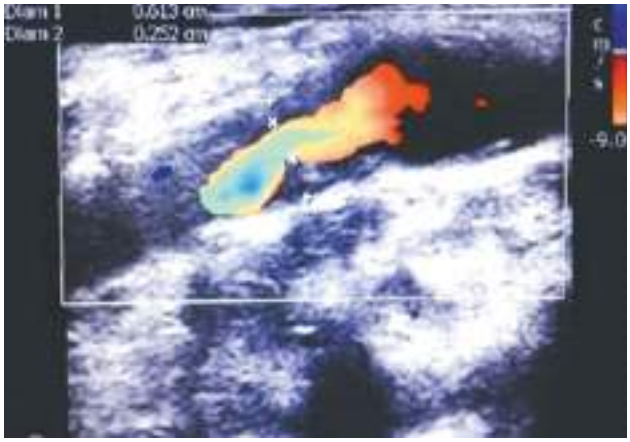

Fig. 14: Colour Doppler images showing reduced colour flow with heterogeneously hyperechoic plaque in Left ICA causing 58.9 % area stenosis

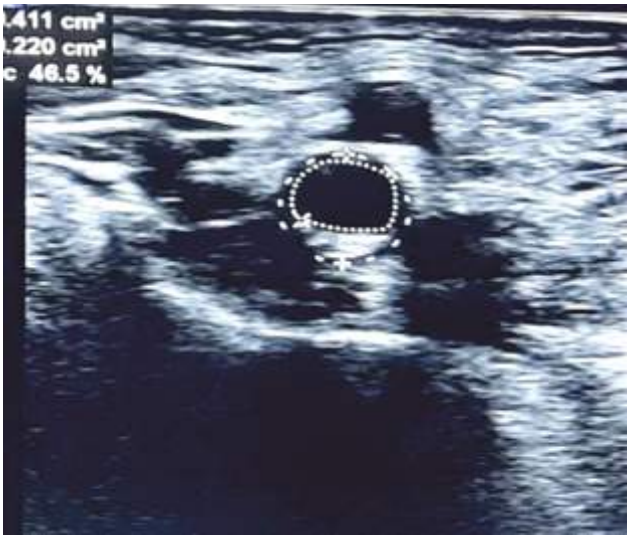

Fig. 15: Gray scale axial image - hyperechoic plaque with smooth margin causing 46.5% stenosis in left CCA

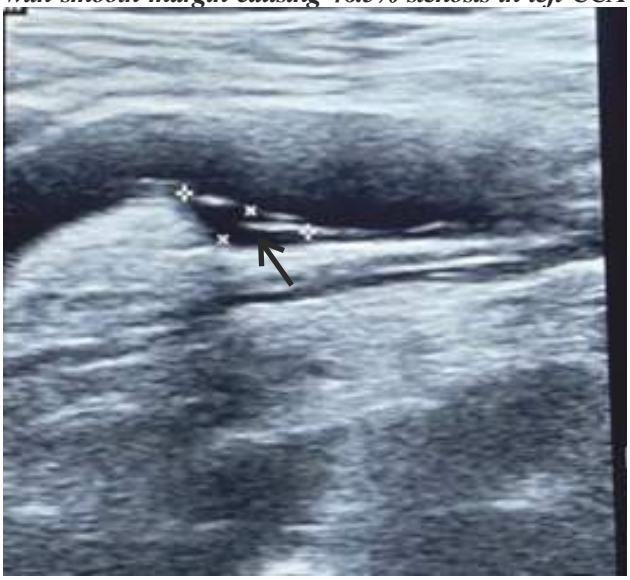

Figure 16:Gray scale longitudinal image showing heterogeneously hypoechoic plaque in left distal CCA

DISCUSSION

The results of this investigation align with previous research highlighting the regularity of carotid artery stenosis in stroke victims. (10). Higher incidence of stenosis in male patients aligns with previous studies that suggest gender as one of the atherosclerotic disease risk factors (11).

This study aimed to evaluate the role of Duplex Ultrasonography in detecting changes in the carotid artery system in 50 patients with suspected cerebrovascular accidents at the Integral Institute of Medical Sciences and Research.

GENDER DISTRIBUTION

Out of 50 patients, 36 (72%) were male, and 14 (28%) were female, consistent with findings from Fernandes et al. and Iemolo et al., showing a similar gender distribution.

AGE DISTRIBUTION

The majority of patients (36%) were in the 60-69 years age group, followed by 26% in the 70-79 age group. The average age of patients was 65.38 ± 11.76 years, comparable to Khatib et al.'s reported mean age of 63.95 ± 10.3 years.

GENDER-WISE AGE DISTRIBUTION

Males predominated in most age groups except for the 50-59 years group, where the gender distribution was equal. In the 60-69 years age group, 13 males and 5 females were represented. Plaque incidence was higher in males, particularly in the 60-70 age group.

PLAQUE CHARACTERISTICS

Plaques were detected in 71 out of 100 arteries, with 39.43% being hypoechoic, 21.13% hyperechoic, and 39.43% calcified. Most plaques (84.5%) had a smooth surface, while 15.49% were irregular. No ulcerations were observed. Calcified plaques were the most common type with irregular surfaces.

PLAQUE LOCATION

Plaques were most commonly located in the carotid bulb (43.7%) and extended into the internal carotid artery (ICA) in 14.1% of cases. Plaques were also found in the common carotid artery (CCA) and external carotid artery (ECA).

STENOSIS DISTRIBUTION

Of the 71 arteries with stenosis, 52 (73.2%) had less than 50% stenosis, with the highest occurrence in the 60-69 age group. Gender differences showed 69.8% of males and 83.3% of females with less than 50% stenosis.

DUPLEX ULTRASONOGRAPHY AND STENOSIS

A correlation between percentage stenosis and increases in peak systolic velocity (PSV) and end-diastolic velocity (EDV) was observed. As stenosis increased, PSV and ICA PSV/CCA PSV ratio also rose.

INTIMA-MEDIA THICKNESS (IMT)

IMT values were higher in patients over 60 years of age, with 48% of arteries exceeding the normal threshold of 0.80mm. Age-wise, a significant increase in IMT was observed with advancing age, consistent with findings from Saxena et al.

IMT AND GENDER

No significant differences in IMT were found between genders in either the left or right CCA. However, males generally had higher IMT values compared to females, a trend observed in similar studies by Mazurek et al. Color Doppler sonography is an effective non-invasive tool for assessing carotid arteries, allowing detailed visualization of plaque morphology and blood flow, aiding in stroke risk evaluation. This study advocates for its routine use in stroke diagnostics, particularly in high-risk patients. However, limitations include its cross-sectional design and small sample size, affecting generalizability. Future research should focus on larger, longitudinal studies to validate these findings and explore the role of carotid sonography in stroke prevention

CONCLUSION

This study demonstrates high rate of carotid artery stenosis prevalence among stroke individuals and underscores the importance of routine carotid evaluation using colour Doppler sonography. Early detection of carotid artery stenosis can lead to timely interventions, potentially reducing the risk of recurrent strokes. Colour Doppler sonography should be considered an integral part of stroke management protocols in tertiary care settings.

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Original Article

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CYTOMORPHOLOGICAL SPECTRUM OF PALPABLE THYROID LESIONS AND THEIR CORRELATION WITH SONOGRAPHIC FINDINGS

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ABSTRACT

In many thyroid disorders, the size of the gland tends to increase presenting as a swelling (1). The thyroid swelling can be diffuse, multinodular or appear as a solitary nodule (2). It is imperative to differentiate the types of thyroid swelling based on etiology and character because nature of the lesion will decide the treatment and prognosis of these swellings (3). Proper nature of the solitary nodules needs to be ascertained as best as possible as only a small fraction of these nodules is malignant and thereby unnecessary surgery can be avoided (4,5). 66 patients including both male and female were selected after applying inclusion and exclusion criteria. The study participants presented with palpable thyroid swelling in the department of ENT and Surgery. They underwent FNAC, Ultrasonography and Histology if the swelling was surgically resected. Findings were correlated with each other. Most of the sample belonged to female gender 80.3% and were of young age (Mean age-37.38 years). On Ultrasonography majority of the cases were of Benign cystic nodule (60.6%). 71.2 % patients belonged to TIRADS grade-1. On FNAC adenomatous nodules were found in 50% of cases. On Bethesda class 66.7% were of Bethesda class 2. Out of 66 cases 15 had Histology report available. Out of 15 cases colloid nodule was found in 53.3% cases. FNAC results confirmed adenomatous nodules predominantly across various USG findings, especially in cases of benign cystic nodules (62.5%) and hypoechoic nodules with irregular margins (50.0%). Lymphocytic thyroiditis was associated with USG findings suggestive of inflammation, notably thyroiditis (50.0%). These findings were statistically significant (P=0.028). When evaluating thyroid swellings, FNAC and ultrasonography are essential diagnostic techniques. Ultrasonography predicts benign and malignant lesions significantly.

KEYWORDS: Palpable thyroid swelling, Fine Needle Aspiration Cytology, Thyroid cancer, Thyroid nodule.

INTRODUCTION

The thyroid gland is made up of two lobes joined by an isthmus, and it weighs between 20 and 25 grams (7). In many thyroid disorders, the size of the gland tends to increase presenting as a swelling (2). The thyroid swelling can be diffuse, multinodular or appear as nodule (3).

It is imperative to differentiate the types of thyroid swelling based on etiology and character because nature of the lesion will decide the treatment and prognosis of these swellings (4).

Proper nature of the solitary nodules needs to be ascertained as best as possible as only a small fraction of these nodules is malignant and thereby unnecessary surgery can be avoided (5,6).

Thus, it becomes very important to search for a diagnostic test which not only differentiate thyroid nodules as benign or malignant as accurately and precisely as possible, but also is non-invasive, cost-effective & easily accessible.A non-invasive, economical diagnostic method that can distinguish between solid and cystic lesions is ultrasonography (7, 8). When diagnosing thyroid lesions,FNAC is thought to be the best investigative technique. **(9).** FNAC as a procedure can detect malignancy with great accuracy and precision. However, it has few drawbacks such as it is minimally invasive and cannot differentiate between follicular adenoma and carcinoma (10,11). There are always chances of inadequate and suspicious (i.e., sample being of thyroid gland) sample (12). Additionally, FNAC has trouble accurately interpreting lymphocytic lesions, hurthle cell lesions, follicular lesions, and cysts. (13).

AIM

To study the cytomorphological spectrum of palpable thyroid lesions.

OBJECTIVES

1. Cytohistological correlation of thyroid lesions wherever surgical resection has been performed.
2. To correlate USG findings of thyroid lesions with cytological diagnosis.

MATERIAL AND METHODS

The study was conducted between September 2022 and May 2024 in a tertiary care hospital of northern part of India. Its an observational analytical study. Sample size consisted of 66 patients who presented as palpable thyroid swelling in the department of ENT and Surgery. Serial and purposive sampling method was used. Patients previously diagnosed and treated for thyroid lesions, including those with a history of thyroid surgery, Patients with bleeding diathesis, Patients who did not provide informed consent for FNAC and Patients with unsatisfactory or inadequate FNAC samples were excluded.

Data collection was done from the patients after obtaining written informed consent. Demographic data such as age, gender, size of nodule, laterality and duration of nodule were recorded. Patients also underwent thorough physical examination by a health care professional. Physical examination findings, including palpation of the thyroid gland, assessment of gland size, nodularity, tenderness, and presence of associated lymphadenopathy, were documented.

Fine-Needle Aspiration Cytology (FNAC)

A 10-milliliter disposable syringe and a 23-gauge needle were used for FNAC, and four to five slides were prepared for each patient. Two smears were air-dried and stained using the MGG technique (May Grunwald-Giemsa stain), while the other two smears were fixed with 95% alcohol and H&E stain. FNAC results, including cytological findings such as cell morphology, presence of colloid, follicular cells, Hurthle cells, lymphocytes, macrophages, and any suspicious or malignant features, were recorded.

Ultrasonography (USG) Findings:

USG of the thyroid gland was performed to assess the size, shape, echogenicity, vascularity, and presence of nodules or masses. USG findings, including features suggestive of benign or malignant lesions such as hypoechoic nodules, microcalcifications, irregular margins, and increased vascularity, were documented.

Histopathology Findings (if available):

For patients who underwent surgical resection of thyroid lesions, histopathological examination of the excised tissue was conducted. The biopsy specimen was fixed in 10% formalin & grossing was done in the department. Relevant sections were taken & given for processing. Sections of each block were cut at a thickness of 4-5 microns and stained with H&E. Histopathology findings, including the type of lesion (e.g., adenoma, carcinoma, goitre), tumour grade and stage (if applicable), presence of vascular or capsular invasion, and lymph node involvement, were documented.

STATISTICAL ANALYSIS

Descriptive statistics summarized demographic and clinical information, while bivariate analysis assessed associations between different variables using chi-square tests and Pearson's correlation. Logistic regression helped identify factors that predict malignancy in thyroid lesions, and subgroup analyses explored variations based on age, sex, and diagnostic results. Microsoft Excel was used to enter the data, and SPSS version 26 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis., ensuring data quality and handling missing values.

RESULTS

The sample has a mean age of 37.38 years and a standard deviation of 16.55 years. The age range is 12 to 95 years old, with 35 being the median age. Out of 66 valid responses, 19.7% identified as male, while 80.3% identified as female. Of the 66 patients, 18.2% exhibited diffuse swelling, 15.2% were left-lateralized, 33.3% were midline, and another 33.3% were right-lateralized.

Thyroid nodule sizes range in size from 3.09 cm on average to 1.90 cm on average, suggesting a moderate degree of variability. Out of the 66 respondents, 51.5% reported a duration of swelling up to 1 year, indicating relatively recent onset of symptoms. Meanwhile, 34.8% reported a duration of 1 to 5 years, suggesting a more established condition.

Ultrasonography (USG) Findings

Table 1 displays the findings from ultrasonography (USG) examinations within the sample. Among the 66 total observations, 1.5% showed normal results. The

USG Finding	N	%
Normal	1	1.5%
Benign cystic nodule	40	60.6%
Thyroiditis	6	9.1%
Isoechoic nodules with regular margins	4	6.1%
Hypoechoic nodule with irregular margins	8	12.1%
Hypoechoic nodules with microcalcification	7	10.6%
Total	**66**	**100.0%**

Table 1: Ultrasonography (USG) Findings

most common finding was benign cystic nodules, accounting for 60.6% of the cases. Thyroiditis was observed in 9.1% of the cases, while isoechoic nodules with regular margins were found in 6.1% of cases.

Thyroid Imaging Reporting and Data System (TIRADS) Grading

Table 2 presents the distribution of TIRADS grading within the sample. Out of the 66 total observations, the majority, comprising 71.2%, were classified as TIRADS grade 1. Grade 2 was observed in 6.1% of cases, grade 3 in 12.1% of cases, and grade 4 in 10.6% of cases. This indicates that a significant portion of the sample had a low TIRADS grading, suggesting a lower likelihood of malignancy according to the TIRADS classification system.

TIRADS Grading	N	%
1	47	71.2%
2	4	6.1%
3	8	12.1%
4	7	10.6%
5	0	0%
Total	66	100.0%

Table 2: TIRADS Grading

FNAC findings	N	%
Inconclusive	2	3.0
Colloid Cyst	5	7.6
Adenomatous Nodule	33	50
Lymphocytic thyroiditis	11	16.7
Follicular lesion of undetermined significance	6	9.1
Follicular Neoplasm	7	10.6
Suspicious of papillary carcinoma	1	1.5
Malignant (Anaplastic carcinoma)	1	1.5
Total	**66**	**100.0%**

Table 3: Fine Needle Aspiration Cytology Findings

FNAC Findings

Table 3 display that among the 66 total observations, 3.0% were inconclusive. Colloid cysts were found in 7.6% of cases, while adenomatous nodules were the most common finding at 50% of cases. Lymphocytic thyroiditis was observed in 16.7% of cases, followed by follicular lesions of undetermined significance at 9.1% and follicular neoplasms at 10.6%. Suspicion of papillary carcinoma and malignant (anaplastic carcinoma) findings each accounted for 1.5% of cases.

Bethesda Classification

Table 4 presents the distribution of Bethesda classes within the sample. Out of the 66 total observations, 10.6% were classified as Bethesda class 1, 66.7% as class 2, 9.1% as class 3, and another 10.6% as class 4. Only a small proportion, 1.5% each, were classified as class 5 or 6. This classification system provides insights into the likelihood of malignancy based on cytological findings, with the majority falling into Bethesda class 2, which typically indicates benign or non-neoplastic conditions.

Bethesda class	N	%
1	7	10.6
2	44	66.7
3	6	9.1
4	7	10.6
5	1	1.5
6	1	1.5
Total	**66**	**100.0%**

Table 4: Bethesda Classification.

Histological Examination

Out of the 66 patients 15 (22.7%) had undergone histological examination. Histological examination was suggested only when there was any suspicion of malignancy on FNAC. This suggests that a significant portion of the sample had their diagnosis derived from clinical, radiological, and cytological studies.

Distribution of Histological Types

In Table 5, the distribution of histological types among cases that underwent histological examination is presented. Among the 15 cases studied, various histological types were identified: Colloid Nodule in 53.3% of the cases, Follicular Adenoma in 33.3% of cases, Papillary Carcinoma in one case (6.66%), Similarly, one case (6.66%) was diagnosed as anaplastic carcinoma, an aggressive and less common type of thyroid cancer associated with poorer outcomes.

Histology type	N=15	% =100
Colloid Nodule	8	53.3
Follicular adenoma	5	33.3
Papillary carcinoma	1	6.66
Anaplastic carcinoma	1	6.66

Table 5: Distribution of Histological Types.

FNAC findings	USG Finding											
	Normal		Benign cystic nodule		Thyroiditis		Isoechoic nodules with regular margins		Hypoechoic nodule with irregular margins		Hypoechoic nodules with microcalcification	
	N	%	N	%	N	%	N	%	N	%	N	%
Inconclusive	0	.0%	0	.0%	1	16.7%	0	.0%	1	12.5%	0	.0%
Colloid Cyst	0	.0%	4	10.0%	0	.0%	1	25.0 %	0	.0%	0	.0%
Adenomatous Nodule	1	100.0 %	25	62.5%	1	16.7%	2	50.0 %	2	25.0%	2	28.6%
Follicular lesion of undetermined significance	0	.0%	1	2.5%	1	16.7%	1	25.0 %	3	37.5%	0	.0%
Follicular Neoplasm	0	.0%	3	7.5%	0	.0%	0	.0%	1	12.5%	3	42.9%
Lymphocytic thyroiditis	0	.0%	7	17.5%	3	50.0%	0	.0%	1	12.5%	0	.0%
Suspicious of papillary carcinoma	0	.0%	0	.0%	0	.0%	0	.0%	0	.0%	1	14.3%
Malignant (Anaplastic carcinoma)	0	.0%	0	.0%	0	.0%	0	.0%	0	.0%	1	14.3%

Table 6: Correlation between FNAC and USG Findings.

Applied $\chi 2$ test for significance. $\chi 2$ value=58.84; df=40; **p-value=0.028; Significant**

DISCUSSION

First, the age distribution of the respondents shows that the majority of them (45.5%) are between the ages of 18 and 35, suggesting that the sample contains a sizable proportion of younger adults. Secondly, gender distribution within sample shows a substantial majority of female respondents, accounting for 80.3% of the valid responses. Lastly, the distribution of laterality among respondents shows a relatively balanced pattern. About one-third of the sample exhibits midline laterality (33.3%), while another one-third is right-lateralized (33.3%). Malakzai HA et al. (2023) examined 686 thyroid nodule patients, and found similar demography in sample size (14)

This study also found the distribution of thyroid nodule sizes, with 43.9% in the 0-2 cm range, 48.5% in the 2.01-5 cm range, and 7.6% in the 5.01-10 cm range, indicating prevalence across small, medium, and larger nodules among 66 observations. According to Majister MJ's research, thyroid nodules ranged in size from 0.5 to 8.8 cm. with an average (standard deviation) size of 2.0 (1.4) cm. (15)

Our result also found that out of the 66 total observations, the majority, comprising 71.2%, were classified as TIRADS grade 1. Grade 2 was observed in 6.1% of cases, grade 3 in 12.1% of cases, and grade 4 in 10.6% of cases. This indicates that a significant portion of the sample had a low TIRADS grading, suggesting a lower likelihood of malignancy according to the TIRADS classification system. Periakaruppan G et al. (2018) assessed 184 thyroid nodules for FNAC using ultrasound and TIRADS scoring, excluding TIRADS 6 (proven malignancies). Their results showed 117 nodules as TIRADS-2, 45 as TIRADS-3, 13 as TIRADS-4, and 9 as TIRAD- 5. (16)

Our study also found that FNAC of thyroid samples, revealing a range of conditions: 3.0% inconclusive, 7.6% colloid cysts, 50% adenomatous nodules, 16.7% lymphocytic thyroiditis, 9.1% follicular lesions, 10.6% follicular neoplasms, and 1.5% each for suspicion of

papillary carcinoma and anaplastic carcinoma.

The distribution of FNAC cases according to Bethesda categories was reported by Hajmanoochehri F et al. as follows: Three cases of chronic lymphocytic thyroiditis and 26 cases of nodular goiter were among the 29 cases (28.7%) that were benign and nonneoplastic. Four cases (4%) were classified as AUS/FLUS. Furthermore, 27 cases (26.7%) were classified as FN/SFN, consisting of 24 follicular cell types and 3 Hürthle cell types. A total of sixteen cases (15.8%) were considered suspicious for malignancy; these cases included one case each of medullary carcinoma, undifferentiated carcinoma, and malignant lymphoma, and thirteen cases suspicious for papillary carcinoma. Finally, 25 cases (24.8%) were malignant; these included 2 cases of undifferentiated carcinoma, 1 case of medullary carcinoma, and 22 cases of papillary carcinoma (17).

Our findings also elucidated that out of the 66 total observations, 10.6% were classified as Bethesda class 1, 66.7% as class 2, 9.1% as class 3, and another 10.6% as class 4. Only a small proportion, 1.5% each, were classified as class 5 or 6. This classification system provides insights into the likelihood of malignancy based on cytological findings, with the majority falling into Bethesda class 2, which typically indicates benign or non-neoplastic conditions.

This study also found correlation between FNAC findings and Ultrasound (USG) findings in thyroid assessments. Adenomatous nodules were confirmed across various USG findings, notably benign cystic nodules (62.5%) and hypoechoic nodules with irregular margins (50.0%). Lymphocytic thyroiditis correlated with USG findings indicative of inflammation, especially thyroiditis (50.0%). Colloid cysts were associated with benign cystic nodules (10.0%) and thyroiditis (25.0%). FNAC also identified follicular neoplasms in hypoechoic nodules with microcalcification (42.9%) and benign cystic nodules (7.5%). These correlations emphasize the importance of integrating FNAC and USG for a thorough assessment of thyroid conditions, offering detailed insights into nodule composition and characteristics detected via USG imaging.

According to Popli et al., the ultrasound diagnosis of benign and malignant thyroid nodules had overall sensitivity, specificity, positive predictive value, and negative predictive value of 81.8%, 87.2%, 59.0%, and 95.5%, respectively. (18)

The study also investigated histological types in thyroid-related cases that underwent examination, revealing a diverse spectrum of findings. Among the 15 cases studied, colloid nodules were the most common (53.3%), representing benign thyroid conditions characterized by colloid-filled follicles. Follicular adenomas, benign tumours arising from thyroid follicular cells, were diagnosed in 33.3% of cases.

These correlations emphasize the importance of integrating FNAC and USG for a thorough assessment of thyroid conditions, offering detailed insights into nodule composition and characteristics detected via USG imaging.

CONCLUSION

The TIRADS classification system emerged as a valuable tool for assessing thyroid nodule malignancy risk, with higher TIRADS grades correlating with increased malignancy probabilities. This classification's utility in reducing unnecessary biopsies and aiding clinical decision-making was evident across various studies.

The spectrum of thyroid pathologies revealed by FNAC results ranged from benign to malignant diseases, with correlations observed among FNAC results, histopathological outcomes, and thyroid function tests. Noteworthy findings included the prevalence of colloid goitre and follicular adenoma. The associations between FNAC results and USG findings emphasized the complementary roles of these diagnostic modalities.

In summary, our study contributes to a nuanced understanding of thyroid nodules, emphasizing the importance of integrating clinical, radiological, cytological, and histopathological assessments for comprehensive thyroid disorder evaluation and management. Future research could explore genetic, environmental, and lifestyle factors influencing thyroid pathology, enhancing personalized approaches to thyroid disease management.

Conflicts of Interest:

The authors declare no conflicts of interest regarding this study.

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Review Article

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ASSOCIATION OF SERUM ELECTROLYTE CHANGES WITH ACUTE CORONARY SYNDROME: A NARRATIVE REVIEW

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ABSTRACT

Blended learning (BL), which merges traditional face-to-face instruction with online education, has become a prominent approach in higher education, including dental science education. This review examines the concept of blended learning, its components, advantages, challenges, and applications within dental education. It emphasizes the value of combining in-person teaching with digital tools, such as online platforms, virtual simulations, and patient management software, to enhance learning outcomes. In dental science, blended learning offers a flexible and integrated approach where students engage in theoretical coursework, develop practical skills, and receive clinical training. Online learning modules provide flexibility, allowing students to learn at their own pace, while in-person classes support active interaction with instructors and hands-on experience. The review highlights that blended learning fosters personalized learning paths, increases accessibility, and promotes greater student-teacher engagement. Despite these advantages, the successful implementation of blended learning in dental education requires addressing challenges such as technological limitations, faculty training, and balancing online and hands-on experiences. The review concludes that with thoughtful planning and execution, blended learning has the potential to improve both the theoretical knowledge and clinical proficiency needed by dental professionals in today's rapidly changing healthcare landscape.

KEYWORDS: Acute Coronary Syndrome, Clinical Correlation, Electrolytes, Electrolyte Imbalance, Myocardial Infraction.

INTRODUCTION

"Acute coronary syndrome" describes a cluster of medical conditions marked by sudden reduction in blood flow to the heart. A heart attack and unstable angina are the terms used to describe these conditions (1). A heart attack happens when cells in the heart tissue die or get damaged. Myocardial infarction is another term for a heart attack. Stable angina may develop if there is a decrease in blood flow to the heart (2), there won't be any cardiac arrest or cell death as a consequence. On the other hand, risk of a heart attack may increase due to the reduced blood flow. Symptoms of acute coronary syndrome may range from mild discomfort to severe chest pain (3). Patient need to be evaluated and treated right away since it is a medical emergency. Early diagnosis and efficient treatment planning aims to improve cardiac blood flow, manage ischaemic injury, and prevent secondary complications.

ACS symptoms often appear all at once. Among them are:

- Chest pain or discomfort. Common symptoms include heat, constriction, pain, or pressure. Chest pain is also known as angina.
- Chest pain that spreads to other parts of the body. The areas that fall under this category include the back, neck, jaw, upper belly, shoulders, and arms.
- Queasy or throw up.
- Indigestion.
- Dyspnea, a medical term for shortness of breath.
- Abrupt, profuse perspiration.
- An irregular heartbeat.
- Having vertigo or light-headedness.
- Passing out.
- Atypical exhaustion.

Pain or stiffness in the chest is the most common sign, but the symptoms could be quite different from person to person based on factors including age, sex, and health conditions (4). Symptoms other than chest pain or discomfort are more common in elderly women, especially those with diabetes (5).

ROLE OF KEY SERUM ELECTROLYTES IN CARDIAC FUNCTION

Without the electrolytes calcium (Ca++), magnesium (Mg++), sodium (Na+), and potassium (K+), the myocardium, the heart's muscle tissue, cannot function properly (6). Muscle contraction occurs when there is an increase in voltage across the semi-permeable membrane of a cardiac cell beyond a certain threshold (7). A serum electrolyte test, which is crucial for tracking these critical ions. To guarantee proper cardiac function, electrolytes—which have an electrical charge—are maintained at physiological concentrations using a variety of techniques (for further details, see table-1, 'Standard serum concentrations'). An electrolyte imbalance may harm the heart, either directly or indirectly leading to arrhythmia and cardiac arrest. Serum calcium and magnesium abnormalities are less prevalent causes of life-threatening arrhythmias, but potassium disorders-particularly hyperkalaemia, which is a high potassium level-are often linked to them (8). Wider repercussions of electrolyte imbalances in the body are also possible, but are beyond the purview of this article.

Electrolyte	Standard Range
Potassium	3.5–5.0 mmol/L
Magnesium	0.7–1.1 mmol/L
Sodium	135–146 mmol/L
Calcium	2.20–2.67 mmol/L

Table 1: Standard serum concentrations (9)

Electrolyte concentrations in the heart may be impacted by changes in renal function since renal excretion is crucial to the body's ability to maintain electrolyte balance. Adrenal insufficiency, hypoaldosteronism, and kidney illness may all affect the potassium balance in the electrolyte balance (10). Apart from the significance of renal function in preserving electrolyte equilibrium, several medications may induce notable variations in serum electrolyte concentration via diverse pathways (see to the section under "Common medicines that can cause electrolyte disturbances") (11)

Electrolyte	Drug Class Causing Serum Deviation
Potassium	
Hypokalaemia	• Thiazide and similar diuretics (bendroflumethiazide, for example) • Loop diuretics, such as furosemide, • Agonists of beta 2 (such as Salbutamol) • Insulin • Aminoglycosides (gentamicin, for example)
Hyperkalaemia	• Diuretics that spare potassium, such amiloride • Antagonists of testosterone, such as spironolactone • Inhibitors of the angiotensin converting enzyme, such as ramipril • Antagonists of the angiotensin-II receptor, such as losartan • Ibuprofen and other non-steroidal anti-inflammatory medications • Heparin
Magnesium	
Hypomagnesaemia	• Thiazide and similar diuretics (bendroflumethiazide, for example) • Loop diuretics, such as furosemide, • Digoxin • Aminoglycosides (gentamicin, for example)
Hypermagnesaemia	• Antacids (such as trisodium magnesium) • Supplements containing magnesium
Sodium	
Hyponatraemia	• Thiazide and similar diuretics (bendroflumethiazide, for example) • Loop diuretics, such as furosemide, are • Vasopressin • Serotonin reuptake inhibitors that are selective, such as fluoxetine
Hypernatraemia	• Supplements containing sodium, such hypertonic saline • Lithium • Tetracycline (demeclocycline, for example) • Amphotericin • Use caution while taking medications that are rich in salt, such as effervescent formulations and injectable medications like acyclovir and benzyl penicillin.
Calcium	
Hypocalcaemia	• Bisphosphonates (such as alendronic acid) • Calcitonin
Hypercalcaemia	• Thiazide and similar diuretics (bendroflumethiazide, for example) • Vitamin D substitutes • Long-term lithium usage • Alpha Lipoic Acid

Table 2: Class of Drugs Causing Deviation in Serum

When treating moderate, asymptomatic electrolyte imbalances, it is typically best to focus on modifiable causes (13). These may include pharmaceutical side effects or changes in the patient's diet (for example, hyperkalaemia might be caused by drinking too much coconut water). When patients present with symptoms (and/or ECG abnormalities), as indicated above, and

when disrupted electrolyte levels have caused clinical manifestations, it is usually required to promptly provide medication to correct the levels (14).

POTASSIUM

When it comes to positively charged ions (cations) that are found within cells, potassium is by far the most common. Since the concentration inside cells is around twenty times greater than that in the surrounding fluid, a noticeable concentration gradient exists (15). This maintains the excitability of the nerve cells and muscles (16).

Some of the primary regulators of potassium levels include the hormone aldosterone (via renal excretion), catecholamines, insulin, and bicarbonate solutions. Potassium concentrations are also affected by pH (17). In acidemia, when the serum pH is low and potassium is released into the bloodstream, the levels of potassium in the serum increase; in alkaemia, when the serum pH is high and potassium is retained in the cells, the levels of potassium in the serum decrease (18). Heart conduction problems are important whether there is hyperkalaemia or hypokalaemia (19). The severity of changes in potassium levels is not well defined; rather, it is considered a continuum, with the associated clinical symptoms being used to rate the change's severity (20).

HYPERKALAEMIA

If treatment for hyperkalemia is not received, the condition's developing conduction abnormalities might result in cardiac arrest and death (21). Suppressed conduction may result in towering T waves as well as extended PR and QRS intervals. Treatment include transferring potassium into cells, protecting the heart, and eliminating potassium from the body (22). Polystyrene sulphonate resins may be used to progressively lower potassium levels in moderate situations, but they shouldn't be administered to people who have obstructive bowel disease (23). A quick change in extracellular potassium is necessary for moderate hyperkalemia, and patients may need intravenous doses of glucose and soluble insulin (24). Both of these therapies are necessary for severe hyperkalemia, in addition to high-dose beta2 agonists and sodium bicarbonate (25). Calcium gluconate (10%) should be used to treat severe hyperkalemia or ECG abnormalities because it raises the myocytes' threshold potential. Digoxin users should avoid rapid calcium delivery since it increases their risk of arrhythmia (26).

HYPOKALAEMIA

Ventricular tachycardia may result from hypokalemia, a condition in which blood potassium levels are less than 3.5 mmol/l (27). Diarrhoea, hypercalcemia, hyperaldosteronism, medications, renal excretion, diabetes, and excessive fluid replacement treatment may all be contributing factors (28). Premature ventricular or atrial complexes, depressed ST segments, flattened T waves, and U waves may all be seen on an ECG (29). While severe instances need intravenous potassium, mild hypokalaemia may be handled conservatively with or without dietary supplements. Both on-going ECG monitoring and routine monitoring are required (30). In extreme situations, magnesium supplementation is advised for quick treatment of hypokalaemia.

MAGNESIUM

Among cations found within cells, magnesium is the second most prevalent. When magnesium and the enzyme sodium-potassium ATPase interact, the enzyme pumps potassium into cells in return for sodium, mostly regulating cellular concentration gradients (31).

HYPERMAGNESAEMIA

Hypermagnesaemia is an electrolyte disorder in which there is a high level of magnesium in the blood (32). It is mostly eliminated by the kidneys, which have a great secretory capacity. Magnesium levels might rise with significant necrosis or soft-tissue damage. Generally asymptomatic, patients with blood magnesium levels between 1.0 and 2.0 mmol/l may be more harmful if they take digoxin (33). When levels exceed 4.0 mmol/l, patients may become weak, nauseous, and undergo respiratory failure, paralysis, and coma. A systole may also be brought on by hypomagnesaemia. Dialysis is used for individuals with severe renal impairment, whereas intensive intravenous hydration treatment is used for hypovolemia and normal renal function. Treatment is based on the patient's fluid and kidney function (34).

HYPOMAGNESAEMIA

Due to genetic predispositions, inadequate magnesium intake, or adverse reactions to beta2-agonists, corticosteroids, or theophylline, hypomagnesaemia-a disorder that impairs the absorption of magnesium from the gastrointestinal tract-can develop in people with either acute or chronic asthma. Neuromuscular signs such as tremors, seizures, delirium, and psychosis are among the symptoms. Prolonged PR and QT intervals brought on by severe hypomagnesaemia might result in longer QRS durations and torsades de pointes (35). Individuals who have hypomagnesaemia brought on by diuretics should stop taking their medication or get a potassium-sparing diuretic. Intravenous magnesium

should be used to treat significant hypomagnesaemia. This may be done as a 6-hour infusion or as an 8–20 mmol bolus dose (36).

SODIUM

Serum osmolality is significantly affected by sodium, the principal extracellular cation in the human body (37). Because it modulates myocardial membrane potentials with potassium, it is crucial for the regulation of cardiac action potentials. Changes in blood sodium levels, in contrast to potassium, do not cause major cardiac problems until there is a significant deviation from normal physiological standards.

Sodium variations often cause nausea, vomiting, weakness, and disorientation. If treatment is not received, these symptoms might worsen and perhaps put a person in a coma or seizure. ECG alterations that are consistent are uncommon (38).

Patients with severe heart failure often exhibit excess total body water relative to sodium, which is caused by inadequate compensatory mechanisms for sodium control (leading in hypervolaemic hyponatraemia). Patients have to be put on a fluid restriction regimen and given diuretics, which will lower water retention and progressively raise sodium levels in the blood.

HYPERNATRAEMIA

When the body loses more water than sodium, the sodium content in the blood rises over 145 mmol/L, a condition known as hypernatraemia. Dehydration is often the source of this, particularly in those with defective thirst systems and people who are physically or mentally disabled. Lethargy, muscular weakness, and irritability are some of the symptoms. Patients may endure disorientation, convulsions, and in extreme situations, a coma or even death, as the illness worsens. There are many situations in which hypernatraemia may arise, such as hypopovolemic, euvolemic, and hypervolemic hypernatraemia. In order to prevent cerebral edema, treatment focuses on replenishing lost fluids and reducing salt levels gradually rather than quickly. Oral water consumption or intravenous hypotonic solutions are often enough in mild instances. Intravenous fluids are given cautiously and gradually in severe instances to lower salt levels and restore water balance without causing brain edema. It's critical to treat the underlying causes of hypernatraemia, such as dehydration or a high salt diet. Throughout the course of therapy, careful monitoring of neurological state and serum salt levels is important.

HYPONATRAEMIA

When the blood's sodium content drops below normal—typically below 135 mmol/L—it is referred to as hyponatraemia. This results in an imbalance between salt and water in the blood, which is typical for people suffering from various medical disorders that cause fluid overload or severe heart failure. From moderate to severe symptoms, early indicators include nausea, headaches, dizziness, and vomiting. As the disease progresses, swelling of the brain cells may cause neurological symptoms. Based on the amount of fluid consumed, hyponatraemia can be categorized as follows: hypopovolemic hyponatraemia, which occurs when sodium loss outweighs water loss; euvolemic hyponatraemia, which results in a normal fluid level but an imbalance of sodium; and hypervolemic hyponatraemia, which results in an increase in both sodium and water but a greater degree of water retention. The intensity and underlying cause determine the course of treatment. Fluid restriction is often enough to minimize water retention and progressively raise salt levels in moderate situations. Hypertonic saline may be used to restore sodium levels in extreme situations, however excessively harsh therapy might result in osmotic demyelination syndrome, a dangerous neurological disorder.

CALCIUM

In the myocardium, calcium plays a crucial role in conduction, intracellular signaling, and fiber contraction. In instance, calcium levels might affect cardiac conduction by changing the duration of the plateau phase (phase 2) of the myocardial action potential.

A short QT interval may be caused by high calcium levels, whereas a longer QT interval can be caused by low calcium levels. Cardiac arrest may result from conduction anomalies at even greater extremes (39).

HYPERCALCAEMIA

It may cause QT intervals to shorten, and AV block may ensue if treatment is not received. Furthermore, hypercalcemia damages smooth muscle fibers, which results in muscular weakness (40).

Patients whose calcium levels are high (>2.67 mmol/l) and whose electrocardiograms reveal a shortened QT interval need urgent treatment. If an electrocardiogram (ECG) shows that a patient has a longer QRS interval, loop diuretics may be used to increase calcium excretion. Thiazides and similar diuretics, on the other hand, might cause hypercalcaemia. Aggressive fluid administration, such sodium chloride 0.9%, may be used to control hypercalcaemia initially. Standard practice for individuals undergoing treatment for both cancer and osteoporosis is the intravenous administration of bisphosphonates to reduce blood calcium levels and slow the rate of bone turnover.

HYPOCALCAEMIA

The QT interval will prolong with hypocalcemia, increasing the risk of AV block and cardiac arrest. Tetany and cramping are signs of hypocalcaemia. Individuals who exhibit these symptoms and have blood calcium levels less than 2.1 mmol/l need to get intravenous calcium therapy as soon as possible. If at all feasible, reversible causes of hypocalcaemia such as medication-induced hypocalcaemia—should be addressed. Intravenous magnesium should be administered to patients receiving treatment for hypocalcaemia in order to assist in restoring serum calcium levels.

ELECTROLYTE IMBALANCES IN ACS

ACS is a medical disorder caused by a reduction in blood flow to the heart's coronary arteries. The ACS is divided into three subgroups:

1. Elevated myocardial infarction with ST segment (STEMI)
2. Elevated MI not in the ST segment (NSTEMI)
3. Unstable Angina (UA), determined by cardiac biomarkers and ECG findings.

The hallmarks of STEMI are total blood artery blockage, which causes a transmural infarct to the myocardium and an increase in troponin levels. Plaque rupture and thrombus development in NSTEMI lead to partial blood artery blockage, which causes a myocardial infarct and an increase in troponins. In unstable angina, angina pain that occurs at rest or increases quickly over a short period of time is accompanied with partial blockage of the artery and normal troponins due to plaque ruptures and thrombus development that occur without an infract.

One of the signs and symptoms of coronary heart disease (CHD) is angina. Cardiovascular disease accounts for 7.2 million annual deaths worldwide and 12.8% of all fatalities. In India, the prevalence of CHD is 2.2% in rural areas and 6.4% in urban areas. The "global burden of disease study age standardized estimates (2010)" states that cardiovascular illnesses account for around 24.8% of all deaths in India (41).

Electrolytes play a critical role in the proper operation of cells and key organs, such as the heart. Calcium (Ca++), potassium (K+), and sodium (Na+) are some of the most crucial electrolytes for the body's essential functions. Other significant electrolytes include phosphate, bicarbonate, magnesium (Mg++), and chloride ions. Normal levels of Na+, K+, and Ca++ control the heart's electrical activity. The proper balance of these electrolytes is essential for the heart to operate normally. After an ACS episode, electrolyte imbalance is often seen, and it may play a significant role in modifying the outcome of ACS.

Myocyte depolarization and myocardial contractility are mediated by calcium. Serum calcium levels (total) should be between 8.5 and 10.5 mg/dL. Atherosclerotic plaque disruption, thrombus development, and coronary spasm are all possible consequences of hypocalcemia.

Early on following ACS episodes, electrolyte imbalance is important for prognosis. Therefore, the purpose of the current research was to evaluate the electrolyte imbalance (Na+, K+, and Ca++) in ACS patents (42).

METHOD

DATA SOURCES AND TERMS OF SEARCH

The project will use patient records from the hospital's cardiac care unit to gather data, with a focus on patients who have been hospitalized with acute coronary syndromes. Serum electrolyte values (sodium, potassium, calcium, magnesium, and chloride) will be provided via laboratory results both at admission and during the patient's hospital stay. Furthermore, pertinent patient data, including demographics, medical history, comorbidities, and therapy specifics, will be retrieved from clinical databases. Key phrases like "acute coronary syndrome," "serum electrolytes," "electrolyte imbalance," "mortality," "morbidity," and "cardiac arrhythmias" will be used to search databases like PubMed, Scopus, and Cochrane Library for the literature review.

DATA EXTRACTION

In order to extract data, pertinent information must be gathered from databases and medical records. Electrolyte levels, clinical outcomes (mortality, arrhythmias, ICU hospitalization), and patient demographic information will be extracted by skilled experts. To guarantee uniformity, a pre-established data collecting sheet will be used (43). Baseline electrolyte levels, variations throughout the hospital stay, and results after discharge will all be included in the retrieved data. Important information about the studies that are part of the literature review, such sample size, electrolyte measures, clinical results, and research findings, will be methodically taken out and compared.

DATA ANALYSIS

An overview of studies on serum electrolytes and associated indicators in different clinical circumstances is provided in the table. The emphasis was on the relationship between baseline electrolyte

imbalances and illness outcomes in COVID-19 patients, as shown by the paper Electrolyte abnormalities in COVID-19: Association with disease outcomes. The significance of these anomalies on the disease's severity and prognosis was brought to light by this inquiry. Rhabdomyolysis: A prevalent condition with different causes and therapeutic options is a noteworthy research that offered a thorough analysis of the etiology, consequences, and therapy of Rhabdomyolysis. It emphasized the range of etiological variables and approaches to treating this illness, which often include abnormalities in electrolytes.

Furthermore, how different blood laboratory values may be utilized for diagnosing and forecasting the course of epilepsy was examined in the review titled Diagnostic and prognostic usefulness of laboratory values in epilepsy. The significance of laboratory testing in differentiating between seizure types and their therapeutic implications was highlighted in this paper. Finally, the function of cardiac and electrolyte indicators in determining myocardial damage in Acute Myocardial Infarction (AMI) was the focus of markers of myocardial damage and their connection with AMI prognosis. This research described the potential predictive significance of these indicators in AMI and how they may indicate the degree of myocardial damage.

ELECTROLYTES AND CLINICAL OUTCOMES IN ACS

One of the most important factors affecting the clinical course of individuals with ACS is the electrolyte balance in the serum. Electrolyte abnormalities are often important factors in determining a patient's prognosis and may directly affect how well the heart functions, raising the risk of problems (49).

IMPACT ON MORTALITY AND MORBIDITY

Patients with ACS often have electrolyte abnormalities, such as hypokalemia, hyperkalemia, hyponatremia, and hypocalcemia. These abnormalities are strongly associated with increased risks of death and morbidity. If these imbalances are not properly handled, they often result in serious difficulties because they impair vital physiological processes in the heart and circulatory system.

References	Topic Covered	Research Study	Title
Nitesh MS *et.al.,(*2023) (44)	Serum electrolyte concentrations in ACS patients	electrolyte imbalances (sodium, potassium, calcium, and magnesium) and the onset/severity of ACS are correlated, emphasizing the significance these imbalances have in cardiac function and possible consequences	Acute Coronary Syndrome: A Serum Electrolyte Study
Challoob H *et.al.*,(2023) (45)	Serum electrolytes and trace elements in AMI patients	assessed the blood electrolytes and trace elements (zinc, copper, magnesium) in patients with AMI, finding notable changes in the electrolyte levels and their significance for the prognosis of AMI	Assessment of Certain Trace Elements and Serum Electrolytes in Acute Myocardial Infarction Patients
Abdalla *et. al.,*(2023) (46)	Relationship between MI, electrolytes, and vitamin D deficiency	investigated how vitamin D insufficiency affects electrolyte imbalances (calcium, potassium, magnesium) and how it affects the severity of myocardial infarction in individuals with acute ACS	Relationship between Electrolyte Level, Vitamin D Deficiency, and Myocardial Infarction in ACS Patients
Hasan *et. al.,* (2019) (47)	Serum electrolyte levels in healthy people, VHD, and MI	highlighted electrolyte abnormalities by comparing the amounts of electrolytes (sodium, potassium, calcium, and magnesium) in normal people, VHD patients, and MI patients	A Comparison of Normal Subjects' Serum Electrolyte Concentrations with VHD and MI
Patil *et.al.,* (2016) (48)	Unbalanced electrolytes in AMI patients	examined the frequency and trends of electrolyte abnormalities (sodium, potassium, and calcium) in patients with AMI, finding hypokalemia and hyponatremia to be prevalent and high-risk variables	An Examination of Electrolyte Disproportion in Patients with Acute Myocardial Infarction at a Maharashtra Tertiary Care Facility

Table 3: Research Study Data

Potassium (K^+) is one of the most important electrolytes for heart function. For people with ACS, low potassium levels (hypokalemia) or high potassium levels (hyperkalemia) may both have detrimental effects. Hypokalemia impairs normal cardiac conduction, which may lead to potentially fatal arrhythmias such ventricular fibrillation. This raises the risk of sudden cardiac death, especially in those with weakened hearts who are already at risk. Conversely, hyperkalemia may make the heart excessively arrhythmogenic, which may result in cardiac arrest. Patients with reduced renal function or those using drugs that affect potassium levels, such as ACE inhibitors or diuretics, are more vulnerable to this imbalance. Thus, there is a significant chance of death in ACS associated with both types of potassium imbalance.

Another essential electrolyte is sodium (Na^+), and hyponatremia in particular is strongly linked to heart failure and worse outcomes in ACS patients. A typical symptom of fluid overload in individuals with compromised cardiac function is hyponatremia. Low sodium levels are a substantial predictor of higher mortality in these individuals, according to several studies. Furthermore, hyponatremia is associated with increased rates of rehospitalization and longer hospital stays, indicating its effect on the exacerbation of heart failure and general decline in health.

The electrolyte calcium (Ca^{++}), which is necessary for cardiac conduction and contractility, is also critical to the prognosis of individuals with ACS. Too high (hypercalcemia) or too low (hypocalcemia) of a calcium level imbalance may cause severe arrhythmias in the heart. Hypercalcemia may lengthen the QT interval on an ECG, which puts patients at risk for arrhythmias, while hypocalcemia can impair the heart's capacity to contract efficiently. These disruptions raise the possibility of death and morbidity while also complicating the clinical course of ACS (50).

Despite being often disregarded, magnesium (Mg^{++}) is essential for preserving adequate cardiac function, especially when it comes to controlling ventricular rhythms. Hypomagnesemia, or low magnesium levels, is closely linked to a higher risk of arrhythmias, especially in individuals who are very sick. Because restoring magnesium levels may greatly lower the occurrence of arrhythmias and improve patient outcomes, magnesium monitoring is crucial in the treatment of ACS patients. Maintaining the proper balance of magnesium is especially crucial since it influences not only heart rhythm but also the stability of other electrolytes such as potassium and calcium via interactions.

ELECTROLYTE MANAGEMENT IN ACUTE CORONARY CARE UNITS

Maintaining electrolyte balance is an essential part of patient treatment in acute coronary care units (ACCUs). Since ACS is associated with potentially fatal consequences, it is essential to continuously monitor blood electrolytes in order to preserve cardiovascular stability. By using this technique, electrolyte abnormalities that would otherwise cause serious consequences can be identified early on. Abnormal levels of potassium, calcium, sodium, or magnesium are examples of electrolyte abnormalities that may exacerbate heart failure and raise the risk of arrhythmias and cardiac arrest. Clinicians may improve patient outcomes and lower the likelihood of further problems during hospitalization by routinely monitoring electrolyte levels and avoiding these potentially harmful episodes.

Crucial treatment choices in ACCUs are also heavily influenced by efficient electrolyte control. For example, low potassium levels, or hypokalemia, may cause dangerous cardiac arrhythmias. Potassium supplements can help treat hypokalemia. On the other side, drugs like calcium gluconate to steady the heart, insulin-glucose combinations to transfer potassium into cells, or potassium-binding resins to remove excess potassium may be used to treat hyperkalemia (high potassium levels), which can cause cardiac arrest. By helping to restore electrolyte balance, these procedures guarantee that the heart continues to beat at its best and lower the chance of unexpected cardiac events.

Vigilant monitoring is even more important in light of the link between electrolyte levels and drugs used to treat ACS. Treatments like beta-blockers, ACE inhibitors, and diuretics may all have a big impact on electrolyte balance. For example, it is well known that diuretics deplete potassium whereas ACE inhibitors increase potassium levels. These drugs may aggravate pre-existing electrolyte imbalances and worsen the patient's health if they are not carefully monitored. In order to prevent difficulties, healthcare providers must make sure that the drugs they administer do not cause harmful changes in electrolytes. This will enable them to make necessary modifications to therapy as required.

In more extreme situations, electrolyte imbalances may need to be corrected quickly, often including intravenous (IV) electrolyte treatment. In patients whose potassium or magnesium levels are dangerously low, IV treatment provides a quick and regulated way to bring their bodies back into balance. In situations when oral supplements may be

inadequate or too slow to treat the critical imbalance, prompt action is essential to stabilize the patient's state. In order to keep patients on a stable recovery path by halting the development of acute illnesses to more severe states, including arrhythmias or heart failure, IV electrolyte treatment is a routine procedure in ACCUs.

COMPARISON OF OUTCOMES WITH AND WITHOUT ELECTROLYTE CORRECTION

Patients with ACS who undergo electrolyte correction on time or not often have extremely different clinical outcomes, which may have an impact on both short- and long-term survival. In critical care environments, stabilizing cardiac function, averting potentially fatal consequences, and guaranteeing the best prognosis for patients depend on the appropriate treatment of electrolyte imbalances.

There are significant advantages for patients who obtain electrolyte correction on time. Heart rhythms are directly impacted by imbalances such as hypo- or hyperkalemia, which must be corrected in order to normalize the heart's electrical activity and lower the risk of potentially deadly arrhythmias. For instance, ventricular fibrillation, a dangerous arrhythmic condition that may be fatal if left untreated, is known to be brought on by hypokalemia (low potassium levels). Healthcare professionals may greatly reduce the risk of these harmful events by restoring potassium levels via supplements or other therapies, giving the heart a more stable environment for healing. In a similar vein, inadequate management of hyperkalemia (high potassium levels) may result in cardiac arrest. Treatments such as potassium-binding drugs, insulin-glucose therapy, or calcium gluconate may be used to rapidly restore potassium levels to a range that is safer and delay the start of sudden cardiac death.

For ACS patients, especially those who have heart failure, maintaining a balanced sodium intake is crucial. Low sodium levels, or hypernatremia, are a typical indicator of declining heart health and are highly correlated with unfavourable outcomes including lengthier hospital admissions and increased death rates. Shortness of breath and fluid retention are two heart failure symptoms that may be improved by promptly adjusting sodium levels by fluid management or sodium supplements. This improves the patient's quality of life and lowers the risk of readmissions to the hospital since stable sodium levels help better control the symptoms of heart failure over the long run. In this situation, electrolyte management may result in a more predictable and effective healing process, assisting patients in regaining stability more quickly and smoothly returning to their regular lives.

On the other hand, patients who do not obtain the proper electrolyte correction will have far severe consequences. Untreated or improperly controlled electrolyte imbalances may have catastrophic consequences for cardiovascular health. For instance, since chronic hyperkalemia severely disrupts heart electrical activity, it might result in cardiac arrest. The likelihood of unexpected, deadly occurrences like asystole—the total stoppage of cardiac electrical activity—increases with the length of time hyperkalemia is left untreated. In a similar vein, untreated hypokalemia may lead to protracted arrhythmias that exacerbate cardiac injury and raise the risk of death. Due to consequences from these imbalances, these patients are also more prone to have longer hospital admissions, which may hinder their recovery and raise their medical expenses.

If left untreated, hyponatremia makes heart failure symptoms worse by making the already weak heart even more strained and retaining more fluid. This worsens cardiac function, raises the possibility of morbidity, and increases the likelihood of unfavorable long-term consequences. Due to inadequate electrolyte management, these patients' conditions worsen and they often need hospital stays, with no improvement in their quality of life. In addition to raising death rates, electrolyte imbalances may cause a vicious cycle of declining health and recurrent medical emergencies if left untreated.

CONCLUSION

The investigation into serum electrolytes in ACS highlights the critical role that key electrolytes such as sodium, potassium, calcium, and magnesium play in cardiac function and their influence on clinical outcomes. Electrolyte imbalances, commonly exacerbated by certain drug classes and disease progression, are strongly associated with increased mortality and morbidity in ACS patients. Effective electrolyte management, particularly in acute coronary care settings, has been shown to improve clinical outcomes, with corrective interventions leading to better patient survival rates and reduced complications. Therefore, precise monitoring and timely correction of electrolyte disturbances are essential for optimizing care in ACS.

Abbreviation

ACS	Acute coronary syndrome
AMI	Acute myocardial infarction
CHD	Coronary heart disease
ECG	Electrocardiogram
MI	Myocardial Infarction

Ca^{++}	Calcium
Mg^{++}	Magnesium
Na^{+}	Sodium
K^{+}	Potassium
VHD	Valvular heart disease
UA	Unstable angina

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Review Article

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BLENDED LEARNING IN DENTAL SCIENCE EDUCATION: A REVIEW

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ABSTRACT

Blended learning (BL), which merges traditional face-to-face instruction with online education, has become a prominent approach in higher education, including dental science education. This review examines the concept of blended learning, its components, advantages, challenges, and applications within dental education. It emphasizes the value of combining in-person teaching with digital tools, such as online platforms, virtual simulations, and patient management software, to enhance learning outcomes. In dental science, blended learning offers a flexible and integrated approach where students engage in theoretical coursework, develop practical skills, and receive clinical training. Online learning modules provide flexibility, allowing students to learn at their own pace, while in-person classes support active interaction with instructors and hands-on experience. The review highlights that blended learning fosters personalized learning paths, increases accessibility, and promotes greater student-teacher engagement. Despite these advantages, the successful implementation of blended learning in dental education requires addressing challenges such as technological limitations, faculty training, and balancing online and hands-on experiences. The review concludes that with thoughtful planning and execution, blended learning has the potential to improve both the theoretical knowledge and clinical proficiency needed by dental professionals in today's rapidly changing healthcare landscape.

KEYWORDS: Dental Education, Learning Model, Clinical Techniques, Modern Digital Tools.

INTRODUCTION

The growing integration of digital technology into education has transformed many disciplines, with dental education being no exception. Traditional dental training, which relied heavily on in-person lectures, hands-on clinical training, and one-on-one instruction, is now increasingly complemented by digital tools and online resources. Blended learning (BL), an approach that combines traditional face-to-face teaching with online learning components, has been widely adopted in many dental schools as an innovative pedagogical model. This hybrid method seeks to harness the benefits of both face-to-face interaction and the flexibility offered by digital learning environments, enhancing the educational experience for both students and faculty.

In dental science education, where students must master a complex combination of theoretical knowledge and practical clinical skills, the introduction of blended learning provides new opportunities for more efficient and effective learning. The practical aspect of dental education requires hands-on training, patient interaction, and clinical supervision. However, the increasing emphasis on evidence-based learning and the growing demand for flexibility in higher education have paved the way for innovative learning models like blended learning. This approach is particularly well-suited to the evolving needs of dental students, who are expected not only to learn the fundamentals of dental science but also to develop expertise in advanced technologies and clinical techniques.

The shift towards blended learning in dental education offers numerous advantages, such as increased accessibility, flexibility, and personalized learning opportunities. Through online platforms, students can access a wide range of resources, such as lectures, videos, and case studies, that supplement their face-to-face

learning. The use of virtual simulations and digital patient management systems further enhances the practical aspects of training, allowing students to practice their skills in a controlled, low-stakes environment. These technologies can help students to better grasp complex dental procedures and patient management strategies before they begin treating real patients.

Despite the many benefits, implementing blended learning in dental education presents a number of challenges. Technological limitations, faculty readiness, and the need to balance online learning with hands-on clinical training are among the primary obstacles that need to be addressed. Nevertheless, the potential benefits of blended learning in dental science education are vast, and when executed thoughtfully, it can lead to improved educational outcomes and better-prepared dental professionals.

UNDERSTANDING BLENDED LEARNING

Blended learning can be described as an instructional model that merges in-person teaching with online components, allowing for a more flexible and interactive learning experience. This model is characterized by students engaging with both digital content and face-to-face classes in a way that complements each other. According to educational experts, blended learning offers a variety of configurations, such as rotating between online and in-person learning or using a flexible approach where students access digital content independently while attending physical classes for hands-on training and guidance (1). In dental education, where students must master both theoretical knowledge and clinical skills, this hybrid approach provides an effective means of balancing traditional teaching with modern digital tools.

COMPONENTS OF BLENDED LEARNING IN DENTAL EDUCATION

Blended learning in dental education generally consists of three major components: classroom instruction, online resources, and practical training. Each of these elements plays an essential role in the educational process.

1. Classroom Instruction

Despite the growing use of online platforms, face-to-face teaching remains a cornerstone of dental education. Instructors deliver lectures on core subjects such as anatomy, pathology, and pharmacology, while also guiding students in developing communication and clinical skills. The classroom environment allows for immediate feedback and interactive discussions, essential for fostering deep understanding and critical thinking (2).

2. Online Learning Platforms

Digital platforms, such as learning management systems, provide students with easy access to various educational resources. These platforms may include video lectures, reading materials, quizzes, and discussion forums. Online content enables students to learn at their own pace, review complex topics multiple times, and participate in interactive activities like online simulations or case-based scenarios. The flexibility provided by online learning encourages self-directed learning and allows students to manage their study schedules effectively (3).

3. Practical Training and Simulations

Practical, hands-on training is essential for developing the clinical expertise necessary for dental practice. Blended learning models increasingly incorporate simulations and virtual training, offering students a safe environment to practice procedures like tooth extraction or filling placement. These simulations help students hone their manual skills and decision-making abilities before working with real patients (4).

APPLICATIONS OF BLENDED LEARNING IN DENTAL SCIENCE EDUCATION

Blended learning is applied in various stages of dental education, from foundational courses to clinical practice and continuing education.

Pre-Clinical and Clinical Courses

In the pre-clinical phase, students typically focus on understanding the theoretical aspects of dental science, such as microbiology, dental anatomy, and medical terminology. By blending online modules with face-to-face lectures, dental schools can enhance student engagement and comprehension. In the clinical phase, students transition to hands-on practice with patients, and blended learning is used to reinforce clinical techniques and patient management through online resources and practical exercises (5).

Assessment Methods

Blended learning also influences assessment strategies in dental education. Traditional written exams can be supplemented with online quizzes, practical simulations, and virtual case studies. These assessments enable instructors to evaluate both theoretical knowledge and practical skills,

encouraging a more comprehensive understanding of the material. This shift to continuous, low-stakes assessments can help reduce student anxiety and improve long-term retention of information (6).

Continuing Education for Dental Professionals

Blended learning extends beyond the classroom to lifelong learning for practicing dental professionals. Online courses, webinars, and digital resources provide dentists with ongoing education to stay updated on new procedures, technologies, and research developments. These learning opportunities ensure that professionals remain competent and knowledgeable throughout their careers (7).

ADVANTAGES OF BLENDED LEARNING IN DENTAL EDUCATION

Blended learning offers numerous advantages for dental students and educators alike.

1. Flexibility

One of the most notable benefits of blended learning is its flexibility. Students can access course materials at any time and from anywhere, allowing them to manage their learning around clinical rotations and other responsibilities. This flexibility is particularly important for dental students who often have demanding schedules (8).

2. Personalized Learning

Blended learning allows for individualized learning experiences. Online resources can cater to different learning styles, whether through video content, reading materials, or interactive tools. This personalization can help students grasp complex concepts and build a deeper understanding of the material (9).

3. Increased Student Engagement

By combining different teaching formats, blended learning keeps students engaged and motivated. The variety of media, such as video lectures, quizzes, and hands-on practice, enhances interaction between students and instructors, as well as among peers. This engagement can lead to higher levels of satisfaction and better educational outcomes (10).

4. Accessibility and Cost-Effectiveness

Blended learning makes education more accessible by reducing the need for physical resources, such as printed materials, and minimizing the constraints of location and time. Additionally, the use of online platforms can lower the overall cost of education by making learning materials more widely available and reducing the need for extensive in-person class hours (3).

5. Development of Technological Competency

In today's digital world, dental professionals must be proficient with the latest technologies. By incorporating digital learning tools into the curriculum, blended learning ensures that dental students are comfortable using technology in their practice, whether for digital imaging, treatment planning software, or electronic patient records (7).

CHALLENGES OF BLENDED LEARNING IN DENTAL EDUCATION

Despite its many benefits, the implementation of blended learning presents several challenges that need to be addressed.

1. Technological Limitations

Not all dental schools have access to the necessary technology to implement blended learning effectively. Virtual simulations, advanced e-learning platforms, and other digital tools require significant investment, which may not be available at all institutions. Additionally, some students may lack the necessary technology, such as reliable internet access or personal computers, to participate fully in online learning (6).

2. Faculty Training

Faculty members need appropriate training to adapt to the demands of blended learning. Many educators may be unfamiliar with online teaching tools and require professional development to design effective online modules and manage digital platforms. Without proper training, faculty members may struggle to integrate technology into their teaching effectively (5).

3. Balancing Online and In-Person Learning

Achieving the right balance between online and in-person learning is crucial. Too much reliance on online content may lead to a lack of hands-on experience, while excessive classroom time could reduce the benefits of online learning. Educators must carefully design courses to integrate both elements effectively, ensuring that students receive adequate theoretical and practical instruction (4).

4. Maintaining Clinical Competency

While online learning can enhance theoretical

knowledge, dental students must also develop practical skills to provide effective care. Blended learning models must ensure that students gain sufficient clinical experience and competence through in-person training and patient interactions. Without this, students may struggle to apply their knowledge in real-world clinical settings (8).

DISCUSSION

The adoption of blended learning in dental education has sparked significant debate regarding its effectiveness and the overall impact on learning outcomes. Blended learning can be seen as a response to the changing dynamics of dental education, as it strives to bridge the gap between theoretical knowledge and practical, real-world application. One of the primary advantages of blended learning in dental education is the ability to provide students with a diverse range of learning experiences. Through a combination of online resources, in-person classes, and clinical practice, students are able to engage with the material in different formats, which caters to various learning styles and preferences. (4,5,6,8).

A significant benefit of blended learning is its ability to promote greater flexibility in scheduling and learning. Dental students are often burdened with tight schedules, balancing between lectures, clinical rotations, and study time. Online modules and digital resources can be accessed at any time, allowing students to engage with the material at their own pace. This flexibility not only accommodates the busy schedules of students but also allows for personalized learning experiences. Students can revisit online lectures, explore supplementary materials, and take quizzes at their own pace, reinforcing their understanding and allowing them to focus on areas where they need improvement. (8,9).

Furthermore, the integration of online learning allows for greater student engagement and interaction. Traditional classroom learning, while effective, often limits the time students can spend interacting with their peers and instructors. Online platforms can foster greater collaboration, enabling students to engage in discussions, share resources, and seek help from instructors in real-time. Virtual learning environments (VLEs) can also create a more interactive learning experience through quizzes, discussion boards, and peer assessments, further enhancing the student's engagement with the subject matter.

However, the successful implementation of blended learning in dental education requires careful attention to several key factors. First, there is a need for robust technological infrastructure. Dental schools must invest in high-quality digital platforms that can support online modules, virtual simulations, and collaborative activities. Faculty members must also be trained in the effective use of these tools to ensure that the online components of the curriculum are well-designed and engaging. Faculty development programs that focus on technology integration into teaching are critical to the success of blended learning models. (7,8,9).

Moreover, balancing the online and in-person components of the curriculum is essential for ensuring that students develop both theoretical knowledge and practical clinical skills. In dental education, hands-on experience is crucial for students to develop competence in procedures such as restorative dentistry, surgery, and patient communication. While online simulations and virtual reality technologies can supplement practical training, they cannot replace the need for direct patient care and clinical practice. Thus, blended learning should not be seen as a replacement for traditional methods but as an enhancement, integrating the best of both worlds to create a more holistic educational experience. (,6,7,8).

Another important consideration is the potential for unequal access to technology. While digital learning platforms provide many benefits, not all students may have access to the necessary technology, such as high-speed internet or personal computers. This can create disparities in learning opportunities, particularly for students in remote or underserved areas. Dental schools must ensure that all students have equal access to the tools they need to succeed, which may involve providing loaner devices or offering in-person alternatives for students who face technological barriers. (8,910).

Additionally, there is the issue of clinical competency. Dental education emphasizes the acquisition of manual and decision-making skills, and these competencies are developed primarily through direct patient interactions. While virtual simulations can provide valuable practice, they cannot fully replicate the experience of working with real patients. Therefore, blended learning models must ensure that students spend ample time in clinical settings, working under

supervision to develop their practical skills and clinical judgment. (3,5,8).

Finally, the transition to blended learning requires a cultural shift in how educators approach teaching and assessment. Instructors must be willing to adapt their teaching methods to incorporate digital tools and foster interactive learning environments. This shift also requires a rethinking of assessment strategies. While traditional exams may still play a role, a more comprehensive approach that includes formative assessments, peer feedback, and self-directed learning will better capture the full range of skills students need to develop as dental professionals.

CONCLUSION

Blended learning is transforming dental education by combining the advantages of traditional in-person teaching with the flexibility and interactivity of online learning. By incorporating both theoretical instruction and practical training, blended learning offers a comprehensive approach that can enhance student learning and prepare future dental professionals for the challenges of modern practice. While challenges such as technological barriers, faculty training, and clinical competency must be addressed, the potential of blended learning to improve dental education is immense. With careful implementation, blended learning can play a pivotal role in shaping the future of dental science education and ensuring that students are well-prepared for their careers.

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Review Article

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ROLE OF IMMUNOGENICITY IN DRUG DEVELOPMENT

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ABSTRACT

Immunogenicity, or a substance's potential to elicit an immunological response, is an important component in the creation of biologic and small molecule medications. Immunogenicity can impair the efficacy of biologics such as monoclonal antibodies, therapeutic proteins, and gene treatments, as well as pose possible safety issues and cause therapeutic failure. Understanding and predicting immunogenicity is thus a critical component of current pharmaceutical development. This study investigates the importance of immunogenicity in drug development, the variables that influence immunogenic reactions, methodologies for measuring and managing these responses, and regulatory implications. In addition, we cover recent advances in immunogenicity prediction and monitoring, as well as the issues associated with immunogenicity in emerging medication classes. The review looks at real-world examples that show how immunogenicity may significantly affect pharmacokinetics and pharmacodynamics. Additionally discussed are the regulatory standards governing the assessment of immunogenicity and the necessity of incorporating this data into regulatory filings. Lastly, future studies on immunogenicity will have an impact on the therapeutic impact landscape, which will have consequences for patient-centered care and precision medicine.

KEYWORDS: Immunity, Precision Medicine, Drug, Antibodies.

INTRODUCTION

The introduction of novel treatment modalities, including as monoclonal antibodies, Modern medicine has changed as a result of gene treatments and CAR T-cells. Cancer and genetic issues are among the many conditions for which these innovative medications provide more individualized and efficient treatments. Immunogenicity is one of the unique challenges that large molecule-based biologics and advanced cellular and gene therapies face, despite their potential.

Preclinical medication research and clinical trials have raised serious concerns about immunogenicity, or a medicinal substance's capacity to trigger an immune response in a patient. The immune system's ability to recognize and destroy foreign invaders is an essential defensive mechanism, but it may also detect and create defenses against therapeutic substances. which can result in safety issues, changed pharmacokinetics, and reduced effectiveness (1-2).The many facets of immunogenicity in preclinical drug development are examined in this review paper, with particular attention paid to its tactics, dangers, and consequences for biologics based on big molecules (3).

The Use of Immunogenicity in Drug Development

When developing immunogenicity of medicinal products is a crucial component that determines the safety and effectiveness of biological medications, such as gene therapies, CAR T-cell treatments, Both bi-specific and monoclonal antibodies. Anti-drug antibodies (ADAs) or neutralizing antibodies are produced when a medicinal substance triggers an immunological response in the body of the patient. The drug's safety, effectiveness, and commercial success may be impacted by this immune response (4). Using Model-Informed Methods to Evaluate Immunogenicity in Drug Development Targeting certain disease processes, such cancer cells or inflammatory pathways, is the goal of therapeutic treatments, especially big molecule-based biologics. The immune system may view these substances as alien when they are put into a patient's body since they are frequently complex molecules with distinctive structures. Antibodies against the therapeutic agent may be produced as a result of this immunological reaction to the perceived foreignness. Both the patient and the medication may suffer significant repercussions from the formation of ADAs (5).

Immunogenicity's Importance in Drug Development:

When developing new drugs, immunogenicity is crucial for a number of strong reasons.

- **Effectiveness:** The therapeutic agent's effectiveness may be diminished by the presence of ADAs. The drug's ability to successfully target the illness may be neutralized by ADAs. This may lead to disease progression, reduced clinical responses, and therapeutic failure.
- Safety: Immunogenicity may raise issues with safety. Adverse effects, including as autoimmune reactions, infusion-related reactions, and hypersensitivity reactions, might result from immune complexes that ADAs can generate when they attach to the medication. Patient injury and regulatory scrutiny may result from these safety concerns.
- Dose Adjustments: Clinicians may need to raise the medication dose in order to offset the effect of ADAs on drug effectiveness. This increases the likelihood of adverse outcomes and drives up treatment expenses.
- Treatment Discontinuation: Severe immunogenicity may occasionally cause a prospective medication candidate to stop taking their medication. This amounts to a significant loss in research and development expenditures as well as delays in providing patients with potentially life-saving therapies.
- Market Approval: When approving regulations such as the FDA (US Food) and Medicine Administration and the EMA (European Medicines Agency) carefully examine immunogenicity data. To secure regulatory approval, it is essential to exhibit a deep understanding of the immunogenicity profile and to establish effective management practices.
- Patient Variability: Not every patient responds to treatment with an ADA. The likelihood of an immunological response can be influenced by patient-specific variables, including genetics and prior exposure to comparable chemicals. Comprehending these elements is crucial for customized medical strategies.

A key factor in the creation of biological medications and treatments is immunogenicity. It is impossible to overestimate its influence on therapeutic efficacy, safety, and market acceptance. Protein engineering, formulation modification, and immunosuppressive treatments are some of the tactics used by drug developers to successfully handle immunogenicity. To guarantee that cutting-edge medicines adhere to the strictest safety and effectiveness guidelines while getting to the people who require them, researchers and pharmaceutical firms must continue to be careful in evaluating and minimizing the impacts of immunogenicity as it continues to shape (4, 6).

Therapeutic agent types: Therapeutic agents, which provide novel ways to treat a variety of illnesses, have completely transformed medicine. Among these, Gene and CAR T-cell therapies, as well as big molecule-based biologics, have revolutionized medical care. An outline of these therapeutic agents will be given in this part, together with information on their mechanisms and importance in contemporary medicine.

- Biologics Based on Large Molecules: Antibodies that are monoclonal and bispecific mAbs, or monoclonal antibodies: Large protein molecules known as monoclonal antibodies are directed against certain antigens, such as soluble components of disease processes or proteins found on the cell surface. They are useful instruments in precision medicine since they are tangible and have little toxicity. mAbs can function in a number of ways, such as:
- Neutralization: mAbs have the ability to stop a particular molecule's action, preventing it from contributing to the development of a disease. For instance, monoclonal antibodies such as trastuzumab block the development of breast cancer cells by targeting their HER2 receptors.
- Immune Activation: Certain monoclonal antibodies, also referred to as inhibitors of immunological checkpoints (e.g., nivolumab and pembrolizumab), stimulate the ability of the immune system's ability to identify and combat cancerous cells.
- Drug Delivery: By acting as drug transporters, mAbs can deliver harmful payloads precisely to the locations of illness. ADCs, or antibody-drug conjugates, employ this strategy.
- Engineered bispecific antibodies are capable of simultaneously engaging with two different antigens. This mechanism amplifies the immune system's ability to detect and eliminate atypical cells by creating a bridge between the target cells and immune cells. In cancer treatment, these antibodies have exhibited encouraging results by directing T-cells to attack tumor cells.
- The specificity of CAR T-cells is derived from their ability to recognize unique antigens on cancer cells, thus ensuring targeted intervention in tumor destruction.

- The binding of CAR T-cells to malignant cells post-injection initiates a robust immune response, enabling the immune system to effectively target and eliminate the tumors.
- Persistence: For long-term monitoring against cancer recurrence, CAR T-cells can remain in the body. When it comes to treating hematologic malignancies like some forms of leukemia and lymphoma, CAR T-cell treatments have demonstrated impressive results. There are still difficulties, though, including as controlling serious side effects and extending its use to solid tumors.

Gene Therapies: By changing a patient's cells' genetic composition, gene therapy is a revolutionary method for curing or preventing illnesses. To improve treatment results or address congenital anomalies, it entails adding, deleting, or altering genes inside a patient's cells. There are two primary categories of gene therapies:

- Gene therapy by somatic means: In order to cure illnesses in patients without changing their germ line, this targets non-reproductive cells. An FDA-approved gene therapy called Luxturna, for instance, treats hereditary retinal degeneration by giving retinal cells a functioning copy of a gene.
- By altering the DNA in reproductive cells, germline gene therapy can have an effect on subsequent generations. It is not often done and has serious ethical and safety issues. Gene treatments have enormous promise for treating uncommon illnesses, genetic problems, and even some acquired ailments. They provide the possibility of curative or long-lasting therapy, but issues including immunological responses, vector safety, and long-term monitoring need to be resolved.
- Gene treatments, CAR T-cell therapies, and large molecule-based biologics are examples of innovative therapeutic approaches that are changing the medical landscape. Patients with diseases that were previously incurable now have new hope thanks to their expanding specialized mechanisms and applications. To optimize their advantages for global healthcare, researchers, physicians, and legislators must overcome the intricate safety, cost, and accessibility issues that accompany these advancements.

Evaluation of Immunogenicity: Particularly when developing gene therapies, CAR T-cell therapy, and large molecule-based biologics, immunogenicity evaluation is essential. It entails assessing the likelihood that these therapies may cause patients to mount an immunological response, which could have serious clinical repercussions. In addition to discussing the significance of predictive immunogenicity tests, this section will examine the techniques and resources utilized for immunogenicity evaluation throughout preclinical research (7-10).

Tools and Techniques for Evaluating Immunogenicity in Preclinical Development:

The enzyme-linked immunosorbent assay, or ELISA, is: The detection and measurement of antibodies to therapeutic proteins is a common use for ELISA. In preclinical research, scientists can administer the experimental medication to animal models and use ELISA to track the formation of anti-drug antibodies (ADAs). This aids in determining how immunogenic the treatment may be (7, 11).

To assess the immune cells' reaction, cell-based tests expose them to the therapeutic substance. As an illustration, tests for lymphocyte proliferation can quantify how many immune cells proliferate in response to a treatment. These tests reveal information on the immune system's response to the therapy (12).

SPR, or surface plasmon resonance, is a potent technique for researching how medicinal substances and antibodies bind together. It can assist in determining the probability of immunogenicity by revealing the kinetics and affinity of these interactions (13).

Mass spectrometry: Peptides produced by the breakdown of the therapeutic protein can be identified and measured using mass spectrometry. Any changes to the peptide profile may be a sign of possible immunogenicity issues.

In Silico Predictive Models: By examining elements such protein sequence, post-translational changes, and HLA binding affinity, computational models are able to forecast the possible immunogenicity of medicinal drugs. These models aid in risk assessment and early screening (4).

The significance of assays for predictive immunogenicity: For a number of reasons, predictive immunogenicity tests are crucial in directing the creation of therapeutic medicines.

Early Risk Assessment: During the early stages of drug development, researchers can detect immunogenicity hazards thanks to predictive tests. Making important decisions on the ongoing development of a potential medication requires the use of this knowledge.

Optimizing Therapeutics: Researchers can alter the structure or formulation of a therapeutic drug to lessen its capacity to trigger an immune response by knowing the elements that contribute to immunogenicity. Drug effectiveness and safety may be improved by this modification.

The role of predictive testing in patient safety: is significant, as it reduces the chances of adverse events related to immunogenicity. When a treatment is expected to elicit antibodies that could undermine its efficacy or provoke negative responses, it allows for further evaluation or alteration to minimize potential risks (6, 10).

Regulatory Compliance: When developing new drugs, regulatory bodies such as the FDA and EMA want thorough immunogenicity evaluations. Approval is facilitated by predictive tests, which assist sponsors in fulfilling these regulatory obligations (7).

Cost-Efficiency: Early detection of potential immunogenicity issues can result in significant cost savings. It facilitates astute decision-making, avoiding expensive post-marketing issues or late-stage failures. Testing for preclinical immunogenicity is crucial to the development of new drugs, especially gene treatments, CAR T-cell treatments, and big molecule-based biologics. Potential immunogenicity issues are proactively addressed by combining experimental techniques with prediction testing. By streamlining the medication development process and improving the safety and effectiveness of therapeutic agents, this makes it easier to provide cutting-edge medicines to patients. (6,10)

Immunogenicity Influencing Factors: Developing safe and efficient therapies requires an understanding of the factors influencing the immunogenicity of medicinal drugs. The term "immunogenicity" explains how a medicinal substance might cause a patient's immune system to react, usually resulting in the development of antibodies against the agent. The immunogenicity of therapeutic agents can be affected by a number of circumstances, and these aspects are important in determining how to design new drugs. We shall examine the main elements that influence immunogenicity in this section:

The structure of proteins:

The primary structure: One of the primary factors influencing immunogenicity is the therapeutic protein's amino acid composition. An immunological reaction can be more likely to be triggered by particular lines.

Secondary and Tertiary Structure: A protein's immunogenicity may be impacted by modifications to its secondary and tertiary structures, which may arise as a result of production procedures or storage circumstances. Aggregation or misfolding may increase the immunogenicity of the protein.

PTMs, or post-translational modifications:

Glycosylation: Proteins' immunogenicity can be greatly impacted by the addition of carbohydrate chains. The stability of the protein and its capacity to elicit an immunological response can be affected by the kind and pattern of glycosylation.

Deamidation: Protein structure can alter and immunogenicity might be impacted when asparagine or glutamine residues are converted to aspartic or glutamic acid.

Factors Associated with Patients:

Genetics: Human leukocyte antigen (HLA) genotypes are the primary genetic factors that influence the tendency of a person to mount an immune response against a therapeutic treatment is influenced by genetic predispositions. Specific HLA alleles may facilitate a more efficient presentation of the therapeutic protein's peptides to the immune system.

Immune Status: Individuals undergoing organ transplantation or chemotherapy who have weakened immune systems may react differently to therapeutic drugs in terms of immunogenicity. Antibodies to biologics, on the other hand, could be more common in people with autoimmune illnesses.

Formulation and Delivery:

Components of the Formulation: Immunogenicity may be impacted by excipients, stabilizers, and preservatives included in a medicinal formulation. Certain additions may alter the protein's stability or cause an immunological reaction.

Administration Route: A therapeutic agent's immunogenicity may be impacted by the way it is delivered. Compared to intravenous delivery, subcutaneous or intramuscular injections may have distinct immunogenic characteristics.

Production Procedures:

The decision regarding which cell lines: to employ for protein expression may affect immunogenicity through its impact on the quantity of host cell proteins and residual DNA found in the end product.

Purification Techniques: In order to separate the therapeutic protein, purification procedures may add impurities or cause structural alterations that affect immunogenicity. Designing therapeutic drugs with lower immunogenic potential requires an understanding of these parameters. It makes it possible to create plans to reduce the risks of immunogenicity, such changing the structure or formulation of the protein, using predictive immunogenicity assays, and performing preclinical research in appropriate animal models. Researchers and developers may enhance the safety and effectiveness of medicinal medicines by addressing these aspects, which will eventually benefit patients and advance the biopharmaceuticals industry (14-15).

Pharmacokinetic and pharmacodynamic effects of immunogenicity and PK/PD:

When it comes to medication development and clinical results, immunogenicity—the ability of medicinal substances to elicit immune responses—is crucial. It can significantly impact pharmacokinetics (PK) and pharmacodynamics (PD), affecting the way medications interact with target molecules as well as how they are absorbed, transported, metabolized, and removed. In-depth discussion of the complex connection between immunogenicity and PK/PD will be covered in this part, along with instances from actual life when immunogenicity impacted medication effectiveness.

Effect on Pharmacokinetics (PK):

- **Modified Drug Absorption:** Immunogenicity may have an impact on how well therapeutic drugs are absorbed. Neutralizing antibodies, for instance, can lower the Bioavailability of oral or subcutaneously administered biologics. In some situations, higher dosages could be needed to reach the appropriate medication levels.
- Modified Distribution: Immunogenicity may have an effect on how medications are distributed throughout the body. Antibodies can alter a drug's distribution profile when they attach to it. This may result in less than optimal therapeutic levels at the intended location and impair the drug's ability to penetrate tissue.
- Elimination and Metabolism: Anti-drug antibodies (ADAs) have the ability to obstruct the drug's removal and metabolism. A shorter half-life and the need for more frequent dosage can result from ADAs' ability to speed up the drug's clearance rate.

Pharmacodynamics (PD) Impact: Decreased Drug Efficacy Immunogenicity can counteract a drug's therapeutic impact by attaching itself to it and blocking its ability to interact with its target. Even at high doses, the medicine may become useless due to its neutralization.

- Immunological Response Induction: Certain medications have the potential to trigger immunological responses, which might result in unfavorable PD consequences. For example, cytokine release syndrome (CRS), a documented adverse event of CAR T-cell treatments, occurs when immune cell activation causes an excessive release of cytokines, which may result in serious adverse effects (16-17).

Real-World Illustrations

- Infliximab, classified as a monoclonal antibody, is indicated for the treatment of autoimmune diseases such as rheumatoid arthritis and Crohn's disease. However, the formation of anti-drug antibodies (ADAs) can arise, which may compromise the drug's effectiveness and contribute to the failure of the treatment regimen.
- Neutralizing Antibodies with Erythropoietin (EPO): Some individuals may develop neutralizing antibodies as a result of EPO, a hormone that promotes the synthesis of red blood cells. A reduced response to therapy results from these antibodies' reduction of the drug's efficacy.
- CAR T-Cell treatments: In the treatment of some malignancies, CAR T-cell treatments have demonstrated exceptional effectiveness. But they can also cause serious immunological reactions, such as CRS and neurotoxicity, which can be fatal if left untreated. (9-10)

Strategies for Risk Mitigation: Handling Immunogenicity:

Drug research and clinical applications are significantly hampered by immunogenicity, the ability of medicinal substances to elicit immunological responses. Numerous risk-reduction techniques have been created to lessen the effects of immunogenicity.

Engineering Proteins:

- Deimmunization: The goal of protein engineering methods is to alter therapeutic proteins' structures in order to lessen their immunogenicity. Modifying certain protein areas that are susceptible to immune recognition is known as deimmunization. Site-directed mutagenesis, which involves replacing amino acids to get rid of T-cell epitopes—the main triggers for the immunological response—can accomplish this.
- Humanization: is the process of substituting human sequences with non-human ones in therapeutic antibodies while maintaining the antibody's therapeutic effects. This lessens the possibility that non-human epitopes may trigger an immunological response.
- Fusion Proteins: Therapeutic proteins can be made less immunogenic by combining them with non-immunogenic domains or antibodies. These fusion proteins can protect against the detecting systems of the immune system (18-19).

Development of Formulations:

Stabilization: The goal of formulation development is to stabilize therapeutic substances so they don't aggregate or degrade and cause immunological reactions. An appropriate formulation can minimize the exposure of immunogenic epitopes while preserving the drug's structural integrity.

Selection of Excipients: In medication formulations, excipients are essential. By reducing protein aggregation and improving stability, excipient selection can reduce immunogenicity. The release profile of the medication can also be altered by excipients, which lowers the possibility of immunological recognition.

Treatments for Immunosuppression:

- Combined Immunosuppressive Drug Administration: Immunosuppressive medications may occasionally be used in conjunction with therapeutic treatments to reduce immunological responses. Gene treatments and organ transplantation are two areas where this strategy is very pertinent. Corticosteroids and calcineurin inhibitors are examples of immunosuppressants that can lower the risk of rejection by lowering the activity of the immune system.
- Immunological tolerance to the therapeutic substance is the goal of tolerance induction techniques. Numerous strategies, such as regulatory T-cell (Treg) treatment and oral or nasal tolerance induction, can accomplish this. The goal of these strategies is to teach the immune system to accept the medicinal protein.
- Corticosteroid Prophylaxis: When delivering highly immunogenic treatments, prophylactic corticosteroid usage is used in some clinical contexts to minimize possible immunological responses. The safety and effectiveness of therapeutic agents, especially large molecule-based biologics like gene therapies, CAR T-cell therapies, and monoclonal antibodies, depend significantly on the management of immunogenicity. Strategies for risk mitigation include formulation improvement to improve stability, immunosuppressive treatments where required, and protein engineering to decrease immunogenic epitopes. When used carefully, these tactics can greatly increase the efficacy and safety of biologics based on big molecules, opening the door to more potent therapies for a range of illnesses.

Gene therapies and immunogenicity:

- Viral Vector-Mediated Delivery: Viral vectors such as lentiviruses or adeno-associated viruses (AAVs) are used in many gene therapies to introduce therapeutic genes into target cells. These vectors can trigger immunological responses in addition to effectively transferring genes.
- Host Immune Recognition: The host's immune system may identify viral vectors as foreign invaders once they are administered. Both innate and adaptive immune responses may be triggered by this identification.
- Neutralizing Antibodies: Neutralizing antibodies against viral vectors that are either pre-existing or developed as a result of treatment may make gene therapy less effective. The therapeutic gene cannot be delivered to the target cells by the vector when it is neutralized.
- Cell-Mediated Immune Responses: Vector proteins or vector-infected cells can cause T-cell reactions. The length of gene expression may be restricted by this cellular immunological response, which might also raise safety issues (22-23).

Reduced Immunogenicity in Gene Treatments:

- Capsid Engineering: By changing the outer shell, a process known as capsid engineering, scientists are attempting to reduce the immunogenicity of the viral vector.
- Immunosuppressive Techniques: To reduce immune responses, immunosuppressive medications and gene treatments may be used in combination. To combine immune suppression with maintaining therapeutic efficacy and patient safety, however, cautious monitoring is needed.
- Other Types of Vectors: Direct genome editing approaches like CRISPR-Cas9 or non-viral delivery methods like lipid nanoparticles are being investigated as potential substitutes for viral vectors. These techniques seek to reduce the immunological reactions brought on by viral vectors.
- Patient Monitoring: To quickly identify and treat any immune-related side effects, patients undergoing gene therapy must be regularly monitored. Although gene treatments provide innovative therapeutic alternatives, immunogenicity is still a crucial factor. Managing immunogenicity involves the use of immunosuppressive techniques, capsid modification, and viral vector selection. The objective of this field's ongoing research is to create gene treatments that are both extremely efficacious

and less immunogenic so that they may be successfully and safely incorporated into clinical practice (6, 18-21).

Managing the Regulatory Environment for Immunogenicity Evaluation:

For large molecule-based biologics, gene therapies, and Drug development depends on the regulatory framework governing immunogenicity assessment, especially for CAR T-cell therapies. Various regulatory bodies, including the Food and Drug Administration (FDA) in the United States and the European Medicines Agency (EMA), have established strict guidelines to ensure that these state-of-the-art treatments meet high standards of safety and effectiveness. Here, we give a quick rundown of the regulatory environment and stress how important it is to address immunogenicity in regulatory filings.

Key Regulatory guidelines

- The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) has established recommendations that guide the assessment of immunogenicity in biologics. These guidelines, particularly ICH S6R1 and ICH S6R2, create a framework for analyzing immune responses and their potential consequences for therapeutic efficacy and patient safety.
- FDA Advice: In materials pertaining to immunogenicity evaluation, the FDA provides guidance on how to plan studies, create assays, and evaluate findings. These recommendations help pharmaceutical companies handle immunogenicity issues in preclinical and clinical settings.(11)
- EMA Requirements: For biologics requesting marketing authorization in Europe, the EMA also offers guidelines on immunogenicity evaluation. These specifications stress the necessity of doing a thorough assessment of immunogenicity risks (7) and are in line with international standards.

Managing immunogenicity in regulatory submissions is crucial:

- Safety Assurance: Patient safety is given top priority by regulatory bodies. To guarantee that therapeutic drugs do not cause detrimental immune responses that might jeopardize patient health, it is essential to comprehend and manage immunogenicity concerns.
- Efficacy Assessing: The effectiveness of therapeutic drugs may be impacted by immunogenicity. Data showing that the medication produces the desired effect in spite of possible immunological reactions must be included in regulatory applications. Strong assays and a comprehensive comprehension of the immunogenicity profile are necessary for this.
- Risk Mitigation: Drug developers are expected by regulatory agencies to put methods in place to reduce the risks of immunogenicity. This might entail employing suitable immunosuppressive treatments, creating biologics with less immunogenic potential, and keeping an eye out for immune-related side effects in patients.
- Patient-Centric Approach: The significance of patient-centric treatment is acknowledged by regulatory bodies. Drug developers may help create individualized treatment plans that meet the needs of each patient by evaluating and controlling immunogenicity, which will guarantee the efficacy and safety of the medication.

The development and approval of gene treatments and CAR T-cell therapy, and biologics based on big molecules depend heavily on regulatory criteria and recommendations for immunogenicity evaluation. In addition to increasing the likelihood of regulatory clearance, heeding these recommendations ensures the therapeutic agent's clinical utility and, more importantly, safeguards patient health. Regulatory agencies must be consulted early in the drug development process, and immunogenicity issues must be thoroughly addressed at every stage of the product life cycle (20).

Future Prospects for Drug Development and Immunogenicity Research:

Within the realm of drug research, immunogenicity is still a vibrant and developing topic that has promise for many new developments in the future. In the upcoming years, academics and pharmaceutical firms are anticipated to focus on the following important areas:

- Precision Medicine in Immunogenicity: Personalized methods of managing immunogenicity are becoming possible because to developments in proteomics and genomes. A major emphasis will be on customizing therapies based on the individual traits of every patient and their genetic vulnerability to immunogenic responses.Advanced Analytics and large Data: Artificial intelligence and large data analytics will be used more often in immunogenicity monitoring and prediction. Patients who are more likely to acquire anti-drug antibodies can be identified with the use of predictive algorithms.
- Biosimilar Development: Knowing the immunogenicity profiles of biosimilars in

comparison to reference biologics will remain a crucial topic of research as they proliferate. It will be crucial to develop methods for proving biosimilarity while reducing immunogenicity variations.

- Next-Generation Biologics: Research and development will continue to produce Better protein engineering and reduced immunogenicity in subsequent-generation biologics, and increased therapeutic effectiveness. Novel delivery methods, different scaffolds, and improved targeting mechanisms are a few examples of innovations.
- Cell and Gene treatments: CAR T-cell and gene treatments depend on the development of strategies to reduce immunogenic reactions to modified cells and vectors. Creating synthetic biology strategies to reduce host immune responses is part of this.
- Advanced Assay Techniques: It will be crucial to create assays that are more sensitive and specific in order to determine immunogenicity. To learn more about immune responses, this involves applying high-throughput methods, single-cell analysis, and microfluidics.
- Immunomodulation Strategies: One promising approach to managing immunogenicity will be to look at cutting-edge immunomodulation techniques like immune checkpoint inhibitors or immunological tolerance induction.
- Regulatory Evolutions: Regulatory bodies will probably keep improving standards and procedures for determining immunogenicity, particularly for new modalities. Global regulators' alignment will continue to be crucial.
- Patient-Centric Approaches: It is becoming more popular to involve patients in the tracking and control of immunogenicity. Feedback and results from patients can improve treatment choices and offer useful information.
- Long-Term Safety Monitoring: Post-marketing monitoring and long-term safety monitoring of biological products, which includes assessing the potential for late-onset immunogenicity, will become increasingly important.

Next-generation biologics, biosimilar development, advanced analytics, precision medicine, and innovative immunomodulation methods will be the main areas of focus for this field's future. Cooperation among regulatory agencies, business, and academia will keep advancing our knowledge of and ability to handle immunogenicity issues in drug development (4, 31).

DISCUSSION

When developing novel pharmacological drugs, it is important to carefully evaluate not only their safety profiles, pharmacodynamics, and pharmacokinetics, but also their capacity to elicit an immunological response. The tendency of a medication to cause the production of antibodies, especially neutralizing antibodies (Nabs), is known as immunogenicity. This can have negative implications on the medication's pharmacological efficacy. Despite being a well-known issue with biologics, immunogenicity is also becoming more and more relevant in the creation of small molecule medications. A major problem that affects patient safety and medication effectiveness is immunogenicity. The year 1986 marked a significant milestone when the Food and Drug Administration (FDA) approved the inaugural monoclonal antibody therapy featuring chimeric sequences derived from both human and mouse sources. Following this landmark event, pharmaceutical companies have made concerted efforts to enhance the pharmacokinetic (PK), pharmacodynamic (PD), and immunogenicity characteristics of therapeutic proteins and antibodies, largely through the optimization of their sequences. Recent innovations in structural and chemical modifications, such as PEGylation, glycosylation, and lipidation, have facilitated the creation of multidomain biotherapeutics (MDB) that bolster stability, aggregation, adsorption, and degradation, alongside improvements in PK, PD, and immunogenicity. An illustrative example of these advancements is the 2013 approval of a recombinant anti-hemophilic factor VIII, aimed at treating and preventing bleeding episodes in individuals with hemophilia A (32-35).

A method for monitoring immunogenicity was developed and applied to support the clinical development program of a novel complex biologic agent during its early clinical development phases. In crafting the strategy for a multidomain biotherapeutic of this type, various considerations were taken into account, as each conjugation results in a distinct domain interface. Risk assessment is based on a range of factors, including the presence of endogenous equivalents, the development and availability of pharmacodynamic biomarkers, and the cell epitopes of T and B lymphocytes (36-41). At the commencement of the first-in-human (FIH) study for the drug under consideration, there were no trustworthy clinical pharmacodynamic biomarkers available for target engagement or response prediction, which are vital for determining safety and efficacy. The ability of GDF15 to suppress food intake, which is integral to energy regulation and is considered a key factor in metabolic

disorders, prompted the establishment of a detailed immunogenicity strategy. Our analysis of the drug as a high-risk candidate regarding immunogenicity risk assessment validated the comprehensive immunogenicity strategy that was both proposed and implemented, especially in light of its chemical alterations (41).

CONCLUSION

To sum up, immunogenicity is essential for creating therapeutic agents, especially gene therapies, CAR T-cell treatments, and biologics based on big molecules. With its emphasis on its importance, evaluation techniques, and consequences for pharmacokinetics, pharmacodynamics, and patient safety, this thorough analysis has shed light on the complex nature of immunogenicity. However, with the use of advanced instruments, predictive tests, and risk reduction techniques, immunogenicity—a complicated phenomenon—can be anticipated and controlled. A new age of tailored therapeutics is being ushered in by the developing field of precision medicine, which provides exciting opportunities to customize therapies and reduce immunogenic reactions. Regulatory bodies are essential to maintaining strict guidelines for immunogenicity evaluation as the pharmaceutical sector innovates. To further our knowledge of immunogenicity and its management, cooperation between stakeholders-including patients, researchers, doctors, and regulatory agencies-will continue to be crucial. Exciting outcomes are anticipated from future avenues in immunogenicity research, including patient-centric methods, next-generation biologics, and sophisticated analytics, which, when combined, might revolutionize the sector and enhance patient outcomes. A better knowledge of immunogenicity will continue to be crucial in this changing environment for the safe and effective development of medications that will ultimately benefit patients and push the limits of contemporary medicine.

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FERROPTOSIS AND THEIR EMERGING ROLE IN DISEASE PROGRESSION AND TREATMENT

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ABSTRACT

The iron dependent pathways known as Ferroptosis that's started by uncontrolled lipid peroxidation and is directed by atomic systems which incorporate different atoms and organelles. Ferroptosis has ended up a basic component in various physiological and obsessive scenarios, driving to significant restorative advance in a wide run of diseases. Ferroptosis may be a modified type of cell death mechanism. This current article represent the brief role Ferroptosis and its part within the pathogenesis of numerous maladies.

KEYWORDS: Ferroptosis, Cancer, Neuronal Disease, Diabetes, Ischemia; NAFLD.

INTRODUCTION

Ferroptosis is distinguished from programmed cell death by its distinct characteristics, including its unique appearance, biochemistry, genetics, and immunological responses. Mitochondrial enlargement, decreased cristae, increased membrane density, and outer mitochondrial membrane rupture are recognised morphological characteristics of ferroptosis. Ultimately, cell death results from an iron-dependent process that encompasses three key metabolic pathways related to lipids, thiol, and iron. The enzymatic reaction of two primary antioxidant systems can effectively prevent ferroptosis. (1).

Programmed cell death is essential for the development of normal tissues, the selection of immune cells, and the removal of damaged and infected cells. These processes encompass the removal of damaged and diseased cells. Accidental cell death and regulated cell death two pathways followed by any cells. In accidental cell death it is transpires independently of human influence and is initiated by irreversible external stimuli, whereas Regulated cell death, governed by molecular network mechanisms and influenced by either experimental or therapeutic substances. Ferroptosis is a metabolic process associated with various metabolic abnormalities and is regulated by a specific set of genes. To enhance research initiatives, it is crucial to recognise these modifications, which act as indicators of ferroptosis(1,2).

THE FUNDAMENTAL MECHANISM OF FERROPTOSIS

Ferroptosis begins with an increase in iron buildup and a rise in lipid peroxidation. Two mechanisms that work to prevent ferroptosis are the first chelation of excess iron and the second activation of antioxidant pathways that are either dependent on or not dependent on GPX4. As will be explained later on, ferroptosis revolves on a disturbance in redox equilibrium. The peroxidation of lipid that is commonly known as lipid peroxidation play very crucial role in the activation of Ferro ptosis mediated cell death. There are various external and internal factors for the activation of lipid peroxidation such as free radicals of oxygen, H_20_2, and $cl^{\cdot}$. These by products directly damage the cellular lipid and play important role in iron mediated death pathways. Lipid peroxidation, which can be caused by an increase in reactive oxygen species (ROS) generation or stimulation, can lead to several types of controlled cell death (RCD). Numerous processes, play important role in ROS generation such as Fenton reaction, Glycolysis and TCA cycle, mitochondrial respiratory chain, and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX. In a wide variety of cell types and tissues, reactive oxygen species can either trigger ferroptosis or make it more likely to occur(3,4).

FERROPTOSIS AND DISEASE

Recently, it was found that ferroptosis may be

activated and has been linked to practically all organ-system illnesses. Ferroptosis is involved in cancer, neurological disorders, infection, ischemia-reperfusion injury, stress, autoimmune diseases, biopolar disorder and metabolic disorders. The peroxidation and free radicals of iron mainly activates and disrupted GPX4 pathway and enhanced ferritinophagy enable ferroptosis in these disorders and others disease conditions (5).

TUMOUR CELLS AND FERROPTOSIS

Apoptosis has long been the main way cancer cells die. Apoptosis-based cancer treatments often fail due to dysregulation of apoptotic pathways, especially anti-apoptotic mechanisms. Recent research have linked ferroptosis to many cancers, particularly drugs that target cancer-related genes and KRAS mutation-associated signalling pathways. Ferroptosis targeting may help fight cancer, especially apoptosis-resistant ones, through different ways. Cancer cells have developed several methods to reduce ferroptosis' metabolic and oxidative stresses (1,6). The Stress-inducible nuclear protein 1 basically increases the lipocalin 2 expression, and inhibit or reducing iron buildup due to this free radical of oxygen generates and oxidative damage occurs. This makes human and mouse pancreatic ductal adenocarcinoma (PDAC) cells more ferroptosis-resistant. In PDAC cells and mice models, HSPA5 stabilises GPX4, inhibiting ferroptosis. Radiotherapy is a common cancer treatment that uses ferroptosis. Radiation induces ferroptosis-mediated immunogenic death in cells, which is connected to its anticancer effects. When irradiated tumour cells produce the Ataxia-Telangiectasia mutant gene, lipid peroxidation increases, blocking SLC7A11. This blocks cystine absorption. (7).

DEMYELINATION

Neurodegenerative disorders are becoming more common, which is a huge problem for society and a major source of stress for those dealing with them. However, there is still a lack of effective treatments for many disorders. The relationship between pathogenic features, disease processes, and neuronal death must thus be further investigated. The primary focus of this research is on ferroptosis and its association with both Alzheimer's disease as well as Parkinson's disease. The pathophysiology of Alzheimer's disease and Parkinson's disease extensively exhibit ferroptosis traits, such as iron dyshomeostasis and lipid peroxidation. Iron builds up in the brain with age, making it a major risk factor for neurodegenerative disorders. Evidence of iron buildup in certain areas of the brain has been found in many neurodegenerative disorders (8,9).

REPERFUSION AND ISCHEMIA MYOCARDIAL ISCHEMIA

Myocardial ischemia is a serious medical disorder that can lead to serious complications and sometimes patient may die. Reduced blood flow to tissues, known as ischemia, happens when arteries are either blocked or ruptured. Cell death is caused by energy depletion and the end of blood flow (10). Returning blood flow as soon as possible is critical. However, once blood flow returns to normal, more substantial functional and structural alterations become noticeable. Myocardial infarction, acute renal injury, circulatory arrest, and sleep apnea are all possible outcomes of the pathological process. However, IRI poses a significant obstacle to organ transplantation, and reducing its negative consequences in real-world settings is no easy feat. As a potential target for treating ischemia-reperfusion injury, iron shows promise (10,11). Children who suffer from severe ischemic-anoxic insults have significantly higher iron levels in different parts of the brain, according to clinical research. Tissue damage in ischemia-reperfusion injury may also be caused by high iron levels during ischemia/reperfusion. Iron chelation was shown to reduce IRI damage in many animal models of the disease. Reactive oxygen species (ROS) can increase upon reperfusion of ischemic tissue, which is known to further worsen tissue damage and deterioration. There is evidence that antioxidants can protect against ischemia-reperfusion injury in a variety of settings. Lipid peroxidation occurs in tandem with the rise in oxidation (12).

FERROPTOSIS AND DIABETES

There are basically two types of diabetes Type 1 diabetes mellitus (T1DM) in which the immune system's attack on and destruction of pancreatic β-cells, leading to a deficiency in insulin production and type 2 diabetes (T2DM) the modest reduction in insulin secretion from pancreatic β-cells. Relative insulin insufficiency, resulting from dysfunctional pancreatic β-cells, aging and other health issues are a significant contributor to type 2 diabetes mellitus (T2DM) and insulin resistance. Studies indicate that individuals with diabetes mellitus exhibit irregularities in iron metabolism and frequently accumulate excess iron in their bodies, and iron overload may be a critical factor in the development of the disease (13). Individuals with diabetes, as well as animal models, exhibit low plasma concentrations of antioxidant enzymes such as glutathione (GSH) and superoxide dismutase (SOD).The reduced amount of antioxidant enzyme play very important role in the

Pancreatic β-cells exhibit susceptibility to oxidative stress-induced damage and activation of ferroptopsis pathways. A study by Liu et al. demonstrated that ferroptosis contributes to pancreatic damage, glucose intolerance, iron accumulation, and diabetic symptoms in mice with type 2 diabetes. The study indicates that islet function may be restored through the inhibition of ferroptosis (13). Type 1 diabetes patients may undergo ferroptosis following islet transplantation, a treatment that has become increasingly favored for its potential to enhance pancreatic β-cell mass, and normal secretion of insulin and mitigate long-term complications (13-15).

NAFALD AND ROLE OF FERROPTOSIS

NAFLD, is a conditions of hepatic steatosis, non-alcoholic steatohepatitis (NASH), fibrosis, cirrhosis, and hepatocellular carcinoma (HCC) are all parts of this chronic, progressive illness. A large body of evidence suggests that ferroptosis has a role in the development of NAFLD (16). One of the main factors that contribute to the development of NAFLD is the abnormal buildup of lipids, which in turn causes oxidative stress. Research by Zhang et al.(17) in 2021 proved that ferroptosis causes inflammation, which propels NASH development and progression. Improvements in liver function, inhibition of inflammatory reactions, and hepatocyte death reversal are all possible side effects of ferroptosis inhibitors (18).

EFFECTS OF OSTEOPOROSIS ON FERROPTOSIS

One prevalent metabolic disorder that affects bones is osteoporosis. A growing body of research is attempting to clarify the role of ferroptosis in the development of osteoporosis. Having too much iron in your system might be harmful. Animal studies have shown that iron excess can lead to osteoporosis and increased oxidative stress in mice (19). Postmenopausal women may have high iron levels in addition to estrogen insufficiency, both of which can lead to PMOP. Overconsumption of iron causes reactive oxygen species (ROS) to build up. In osteoporosis, ROS trigger the NF-κB/NLRP3 signaling pathway, causing osteoclasts to cause bone loss. Reactive oxygen species may help maintain metabolic bone homeostasis, according to Gao et al. (12,20).

CONCLUSION

There has been a rising realization in recent years that ferroptosis is an important disease mechanism in the pathogenesis of practically every organ system disease. This recognition has occurred in the course of recent years. Ferroptosis is commonly found in a wide range of diseases, including cancer, neurodegeneration, ischemia-reperfusion injury, metabolic abnormalities, and other associated conditions. These disorders are extremely prone to ferroptosis because they contain a large amount of lipids and iron, both of which are factors that promote lipid peroxidation on the cell surface. Because of the discovery of ferroptosis, new channels have been opened in the knowledge of the processes that lead to cell death. As a result, the possibilities for therapeutic intervention have been expanded. This is particularly true in situations where dysregulated cell death is a significant component, such as in the case of neurodegenerative illnesses and cancer. For the purpose of determining whether or whether there is a potential therapeutic advantage, researchers are conducting extensive research on pharmacological and genetic approaches to controlling ferroptosis. However, despite the fact that it shows promise, research on ferroptosis is severely hindered by a multitude of issues that restrict our capacity to fully comprehend and exert control over this cell death mechanism.

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Review Article

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GUT MICROBIOTA IMPACT ON HUMAN HEALTH AND DISEASES

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ABSTRACT

The human gastrointestinal microbiota, an intricate consortium of microorganisms, profoundly impacts numerous facets of health, encompassing digestion, metabolic processes, immune functionality, and even psychological well-being. These microbial entities facilitate the degradation of food substances, biosynthesize vital nutrients, and modulate immunological reactions. A shift in the gut microbiome linked to several clinical conditions such as Dysbiosis including inflammatory bowel disease (IBD), obesity, hyperglycaemia, cardiovascular disease, autoimmune diseases, irritable bowel syndrome (IBS) and certain malignancies. Furthermore, burgeoning research has elucidated the association between intestinal bacteria and psychological well-being via the gut-brain axis, impacting emotional states, stress reactivity, and disorders such as anxiety and depression. Nutritional determinants, particularly a diet rich in fiber and derived from plant sources, can foster robust microbiota, whereas suboptimal dietary practices may lead to dysbiosis. Interventional approaches, such as probiotics, prebiotics, and fecal microbiome implants are currently being investigated as viable therapeutic modalities aimed at reinstating microbial equilibrium and enhancing health outcomes.

KEYWORDS: Gut Microbiome, Inflammatory bowel disease, obesity, hyperglycaemia, cardiovascular disease, irritable bowel syndrome etc.

INTRODUCTION

The microorganisms known as bacteria inhabit various parts of the human body. However, within the human abdomen, exists an assorted population of approximately 300 to 500 distinct bacterial species, collectively harboring around 2 million genes. These microorganisms significantly influence human health; in conjunction with other minuscule entities such as viruses and fungi, they constitute what is termed the Microbiota or Microbiome. The quantity of bacteria residing in the gut is estimated to be roughly tenfold that of all cells present in the human body, and the aggregated bacterial genome is substantially more extensive than the human genome. The composition of an individual's microbiome is inherently unique.

These bacteria are distributed throughout the entirety of the digestive system. The majority are localized within the intestines and the colon. They influence a wide array of physiological processes, including metabolic function, emotional state, and immune response.

The human gastrointestinal microbiota has its origins in the colonization by environmental microorganisms at the time of parturition, and it coexists in a symbiotic relationship with host association throughout its lifespan. The intestinal tract harbors trillions of microorganisms, which significantly contribute to both health and illness by engaging with the host through numerous metabolic, defense system, neural, and endocrine pathways (1). The investigation of the gut microbiota about human health and illness continues to show several challenges (2). The gut microbiota constitutes a complex and adaptive assemblage, shaped by a myriad of influencing factors. Various populations of gastro-intestinal bacteria exert their significant effects on health through the fermentation of dietary fibers, resulting in the production of volatile fatty acids, which serve as endogenous signals playing critical roles in lipid equilibrium and the attenuation of inflammation (3).

Common gut microbiota and its positive impact on human wellness:

Human health and illness are greatly impacted by the microbiota; in fact, it is frequently called our "forgotten organ." In addition to performing several metabolic tasks like digesting and absorbing undigested carbohydrates, the gut microbiome is intricate in energy harvesting and deposit. This

characteristic has most likely been a major evolutionary factor in the development of bacteria as human symbionts. More significantly, the gut microbiome communicates with the defense system by sending indications that support immune cell maturation and the proper development of immunological activities (4).

Below is a description of several common bacteria and their impact on human health are :

Bifido bacteria

Bifidobacteria are characterized by their V- or Y-shaped branched morphology, exhibiting a rod-like form, and are classified as immobile, non-spore-forming, Gram-positive, anaerobic probiotics that are catalase-negative and members of the family Bifidobacteriaceae within the Actinobacteria phylum. These microorganisms are predominantly located in the intestinal microbiota of neonates and within the uterine environment of expectant mothers.

The genus Bifidobacterium was initially recognized from fecal samples of breast-fed infants; however, it has since been isolated from different ecological environments like sewage, dairy products, and anaerobic digestion systems. Nonetheless, the majority of isolations are predominantly linked to the gastrointestinal systems of both humans and various animal species (5). Certain strains of the Bifidobacterium genus are extensively utilized as probiotic agents and are intricately associated with human health, being particularly recognized for their roles in enhancing the immune, digestive, and metabolic systems (6).In addition to reducing inflammation and oxidative stress, it also enhances intestinal barrier function and controls the metabolites produced by intestinal microbes (7).

Bacteroides

Bacteroides is a Gram-negative, non-spore-producing, obligatorily anaerobic, bacillary bacteria. A significant portion of the intestinal bacterial community in vigorous adults is composed of Bacteroidota, called as Bacteroidetes a significant phylum of the gut microbiota. Intestinal homeostasis and general human health profile depend on several genera in this phylum, including Bacteroides, Parabacteroides, Prevotella, and Alistipes. According to studies, bacteriaroidota can comprise 20–80 percent of the gut microbiota, indicating its significance in the gastrointestinal habitat (8).

Bacteroidota is essential for the breakdown of complex carbohydrates, which results in the synthesis of butyrate and other volatile acids that have anti-inflammatory, gut barrier-maintenance, and colonocyte-energy-related functions. By affecting immune cell maturation and cytokine production, this phylum contributes to the modulation of the host defense system. Immunological tolerance and pathogen protection depend on such modulation (9).

Lactobacillus

A taxonomic group of rod-shaped, facultatively anaerobic, Gram-positive, non-sporing bacteria classified within the phylum of Firmicutes is designated as Lactobacillus (10). Lactobacilli constitute the predominant genus within the lactic acid bacteria (LAB) classification due to their capability to metabolize carbohydrates and synthesize lactic acid as a metabolic by-product (11). Various anatomical regions of the human organism, notably the female reproductive system and the gastrointestinal tract, including the oral cavity, have been inhabited by lactobacilli (12).

Certain strains of Lactobacillus are good for human health because they affect metabolic processes (like the production of vitamins, lactase activity, and cholesterol assimilation) and immune responses (13). They have also been shown to enhance the function of the gastro-intestinal barrier by promoting the growth of pathogenic bacteria in IBD and non-alcoholic fatty acid liver disease.

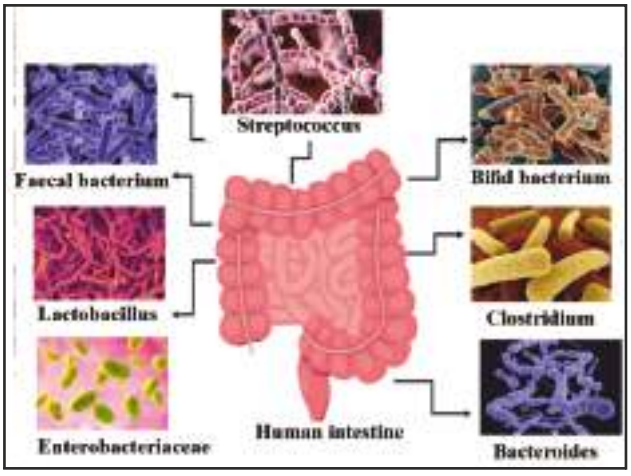

Fig. 1: Some common Bacteria Living in Gut and influence Gut Health accordingly

Clostridium

The microorganisms classified within the genus Clostridium exhibit a rod-like morphology, possess Gram-positive characteristics, and are capable of forming spores as obligate anaerobes. Their presence is noted in various environments including soil, the intestinal tracts of fauna, aquatic systems, and other ecological niches. These bacteria are categorized as chemoorganotrophs, demonstrating the ability to ferment an array of substrates such as carbohydrates, proteins,

organic acids, and various other organic compounds, leading to the production of metabolic derivatives including butyric acid, propionic acid, acetic acid, and certain solvents like acetone and butanol. Within the animals and humans' intestinal system, species of Clostridium predominantly metabolize indigestible polysaccharides. Furthermore, the metabolic by-products generated by these organisms confer numerous advantages to the health of the gut bacteria (14) .

Clostridium butyricum enhances the immune system's efficacy by strengthening the gut barrier, thereby inhibiting the colonization of harmful pathogens within the gastrointestinal tract. Additionally, it mitigates inflammation in the bowel, known as colitis, and is modulated with a reduced risk of developing colorectal cancer (15).

Faecal bacterium

Faecal bacterium is a rod-shaped, nonmotile, Gram-positive, strictly anaerobic, extremely oxygen-sensitive (EOS), and non-sporing bacteria(16). It is one of the most functionally active elements of the microbiome, as evidenced by the modification of eight urine metabolites of various structures linked to population variance(17). One of the most important functions of Faecalibacterium is energy production for the colonocytes, and anti-inflammatory metabolites collaborate to maintain gut health. The primary contribution of this microbiota metabolism is thought to be the prebiotic fermentation process, a no-digestible dietary complex that defines and stimulates the healthy microbiota inhabitants (18).

Streptococcus

Streptococci are classified as Gram-positive, nonmotile, nonsporing, and catalase-negative cocci that manifest in pairs or chains, possessing considerable relevance in both medical and industrial contexts. Various species of streptococci play a crucial ecological role as constituents of the normal microbial flora in both animals and humans (19). The genus Streptococcus is extensively utilized in dairy fermentation processes for the production of yogurt and cheese. These microorganisms confer benefits to human gastrointestinal health and are primarily linked to the alleviation of diarrhoea symptoms as well as the prophylaxis of irritable bowel diseases. Furthermore, they possess the capacity to synthesize thermophilins, which are a class of bacteriocins—small peptides that can inhibit the proliferation of or eliminate closely related bacterial strains (20).

Streptococcal species are not only pivotal for gastrointestinal health but also serve as a critical determinant of oral health. Subsequent to parturition, members of the genus Streptococcus are among the initial inhabitants of the oral cavity and they significantly contribute to the foundational organization of the oral microbiota. This underscores the rationale for the selection of specific streptococcal species for their potential influential components used as oral probiotics (21).

Among the Streptococcal strains, S. salivarius is also detected in human breast milk, which constitutes a critical reservoir of the bacteria during the initial stages of life, it is recognized as a remarkable and seemingly significantly constituent of the gastro microbiome (22).

Enterobacteriaceae

Enterobacteriaceae constitute a significant family of gram- negative, non-spore producing bacterium. In the context of gut homeostasis, these bacteria plays a precarious role in resisting the colonization of foreign pathogens. The gastro-intestinal microbiota offers protection through various mechanisms, such as immune system activation, engagement for nutrients, synthesis of antimicrobial substance's, and maintenance of the integrity of the epithelial barrier (23).

Gut Microbiota influence in Disease

The human gut microbiome, along with its contributions to both health and disease, has been a focal point of considerable scholarly investigation, thereby delineating its integral role in host metabolism, nutrition, physiology, and defense responses. Disruptions in the equilibrium of the gut microbiota have been correlated with several irritable bowel syndrome, gastrointestinal disorders, inflammatory bowel disease including broader systemic disease manifestations such as obesity and chronic diabetes and cardiac disease to colorectal cancer (24).

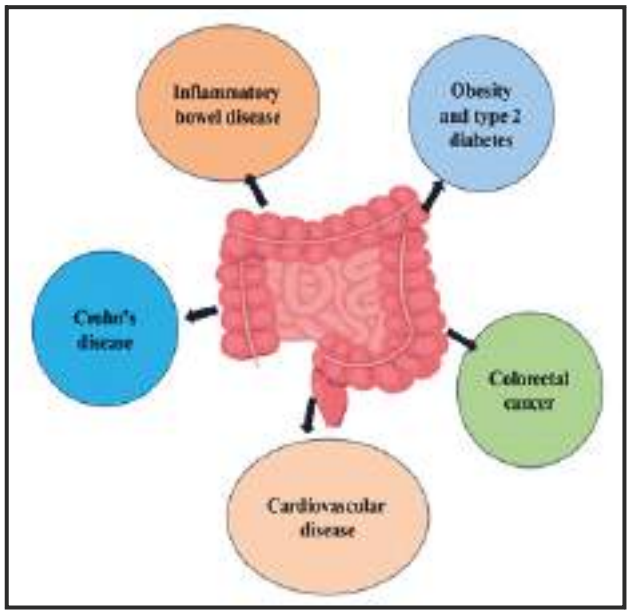

Fig. 2: In the negative environment Gut Microbiota can caused Disease in Intestine

Inflammatory Bowel Disease is a persistent gastrointestinal disorder i.e. demarcated by an exaggerated immune reaction to the gut microbiome. This condition, which is both severe and incapacitating, adversely contribute progress and improvement in pediatric populations, heightens the likelihood of colorectal malignancies, and has the potential to result in life-threatening sequelae(25). IBD manifests in two distinct forms, namely ulcerative colitis and Crohn's disease which are differentiated through the specific regions of the intestine that are inflamed (26).

Typically, anaerobic microorganisms residing in the gastrointestinal tract acquire their sustenance through the fermentation of non-digestible oligosaccharides and other carbohydrates that evade proximal digestion. The repercussion of the gut microbiome on individual health has prompted researchers to explore novel therapeutic interventions for a variety of health issues, including obesity or fats. A bidirectional interaction occurs between gut microbiota and nutritional habits, in which dietary components modulate the composition and functionality of the microbiota. Microorganisms present in the human digestive tract significantly affect the processes of nutrient assimilation, degradation, and deposition, which may have profound implications for host physiological functions (27). Further, overuse of antimicrobial medication has been linked to the onset of weight gain or obesity (28).

Individuals with type 2 diabetes experience metabolic dysfunctions that are related with imbalances in gut flora. The population of gut flora in humans is over 10 times greater than the number of human tissues and they are crucial for metabolic processes and defence system regulation. In T2D, the dysbiosis of gut microbiota leads to abnormal intestinal metabolites and interrupts the gastro-intestinal barrier, letting pathogenic bacteria and their metabolites to enter the blood vessels. This abnormal entry can cause damage to various organs by impairing insulin sensitivity, glucose metabolism, and immune balance (29).

The microflora may significantly participate to the functioning of the brain and the central nervous system, thereby elucidating the intricate interaction between gut microbiome and overall health profile. The gastrointestinal tract, often labelled as the 'second brain', comprises trillions of microorganisms that exert direct influence on both brain activity and neural signalling, thereby modulating stimuli associated with appetite or hunger. The variety and configuration of the gut flora are subject to modulation by several aspects, including mode of birth, eating practices, the administration of antibacterial and other suppositories, the aging process, and additional ecological influences. The colonization of human microbes initiates at the moment of birth and subsequently undergoes progression and alteration in species abundance over a period of three years, culminating in the establishment of a mature microbiota (30).

Furthermore, within the realm of respiratory pathologies, the gut microflora is acknowledged to use a substantial influence. The gastrointestinal and respiratory systems exhibit a shared epithelial framework, having both developed from a unified ancestral lineage that can be traced back to the foregut, and they display the presence of secretory immunoglobulin A (IgA) alongside goblet cell. Respiratory diseases encompass a myriad of disorders that impact both the upper and lower respiratory tracts. These conditions are characterized by elevated mortality rates and may arise from physiological or immunological dysregulations or from pathogenic microorganisms. Chronic respiratory conditions include asthma, cystic fibrosis and chronic obstructive pulmonary disease , while pneumonia and tuberculosis serve as examples of diseases induced by microbial agents (31). Respiratory diseases represent a substantial burden on global healthcare infrastructures; projections indicate annual fatalities of 3.9 million individuals worldwide. The effect of gut micro flora in the establishment of pulmonary immunity, particularly during the initial stages of life, has been well-documented. This correlation between the gastrointestinal tract and the respiratory system is further illustrated by the observation that perturbations in gut microbiota during early life can precipitate enduring respiratory complications(27).

Mechanism for disease:

The initial phase in elucidating the symbiotic interactions between gastrointestinal microbiota and their hosts necessitates a inclusive characterization of the equilibrated configuration of gut microbiota alongside variations associated with disease (32).

Alterations in gut microbiota and immune responses in intestinal disorders are critical. The gut microbiome, surrounding bacteria, viruses, and fungus, besides with dysregulated immune responses involving regulatory T cells (Tregs), T-helper type 1cells, and T-helper type 17 cells, are recognized as pivotal factors in the pathogenecity of inflammatory bowel disease. Under homeostatic conditions, gut microbiota foster an immune tolerance phenotype within the host, whereas in inflammatory states such as IBD, antigens derived from dysbiotic microbiota activate Th1 and Th17 cells, leading to tissue damage, a reduction in the mucus layer, and the penetration and tenacity of microbiotas

within intestinal nerves. The resultant mucosal barrier injury facilitates the further absorption of microbial antibodies, Toll-like receptor (TLR) ligands, and viable creatures, thereby sustaining the defensive responses.

Therapeutic Interventions that taegets the Gut Microbiota

The utilization of gut microbiota as probiotics for the amelioration of diseases has been a longstanding practice. Furthermore, their incorporation into the food and feed industries as dietary supplements has experienced significant growth, attributable to their beneficial effects on gut homeostasis.

Probiotics participate to the enhancement of intestinal hemorrhage, the fortification of intestinal barrier functionality, immunomodulation, and the regulation of the production and secretion of metabolites and small reactive molecules associated with intestinal microbiome, such as volatile acids, tryptophan and its by-products, gamma-aminobutyric acid, bile acids (Bas), amino acids (AAs), trimethylamine (TMA), sphingolipids, and bacteriocins, as well as extracellular polysaccharides (EPS), thereby facilitating the alleviation or management of a variety of diseases, including metabolic disorders, neurological conditions, inflammatory bowel diseases, cardiovascular ailments, and tumorigenesis (33).

Dysregulation of gut microbiota is frequently correlated with a multitude of immune system disorders. Subsequently, these microorganisms have been shown to modulate the efficacy of immunotherapeutic interventions for diseases. Evidence from preclinical and clinical investigations indicates that the gut microbiota may markedly affects the success of cancer immunotherapy. The observed diminished response to immunotherapy in patients who received antibiotic treatment further substantiates the critical role of the microbiota in this context (34).

Conclusion

The human gastrointestinal microbiome represents a composite and dynamic ecological entity that fulfills a perilous role in the maintenance of health is crucial for promoting overall well-being and the reduction of disease incidence. The interaction between gut microbiota and human health is bidirectional, with gut microorganisms influencing a broad spectrum of physiological processes, which encompass, but are not limited to, digestion, immune modulation, and even mental health. The maintenance of a well-regulated gut microbiota through nutritional strategies, the implementation of probiotics, and various therapeutic measures may provide considerable benefits in the anticipation and management of innumerable diseases.

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Review Article

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BONE BUILDING HORMONES: A REVIEW

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ABSTRACT

Bone health is a critical aspect of overall health, influenced by a combination of genetic, environmental, and lifestyle factors. Central to bone formation and remodeling are hormones that regulate osteoblast function, osteoclast activity, and mineralization. These bone-building hormones play a pivotal role in maintaining bone density, preventing osteoporosis, and supporting the repair of bone fractures. This review explores the major hormones involved in bone metabolism, including estrogen, testosterone, parathyroid hormone (PTH), calcitonin, growth hormone, and insulin-like growth factors (IGFs). We will examine their mechanisms of action, interactions, and implications for clinical practices and therapies aimed at enhancing bone health.

KEYWORDS: Bone Health, Bone Building Hormones, Testosterone, Parathyroid Hormone

INTRODUCTION

Bone health is a cornerstone of overall well-being, contributing to structural integrity, movement, and the storage of minerals such as calcium and phosphorus. The human skeleton is a dynamic system, undergoing continuous remodeling throughout life. This remodeling process involves a delicate balance between bone resorption, carried out by osteoclasts, and bone formation, driven by osteoblasts. Bone homeostasis is regulated through various molecular signals, including hormones, that coordinate the actions of these bone cells. Hormones, produced by different organs and tissues, influence bone metabolism by modulating the activity of osteoblasts and osteoclasts, thus regulating bone mass, strength, and mineral content.

The regulation of bone metabolism is not only vital for maintaining skeletal structure but is also crucial for preventing bone diseases such as osteoporosis, which is characterized by reduced bone density and increased fracture risk. Osteoporosis is a significant public health concern, particularly in postmenopausal women and the elderly population, where the decline in bone mass can lead to debilitating fractures and decreased quality of life. The loss of bone mass and structural integrity typically occurs when bone resorption outpaces bone formation. This imbalance can be exacerbated by a variety of factors, including hormonal deficiencies, genetic predispositions, and environmental influences such as diet and physical activity.

One of the most critical factors influencing bone remodeling is the complex interplay of hormones that regulate both osteoblasts and osteoclasts. These hormones can either stimulate or inhibit bone formation, thus directly affecting bone density and strength. Among the key hormones involved in bone building are estrogen, testosterone, parathyroid hormone (PTH), calcitonin, growth hormone (GH), and insulin-like growth factors (IGFs). These hormones each have distinct mechanisms of action, and their levels fluctuate during different stages of life, with significant effects on bone mass, especially in response to aging, menopause, or conditions like hypogonadism.

Estrogen, which plays a pivotal role in bone health, is most commonly associated with protecting bone density, particularly in women. After menopause, the sharp decline in estrogen levels leads to accelerated bone resorption, significantly increasing the risk of osteoporosis. Testosterone, often considered a male hormone, also has a significant impact on bone density in both men and women. In men, testosterone promotes osteoblast function, while in women, it has an important, albeit less understood, role in preserving bone mass post-menopause. Parathyroid hormone (PTH), while primarily involved in calcium regulation, also exerts profound effects on bone

remodeling. Intermittent administration of PTH has been shown to stimulate bone formation, which has important clinical applications for treating osteoporosis.

Growth hormone (GH), and its downstream signaling molecule insulin-like growth factor 1 (IGF-1), are essential for normal bone development and the maintenance of bone mass. GH stimulates the production of IGF-1 in the liver, which in turn has direct anabolic effects on bone cells, particularly osteoblasts. Additionally, calcitonin, a hormone secreted by the thyroid, can modulate bone resorption by inhibiting osteoclast activity, thus helping to preserve bone mass, although its effects are less significant compared to other hormones.

The interaction between these hormones is a critical aspect of bone homeostasis. Estrogen, for example, not only directly regulates osteoblast and osteoclast activity but also interacts with other hormones such as PTH to modulate bone turnover. Similarly, testosterone works in synergy with other growth factors, such as IGF-1, to stimulate osteoblast proliferation and activity. Understanding how these hormones work individually and in concert is key to developing targeted therapies for bone diseases.

The clinical implications of these hormones are vast. Hormone replacement therapies (HRT), which are commonly used to treat conditions like postmenopausal osteoporosis, often target estrogen or testosterone to restore balance in bone remodeling. Parathyroid hormone analogs, such as teriparatide, are used as anabolic agents to stimulate bone formation in patients with severe osteoporosis. Similarly, growth hormone therapy is being explored for its potential to treat osteoporosis and other bone disorders. However, the use of these therapies must be carefully monitored, as hormonal imbalances can have significant side effects, including an increased risk of certain cancers, cardiovascular events, and metabolic disturbances.

This review aims to provide a comprehensive overview of the key hormones involved in bone metabolism, their mechanisms of action, and their clinical implications for bone health. By examining the role of each of these hormones in bone remodeling, we hope to offer insights into potential therapeutic strategies for the prevention and treatment of bone diseases, particularly osteoporosis. As we continue to deepen our understanding of the molecular mechanisms driving bone health, the development of more effective and targeted treatments will become increasingly feasible, offering hope for individuals at risk of bone-related disorders.

In the following sections, we will delve into the individual roles of estrogen, testosterone, parathyroid hormone, calcitonin, growth hormone, and insulin-like growth factors, exploring their contributions to bone formation and remodeling, as well as their clinical relevance in the management of bone diseases

MAJOR BONE-BUILDING HORMONES

ESTROGEN

Estrogen, primarily produced in the ovaries, plays a significant role in bone health, especially in women. It maintains bone density by promoting osteoblast differentiation and activity while inhibiting osteoclast function. Estrogen receptors are found on osteoblasts, osteoclasts, and other cells in the bone microenvironment, indicating estrogen's broad influence on bone metabolism (1).

In premenopausal women, estrogen levels are high, which helps maintain bone mass. However, following menopause, a sharp decline in estrogen levels leads to an increase in osteoclast activity, resulting in bone loss and an elevated risk of fractures. Estrogen's protective effects on bone are primarily mediated through its ability to reduce osteoclast formation and activity, which in turn decreases bone resorption (2, 3).

Moreover, estrogen has an indirect effect on bone by modulating other hormones such as parathyroid hormone (PTH). Studies have shown that estrogen deficiency can lead to a dysregulated response to PTH, further contributing to bone loss (4).

Clinical Implications: Estrogen replacement therapy (ERT) has been used to mitigate postmenopausal bone loss. However, the potential risks, such as increased incidence of breast cancer and cardiovascular events, must be carefully weighed. Selective estrogen receptor modulators (SERMs) are also used as alternatives to ERT, as they offer bone-protective effects with a more favorable side effect profile (5).

TESTOSTERONE

Testosterone, primarily known as a male sex hormone, also plays a critical role in bone health in both men and women. In men, testosterone stimulates the proliferation and activity of osteoblasts, leading to an increase in bone formation (6). In women, testosterone contributes to bone density, particularly after menopause when estrogen levels decline (7).

Testosterone influences bone metabolism by promoting the production of insulin-like growth factor 1 (IGF-1), a potent osteogenic factor. Additionally, testosterone directly inhibits osteoclast formation, which helps to preserve bone mass (8).

Low testosterone levels, as seen in conditions such as hypogonadism or age-related decline, are associated

with decreased bone density and an increased risk of osteoporosis. In older men, testosterone therapy has been shown to improve bone mineral density (BMD) and reduce the risk of fractures (9, 10).

Clinical Implications: Testosterone replacement therapy is a common treatment for men with low testosterone levels and has shown positive effects on bone health. However, concerns regarding its cardiovascular risks and potential for prostate cancer need to be considered in clinical decisions (11).

Parathyroid Hormone (PTH)

Parathyroid hormone (PTH), produced by the parathyroid glands, plays a pivotal role in calcium homeostasis and bone metabolism. PTH is released in response to low blood calcium levels and stimulates bone resorption by increasing osteoclast activity. However, intermittent PTH administration has been found to have a bone-building effect (12).

PTH stimulates osteoblasts to produce growth factors, including IGF-1 and bone morphogenetic proteins (BMPs), which promote bone formation. Continuous high levels of PTH, as seen in hyperparathyroidism, lead to excessive bone resorption and loss of bone mass. Conversely, intermittent administration of recombinant PTH (teriparatide) has been shown to enhance bone formation and increase bone density (13, 14).

Clinical Implications: Teriparatide, a synthetic form of PTH, has been approved for the treatment of osteoporosis in postmenopausal women and men at high risk for fractures. It is considered one of the most potent anabolic agents for bone formation (15).

CALCITONIN

Calcitonin, a hormone secreted by the thyroid gland, has an antagonistic effect on PTH and plays a minor role in bone metabolism. It helps regulate calcium levels by inhibiting osteoclast activity, thereby reducing bone resorption. Although its bone-building effects are not as profound as those of other hormones like estrogen or PTH, calcitonin can be useful in specific clinical settings (16).

Calcitonin exerts its effects through binding to calcitonin receptors on osteoclasts, which inhibits the differentiation and activity of these cells. This leads to a decrease in bone resorption and a modest increase in bone density (17).

Clinical Implications: Calcitonin has been used in the treatment of osteoporosis, particularly in patients with vertebral fractures. It is also used for conditions such as Paget's disease and hypercalcemia, where reducing bone resorption is beneficial (18).

GROWTH HORMONE (GH)

Growth hormone (GH), produced by the pituitary gland, is critical for skeletal growth and development, particularly during childhood and adolescence. GH stimulates the production of insulin-like growth factors (IGFs) in the liver and other tissues, which in turn promote bone growth and mineralization (19).

GH enhances osteoblast activity and the deposition of bone matrix, leading to an increase in bone density. In adults, GH has a less pronounced effect on bone growth but still plays a role in maintaining bone strength. Low levels of GH, as seen in growth hormone deficiency, are associated with decreased bone density and an increased risk of fractures (20).

Clinical Implications: Recombinant human growth hormone has been studied as a treatment for osteoporosis and other bone disorders, although its use in adults remains controversial due to limited efficacy and potential side effects (21).

INSULIN-LIKE GROWTH FACTORS (IGFS)

Insulin-like growth factors (IGF-1 and IGF-2) are peptide hormones that play a key role in bone metabolism. IGF-1, in particular, is produced in response to GH stimulation and has direct anabolic effects on bone cells. IGF-1 promotes osteoblast differentiation and activity, stimulates collagen synthesis, and enhances mineralization (22).

IGFs also regulate the proliferation and differentiation of chondrocytes, which are involved in the formation of the cartilage model of bone. The interplay between IGFs and other growth factors like transforming growth factor-beta (TGF-β) and BMPs is essential for normal bone development and remodeling (23).

Clinical Implications: IGF-1 therapy has been explored for the treatment of growth disorders and bone diseases. However, its use remains limited due to challenges in achieving targeted delivery and managing potential side effects such as hyperglycemia (24).

DISCUSSION

Bone health is a complex process regulated by an intricate balance of hormonal signals. The major bone-building hormones discussed—estrogen, testosterone, parathyroid hormone, calcitonin, growth hormone, and insulin-like growth factors—work in concert to maintain bone mass and strength. These hormones interact in ways that are still being elucidated, highlighting the complexity of bone metabolism.

One important observation is the hormonal synergy between estrogen and testosterone. Both hormones have osteoprotective effects, although their

mechanisms differ. Estrogen predominantly inhibits osteoclast activity, while testosterone promotes osteoblast function, with both hormones preventing excessive bone loss. This interplay is particularly relevant in postmenopausal women, where the sharp decline in estrogen levels leads to accelerated bone resorption, which is partially offset by testosterone's effects.

PTH also plays a crucial role in bone metabolism, but its effects on bone resorption and formation depend on the pattern of secretion. Intermittent PTH administration has been shown to stimulate osteoblast activity and increase bone formation, a finding that has led to the development of therapies like teriparatide. In contrast, continuous elevated PTH levels lead to bone loss, emphasizing the need for precise regulation of PTH signaling in clinical settings.

While calcitonin has less of an anabolic effect than other hormones, it provides a valuable tool in treating conditions characterized by excessive bone resorption, such as osteoporosis and Paget's disease. Its ability to inhibit osteoclast activity and reduce bone turnover provides a therapeutic option when other interventions are not suitable.

Growth hormone and IGF-1, which work together to promote bone growth and remodeling, have important roles in both childhood development and the maintenance of bone mass in adults. However, their use in clinical practice remains limited due to the challenges associated with growth hormone therapy, including the potential for side effects and the variability in patient responses.

The clinical implications of these hormones extend beyond replacement therapies. For example, selective estrogen receptor modulators (SERMs) and bisphosphonates represent alternatives to traditional hormone replacement therapy, offering options with fewer side effects. Ongoing research into the molecular mechanisms of these hormones is expected to lead to the development of more targeted therapies, improving the treatment of osteoporosis and other bone-related diseases.

CONCLUSION

Hormones are essential regulators of bone health, influencing the activity of osteoblasts and osteoclasts to maintain bone density and strength. Estrogen, testosterone, parathyroid hormone, calcitonin, growth hormone, and insulin-like growth factors each play distinct yet complementary roles in bone metabolism. Advances in our understanding of these hormones' mechanisms of action have led to the development of more effective therapies for bone-related conditions. Continued research into the interactions between these hormones and their therapeutic potential will likely yield further insights into the prevention and treatment of osteoporosis and other bone diseases.

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Review Article

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SYSTEMATIC REVIEW ON RELATIONSHIP OF NEUROLOGICAL TUMORS WITH ABO BLOOD

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ABSTRACT

Background: ABO blood type markers are present on the cell membranes of epithelial and endothelial layers, as well as on nerve cells. Numerous studies have highlighted a correlation between the risk of developing certain cancer types and ABO blood group antigens. Risk factors like smoking, alcohol consumption, diet, and radiation exposure play a significant role. Neuroma, a benign tumor of nerve tissue, is often associated with pain or various other specific symptoms. It typically develops from non-neuronal nervous tissue following amputation or trauma, though it can also be a true neoplasm. Approximately 6% of individuals may develop a neuroma. Aim and Objective: The main goal of this research was to analyze existing studies and Exploring the correlation between blood types and brain tumors. Material and Methods: Original, relevant, and up-to-date articles in the same field were reviewed to provide a comprehensive analysis of this topic. In doing so, critical discussions were included, offering not just a descriptive overview but also a thorough presentation of contradictory viewpoints in a clear manner. Research queries were carried out by matching terms associated with blood groups and tumors of the nervous system. Result: People with blood group B showed an increased incidence of cavernomas, gliomas, meningiomas, pituitary adenomas, schwannomas, and other tumors, with a declining trend in prevalence across blood type O, A, and AB. The link between blood type O and neuroma was the sole correlation to reach statistical significance. The likelihood of glioma was greater among individuals with AB blood type regarding other ABO blood types. Those with blood type A were more susceptible to developing glioblastoma compared to individuals with blood type O. Conclusion: It was determined that no meaningful correlation existed between blood group antigens and brain neoplasms in the general population. While neuroma showed a distinct association with blood group O, its occurrence in the population is relatively rare.

KEYWORDS: Brain tumors, Neuroma, Glioma, Blood types.

INTRODUCTION

Tumors are a major contributor to global mortality rates. A large portion of research is committed to investigating potential risks for these cancers, like tobacco use, Alcohol intake, dietary habits, excess weight, microbial diseases, toxic environmental agents, and contact with radiation. Hereditary factors, including ABO blood groups, were also recognized, along with genetic mutations associated with a higher likelihood of tumors (1).

The ABO blood type system, identified by whether A and B antigens are present or lacking on red blood cells, was identified by Karl Landsteiner in 1900. These antigens are intricate carbohydrate formations found on erythrocyte membranes (2).

These ABO blood type markers indicate unique phenotypes and genetically encoded carbohydrate-protein structures located on the outer layer of red blood cell membranes, actively involved in cellular functions and disease processes. The specific oligosaccharide structures of the antigens define the blood type. Consequently, secondary gene products correspond to blood group antigens, while primary gene products are diverse glycosyltransferases involved in oligosaccharide chain synthesis.

In certain blood groups, the absence of antigens has sparked debate regarding the relationship between susceptibility for particular infectious and noninfectious conditions and the ABO blood type. In certain blood types, the existence or lack of antigens leads to changes in the blood membrane's structure and function. The structure of blood types influences their functions, linking blood groups to both diseases and overall health (3). Besides blood group markers and red blood cells,

they may also be found on particular tissues, leukocytes, thrombocytes, plasma-derived proteins, and various membrane-bound enzymes (4). ABO blood type markers can also appear in bodily fluids like perspiration, oral fluid, and human milk, semen, urine, gastric liquid, and amniotic sac fluid in a dissolved state (4).

The most frequent primary symptom in individuals experiencing peripheral traumatic neuromas (5) in the affected area, it can result in pain, tingling, as well as sensory and motor deficits (6). Gliomas, meningiomas, and pituitary adenomas are the most frequent forms regarding brain tumors. Glioma is leading category of primary brain tumor. According to histological features, gliomas are categorized into the following subtypes: glioblastoma, Astrocytic tumor, Oligodendrocyte tumor, Ependymal tumor, combined glioma, and aggressive glioma. Annually, about 100,000 individuals are diagnosed with glioma worldwide. It represents less than 2% of all new cancer diagnoses and is associated with high rates of death and illness.

As per the World Health Organization's classification, glioblastoma is most aggressive glioma, designated as a grade 4 tumor, and makes up 50% of all gliomas.[7]

Numerous studies have produced inconsistent results regarding link among ABO blood types along with glioma susceptibility. Effect of blood types on brain tumors formation Persists uncertain due to the conflicting findings from research on ABO blood type distribution and glioma risk (7).

Despite the contradictory findings, certain ABO blood types have been associated with brain tumors. For instance, Individuals with blood type A may face a higher chance of developing astrocytoma, glioblastoma, and craniopharyngioma. Nevertheless, a study involving 107,472 participants found no correlation between blood type A and gliomas. On the other hand, blood type B was the most common ABO group 56.1% in Neurogenic tumors at a prominent in India. Additionally, Grade IV was more prevalent in individuals with blood type B among glioblastoma multiforme cases, though one study found no correlation, while another considered non-O blood types as an isolated adverse prognostic indicator (8).

Incidence rates are typically greater in highly developed nations compared to less industrialized regions. The five most frequently observed tumors were astrocytic tumors 47.3%, posterior fossa tumors 11.4%, Rathke's pouch tumors 9.7%, ependymal neoplasms 4.8%, and Schwann cell tumors 4.1%. Glial cell tumors represent the most common form of primary brain tumor, comprising roughly 27% of all brain tumors and nearly 80% of malignant cases. These tumors originate from glial cells or their precursor forms and include astrocytic tumors, glioblastomas, oligodendroglial tumors, ependymal neoplasms, mixed glial tumors, high-grade glial tumors, and several rare histological subtypes. The precise cause of glial tumors remains unclear (9).

METHODOLOGY

The present review is held under the guidance of meta-analysis and systemic review for preferred items.

Research criteria: Authentic and current studies on the same topic existed examined along with helped form a detailed overview of this topic. The search of 43 articles, time duration 1956-2023 was performed from Pub Med, Scopus, Wave of science, Medline etc. Therefore, these discussions include not only a detailed overview of the topic but also opposing viewpoints, which were thoroughly explored and presented in a clear manner. Additionally, pertinent scientific studies from prior years were also included. The literature search concentrated on blood groups and associated conditions. The studies were evaluated and selected according to the title and summary. The key words are Blood groups, neurological tumors, neuroma, glioma, which has been extracted from the articles itself. These keywords were helpful in search purpose.

Study selection: Studies were chosen according to defined inclusion and exclusion criteria.

Selection criteria: This study is particularly on brain tumors and its relation to ABO blood group system was included.

Exclusion criteria: All the articles which not include the ABO blood type and brain tumors.

As per all the articles, procedure prior to performance of any type of brain tumors and related conditions. Significance to the ABO blood group system.

RESULT

Connection among ABO blood group antigens along with Brain neoplasm prevalence has occurred studied for a long time, (10) No defined hypothesis has been advanced concerning that relationship among ABO blood groups together with central nervous system Tumors. The researchers Kumarguru et al. proposed a reasonable hypothesis, suggesting that environmental or genetic factors could influence the characteristics of blood type System markers on outer layer of originating cells, possibly affecting tumor formation. Under this context, the process may function not solely in primary tumor growths but also in metastatic abnormalities of the central nervous system in individuals with a genetic predisposition (11). The impact of blood group categories on brain tumor development remains unclear. Periayavan

S. et al. noted that central nervous system lesions were most commonly associated with blood group O, including meningeal lesions 37.57%, neuroepithelial tumors 38.45%, pituitary tumors 43.62%, Cranial and spinal nerve neoplasms accounted for 39.67%, while metastatic tumors represented 43.18%.

Mehrazin M et al. noted that head and spinal nerve tumors 35.9%, neuroepithelial tumors 38.4%, and pituitary tumors 4.40% occurred more often observed within patients with blood type O under their research (12).

Several earlier studies have examined the prevalence of blood type ratios within glioma individuals. Yates and Pearce carried out the first investigation into the connection between ABO blood types along with glioma probability, finding no significant association in patients diagnosed before 1945. An Italian case-control research involving 195 histologically verified gliomas cases revealed an affirmative correlation to blood type A, specifically Campbell et al. found that, When low-grade astrocytic tumors were analyzed individually, the prevalence of glial tumors was significantly higher among individuals with blood type O compared to the general population (13).

Mehrazin et al., in their retrospective study, No significant variations detected in intracranial tumor types along with proportion of four blood types. Conversely, Akhtar et al., through A comparative study of 112 brain and spinal cord tumors identified a markedly stronger link between such tumors and patients possessing blood type B (14-15). Akca et al. conducted an observational study aiming to evaluate glioblastoma multiforme patients using control groups to study ABO blood group distribution. These findings revealed no notable differences between blood types O, A, B, and AB. Similarly, Turowski along with Czochra analyzed ABO blood type distribution within 271 glioblastoma multiforme patients, using a sample of 500 control individuals with traumatic brain injury. Consequently, a statistically relevant variation existed noted within the frequency of ABO blood types among these individuals. Additionally, Patients with glioblastoma multiforme showed a higher frequency of blood type A and a lower frequency of blood type O (16).

Another investigation involved 2,077 histologically verified glioma cases admitted to the hospital between 2001 and 2016, alongside a control cohort of 2,716 non-tumor patients from the same institution. The results demonstrated a significant association between blood groups B and AB and the likelihood of glial tumor development. Nevertheless, a long-term study tracking more than 100,000 adults in the U.S. for almost 20 years found no substantial differences in glioma risk associated with ABO blood groups. As a result, the study concluded that ABO blood type likely does not affect glioma development (7, 37).

Nevertheless, the impact of blood group types on glioma development remains uncertain.

As reported by Gopal K. Patidar, Yashaswi Dhiman, and Anjali Hazarika, glioma was more common in male individuals blood type O 35.49% compared with blood group B individuals 34.8%. In contrast, among females, the trend reversed, with blood group B at 36.95% and blood group O at 31.3%. However, this difference was not statistically significant for either gender. Meningioma was observed more often in females with blood groups O and AB, and this association was statistically significant $P > 0.05$. Other tumor types were also more frequently identified in male patients with blood group O, as well as in female individuals with blood group B. Consequently, meningioma occurred more often in individuals above age of 50, while glioma was greater frequently seen in patients younger than 50. Cavernoma and neuroma were more frequently observed among adulthood individuals 11–40 years and less common at the younger and older age extremes, under 10 and over 60 years. Among individuals aged 11 to 30 years, blood type B exhibited a greater occurrence of meningioma, cavernoma, pituitary adenoma, and other tumors compared to blood type O, In contrast, Glioma and neuroma exhibited the contrary trend, being higher prevalent with blood group O compared to B. Meningioma, glioma including pituitary adenoma existed more commonly seen in people who have blood group O relative to individuals have blood type B, with a greater prevalence in the 51 to 60-year age range. Likewise, Meningioma occurred greater frequently within individuals aged over 60 years old.[1]

According to M. Allouh, A notable correlation was observed between the presence of ABO blood group antigens and the occurrence of glioblastoma, with individuals in blood group A showing a greater likelihood of developing glioblastoma compared to those in group O (9).

Another study found that individuals with blood group AB had a 3.5-fold increased risk of developing glial tumors compared to those with other ABO blood groups. ABO blood type system is vital in tumor development, as it influences the levels of circulating pro-inflammatory and adhesion molecules. Furthermore, the recent identification of von Willebrand factor as a key regulator of blood vessel formation and cell death offers a strong rationale for the involvement of the ABO blood type in tumor development (7, 41).

Citation	Study Characteristics	Variables Measured	Results
Zheng et al., 2023[41]	Retrospective study 158 patients were include	Age, blood group	Blood type AB was linked to a higher risk of mortality in patients who underwent surgical removal of brain metastases.
Patidar et al., 2022[1]	Out of 1,970 patients, 33.55% had glioma, 20.05% had pituitary adenoma, and 2.23% had neuroma.	Age, gender, frequency, ABO blood type	Individuals possessing blood type B exhibited a greater frequency of glioma, cavernoma, meningioma, pituitary adenoma, schwannoma, and similar tumors, with types O, A, and AB following. Neuroma occurred solely in those with blood type O.
Cornelia Englisch et al., 2022[38]	Cohort Study	ABO blood type	Individuals with AB, A, or B blood types showed a greater propensity for cancer-associated venous thromboembolism, with a risk on par with the general population lacking cancer.
Al Shudifat et al., 20218	Observational study 81 children diagnosed with primary brain tumors and 148 healthy controls	Age and gender, higher birth weight	An elevated probability of pediatric primary brain tumors was observed in individuals with blood type. AB, whereas type O was not associated with a higher risk relative to types A and B.
Arsic, 2021[7]	Case–control study 100 individuals include	ABO blood group, age and sex-matched gender	Individuals possessing blood type AB showed a 3.5-fold higher likelihood of developing glioma compared to individuals with other ABO blood types.
Lin et al., 2020[18]	Cohort study	Age, gender	Glioma occurred more frequently in men than in women. For assessing risk, appropriate age classifications divide individuals into 15–47 years as the youth category, and48-63 years as the middle-aged group and 64 years and older as the elderly category. This grouping is useful for evaluating glioblastoma risk in glioma patients.
Hilde E. Groot et al. 2020[43]	Cohort study 406755 unrelated individuals were included	ABO blood group, age, gender	ABO blood types were mainly linked to cardiovascular outcomes. In contrast, individuals Possessing blood types A and B had up to 1.56 times higher chances of thromboembolic events, while showing reduced odds of hypertension compared to those with blood type O.
Fevzi Coskun et al., 2020[39]	Retrospective study 2038 patients	Age, gender, surgery, type chemotherapy or radiotherapy	In elderly patients, incomplete tumor resection, the absence of adjuvant treatment and non-O blood type were identified as negative prognostic factors in the multivariate analysis.
Azanjac Arsić A, et al., 2019[31]	Observational study included 100 glioma cases confirmed by pathology.	Age- and sex-matched, gender, age, place of birth and residence, blood type, Rh factor	AB Blood type connection with an increased likelihood of developing glioma compared to other blood types.

Table 1: Summary of included eligible studies on Relationship of Neurological Tumors with ABO Blood Group

Koul et al., 2018[33]	Retrospective, non-randomized snapshot study	Gender, Living conditions, Life style choices and dietary behavior	The most common blood groups across all cancers were Blood Groups A and B.
Allouh MZ et al., 20179	Cohort study consisted of 115 glioblastoma patients	Age, gender, ABO grouping and Rh classification.	Individuals with blood group A demonstrated an increased tendency for glioblastoma occurrence compared to predictions, whereas those with blood type O showed a diminished probability.
Renu Thambi et al., 2017[32]	Retrospective analysis 510 cases of brain tumors taken	Age category and Male/female classification	Most brain tumors occur in individuals aged 40 to 60, with amale-to-female ratio of 0.9:1. Meningiomas and glial neoplasms were the most commonly observed histopathological types.
B.N. Kumarguru et al., 2017[11]	Analytical type of study	ABO blood type	The preponderance of brain tumors is seen in individuals aged 40 to 60, with a male-to-female ratio of 0.9:1. These tumors mostly impact the dura and cerebral regions, excluding the occipital lobe, with meningiomas and glial neoplasms as the predominant histological forms. WHO grade IV tumors and metastatic lesions were more commonly observed in males than in females.
Xu et al., 2017[34]	Retrospective evaluation	Age, Sex category, marital condition, health coverage status, Cultural background, Histopathological, tumor size, Surgery, radiation therapy, and a combination of surgery and radiation	Results from the multivariable Cox regression analysis showed that patients of Asian or Pacific Islander background experienced better overall survival.
Akca et al., 2014[15]	Case control study, 72 patients with Glioblastoma Multiforme	Age, sex, ABO Blood Group	ABO blood type showed no influence on patients diagnosed with glioblastoma multiforme.
Jain A et al., 2011[35]	Retrospective study 3936 pediatric patients	Age	The most commonly observed the astrocyte-derived tumor was identified as pilocytic astrocytoma. In children, oligodendrogliomas and lymphomas were less common than in adults.
K. Akhtar et al., 2010[14]	Crossectional study 2640 histologically proven cancer patients	age, sex, ABO blood type	All cancers were compare together, then the maximum distribution of blood types existed as follows: B at 40.5%, followed by A at 34.2%, O at 16.0%, and AB at 9.3%.
Masoud Mehrazin, 2006[13]	Retrospective study 907 patients 1980-2002	Different Blood groups	No notable differences were observed between the different categories of brain tumors and the occurrence of the main blood group types.

Cont. Table 1: Summary of included eligible studies on Relationship of Neurological Tumors with ABO Blood Group

DISCUSSION

In India, brain tumor cases range from 5 to 10 per million people, contributing to 2% of all cancer cases (1,32,36). For a long time the researcher has been studied the correlation between blood group markers and brain tumors, discovered within blood groups and many tumors (18,40). Risk factors of the neurological tumors are the genetic changes in the chromosomal region. According to Lin et al, in patients which aged group 21 to 40 years have found mostly glioma tumors and lowest in age >60 years (18). Glioma occurrence was higher in blood group B, then O, A, and AB. According to certain other studies, blood type O exhibited a greater prevalence compared to blood group B (17,19). Conversely, another study revealed that blood type A shows a greater prevalence of glioma (20). A large long-term cohort study also found no correlation between ABO blood group antigens and glial tumors (21).

In these studies, the relation in Blood type and age the Glioma occurred more Within <40 years age group patients having blood group O rather than glioma higher in >40 years patients with B blood group. According to this study glioma was less in female patients compare to male Patients and it appeared approximately same B and male patients with blood group O. In comparison, female patients showed a higher prevalence in blood group B (22).

Approximately 20% of the patient group in our study was found to have pituitary adenoma and meningioma (22). Mayr and colleagues (23) a larger number of pituitary adenomas were found in people with blood type O, while Chang et al (17). observed a significantly reduced incidence was seen in individuals with blood types B and AB. There was no difference in the prevalence of pituitary adenoma between genders across all blood groups. Considering age and blood group distribution, pituitary adenoma was more frequently observed in individuals with blood type B aged between 21 and 40. Earlier studies have shown different correlations between the occurrence of meningioma and ABO blood groups, such as Sowbhagya et al (24). which reported a greater occurrence in individuals with blood type O, Whereas Pearce and Yates (25) discovered a higher prevalence among those with blood type A, Furthermore, Mayr and colleagues (23) reported a greater occurrence in those with blood group B, the prevalence was nearly the same across all blood groups. Meningiomas were notably more prevalent in women with blood groups O and AB (26-29). Neuromas were detected in about 2.23% of individuals in our research. Schwannomas were more frequently observed in individuals with blood type O compared to those with other blood types, exhibiting a statistically significant difference. To the best of our knowledge, no previous studies have established a connection between neuroma tumors and ABO blood types. This frequency occurred greatest within the adulthood aged group 21 to 40 years, compared to the younger 0 to 10 years and older over 60 years age groups. Bondy et al. 2010 (30) conducted studies on syndromes, familial clustering, genetic association, and mutagen sensitivity in adults, suggesting a hereditary predisposition to glioma. While genetic conditions caused by rare inherited mutations are linked to an increased risk of brain tumors.

CONCLUSION

After reviewed the various studies the findings suggested that there was no substantial correlation within brain tumors along with blood group antigen. Blood type O showed significantly connected to neuroma, while blood group AB showed a higher association with glioma tumors. We also found that glioblastoma presents a greater likelihood for individuals with blood type A compared to those with blood type O.

So its need to identify shortcomings in the current system review and conduct more rigorous experiments on brain tumors for future research that address the above shortcomings using this system review on connection among ABO blood groups and brain tumor formation.

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Review Article

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ADENOSINE IN CARDIOVASCULAR PHYSIOLOGY: MULTIFACETED ROLES IN CORONARY VASODILATION, ATHEROPROTECTION, AND PLATELET REGULATION

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ABSTRACT

This review delves into various aspects of acute coronary syndrome (ACS), emphasizing recent advancements. Despite progress, ACS remains a major global health concern. The classical view linking coronary stenoses to chronic syndrome is challenged, with optimal medical therapy often showing better outcomes. Diverse ACS mechanisms include plaque rupture, calcified nodules, spontaneous dissection of the coronary arteries, and coronary artery spasm. Immune factors, particularly neutrophils and their extracellular traps, play a dual role in both inflammation and tissue healing. The adaptive immune response involving T and B lymphocytes adds complexity. Metabolic and lipid-related factors like adenosine pathways, vitamin D, and lipoprotein-associated phospholipase A2 impact atherothrombotic processes. Non-coding RNAs, including circular, long, and microRNAs contribute to ACS. Genic therapies like Olpasiran and Inclisiran show promise in targeting specific molecular pathways to reduce cardiovascular risk factors. Overall, this review offers a comprehensive understanding of ACS, incorporating recent molecular, immunological, and therapeutic advances, highlighting the need for ongoing research to improve diagnostic and treatment strategies.

KEYWORDS: Acute coronary syndrome (ACS), Coronary artery disease (CAD), Plaque rupture, Plaque erosion, Calcified nodules, Spontaneous coronary artery dissection, Coronary spasm, Immune response, Neutrophils.

INTRODUCTION

Advances in acute coronary syndrome (ACS) diagnosis and treatment have been significant over recent decades, especially concerning procedures like percutaneous intervention and the development of antithrombotic medications (1). Despite these improvements, Ischemic heart disease contributes significantly to mortality rates, and cardiovascular illnesses continue to be the world's leading cause of death. Identification of atherosclerotic lesions through angiograms is crucial in diagnosing coronary artery disease (CAD). Coronary stenoses development has been linked to acute cardiac events such unstable angina, and cardiac death, which greatly hinder blood flow and were thought to be the main lesions causing chronic coronary syndrome (CCS) (2). Revascularizing significant coronary artery stenoses has shown to relieve symptoms as well as improve quality of life. However, as compared to the best medical care alone, certain trials have not demonstrated statistically significant prognostic benefits from interventional techniques (3). Optimal It has been demonstrated that medical therapy lowers the rates of cardiac mortality as well as myocardial infarction (MI). Despite implementing therapies based on guidelines, a portion of patients with chronic coronary syndrome (CCS) still experiences progression to acute events, which adversely affects overall patient outcomes (4). Consequently, there has been a shift in research towards identifying unique features of atherosclerotic plaques to enhance the categorization of patient risk. Moreover, advancements in understanding the genetic elements and pathogenic pathways have demonstrated fresh understanding of the atherothrombotic mechanism (5).

Clinical Acute Coronary Syndrome Presentation

ACS encompasses a range of clinical conditions, such as unstable angina, ST-segment elevation myocardial infarction (STEMI), and non-ST-segment elevation myocardial infarction (NSTEMI). Such circumstances are differentiated based on the severity and urgency of

required treatment (6). Unstable angina, the mildest form of angina, is characterized by symptoms suggestive of sudden myocardial damage but lacks supporting biochemical evidence. MI, as defined by the Fourth Universal Definition, both NSTEMI as well as STEMI are categorized as type 1 myocardial infarctions, requiring not only clinical symptoms of ischemia but also evident increases in troponin levels (7). Due to improved management of established risk factors, STEMI within ACS is becoming less common in Western nations, although in-hospital death and morbidity rates are still significant (8). Additionally, there has been a shift from the traditional understanding of non-ST-segment elevation acute coronary syndrome (NSTE-ACS). Intravascular ultrasonography (IVUS) as well as optical coherence tomography (OCT) has permitted the examination of the plaque content, morphology, and characteristics in vivo (9). While thrombus formation and ruptured lipid-rich plaques are the main contributors to ACS, research suggests that a significant number of patients also experience plaque erosion, spontaneous coronary artery dissection (10).

Physiopathology of Acute Coronary Syndrome

The pathophysiology of ACS involves two primary mechanisms: plaque rupture and plaque erosion. Plaque rupture, An event that frequently results in the abrupt development of coronary atherosclerosis, involves the luminal rupture of a "vulnerable" plaque (11). The characteristics of these plaques include a significant lipid core, foam cells, macrophages, covered by a thin tissue that is fibrotic cap (12). Rupture releases prothrombotic substances, initiating the coagulation cascade and leading to thrombus formation. Inflammatory mediators hinder extracellular matrix production and prompt release of proteases, contributing to cap degradation (13). The production of plasminogen activator inhibitor-1 and fibrin, two prothrombotic components, increases the risk of clot formation. Core elements revealed during rupture activate circulating platelets, enhancing the coagulation process and causing swift thrombus formation (14).

However, plaque erosion is relatively recent conceptual framework in ACS, involving the superficial erosion of an atherosclerotic plaque. Although historically reported at around 20% prevalence, recent research suggest an raised prevalence of approximately 40% (15). Plaque erosion is typically identified in vivo using OCT as well as it is associated with younger patients, With an average age of 53.8 years, plaque rupture occurs at 65.1 years (16). Vascular risk factors are distributed unevenly in plaque erosion, with greater hemoglobin concentration, lower rates of diabetes and hypertension, and lower levels of LDL cholesterol and C-reactive protein. Compared to plaque rupture, plaque erosion has less complexity and severity in CAD (17). Molecular mechanisms involve local shear stress, leading to thrombus formation in high endothelial shear stress areas, as well as basement membrane degradation, endothelial cell desquamation, and death due to fluid dynamic impact (18). Toll-like receptor (TLR)-2 activation sustains inflammation and promotes granulocyte recruitment, with recruited granulocytes, mainly neutrophils, forming neutrophil extracellular traps (NETs) linked to plaque erosion and thrombus formation (19).

Lipid and Metabolic Factors in the Process of Atherothrombosis

Adenosine, initially recognized by Berne for its role in coronary vasodilation within the cardiovascular system, influences various pathways associated with coronary blood flow and atherothrombotic events. The A2a subtype, found widely in smooth muscle and endothelial cells and functioning via four G protein-coupled receptors, significantly impacts cardiovascular functions. Adenosine exhibits a protective effect against atherosclerosis by stimulating endothelial cell growth during angiogenesis and suppressing pro-inflammatory cytokine reactions (20). Adenosine plays a crucial role in promoting collateral circulation and mitigating damage caused by ischemia, particularly in hypoxic conditions where elevated levels of A2a receptors enhance its effects. This increased expression effectively balances inflammatory responses mediated by pathways such as HIF-1α and NF-kB. Another significant aspect of adenosine's function is its role in regulating platelet aggregation. Studies demonstrate that elevating intracellular cAMP concentration in platelets promotes increased aggregation while reducing internal calcium mobilization. These experiments often involve mice lacking the A2a receptor. The genetic variations of adenosine and its interactions with drugs like ticagrelor underscore its importance, particularly in influencing platelet reactivity. Therefore, caution should be exercised when using adenosine during procedures such as fractional flow reserve measurement (21).

Lipoprotein (a)

Similar to low-density lipoprotein (LDL), lipoprotein (a) or Lp(a) contains apolipoprotein B (apoB), which binds to the surface of apolipoprotein (a) (apo(a)). Apo(a), highly resembling plasminogen and encoded by the gene for lipoprotein(a), is crucial in Lp(a) function. Lp(a) serves several clinical and

physiological functions, such as affecting blood coagulation, interacting with immune cells, as well as participating in adhesion molecule activities. Additionally, It is an important factor in transporting human plasma's oxidized phospholipids, which have pro-inflammatory and pro-atherogenic properties. Lp(a) aids in the onset and advancement of atherosclerotic plaques in disease settings, elevates the risk of blood clot formation leading to conditions like myocardial infarction (MI) or ischemic stroke, as well as it triggers inflammation. Similar to LDL, lipoprotein (a) or Lp(a) contains apolipoprotein B (apoB), which binds to the surface of apolipoprotein (a) (apo(a)) (22). Apo (a), highly resembling plasminogen and lipoprotein(a) gene encodes, is crucial in Lp(a) function. Lp(a) serves various physiological as well as pathological roles, including influencing blood coagulation, interacting with immune cells, promoting the growth of vascular smooth muscle, and participating in adhesion molecule activities (23). For instance, in large-scale studies like the REVEAL trial, which observed a decrease in major coronary events with anacetrapib, both the cost-effectiveness ratio and the overall benefits presented challenges for its widespread adoption in routine clinical practice.

Regulation of Vitamin D and Calcium Balance

Vitamin D is essential for several organs, such as the cardiovascular system, and is vital for maintaining the balance of Ca^{+}, P, as well as bone tissue. It is synthesized by the skin or obtained from dietary sources and undergoes modifications to produce calcitriol, its active form. The vitamin D receptor, commonly found in the cardiovascular system, initiates cascades of signals with anti-inflammatory and antioxidative properties, thus safeguarding cardiovascular health. Approximately 9 percent of individuals with ACS exhibit a deficiency in calcitriol, which is distinct from their 25(OH) vitamin D levels and it has potential for predicting cardiovascular risk (24). The idea of the vascular-bone axis highlights the relationship between abnormal calcium deposition in vessel walls and accelerated bone resorption, leading to vascular calcification. Numerous mediators connect vascular calcification with bone homeostasis, underscoring the importance of calcium deposition in coronary arteries during acute events. Clinical trials investigating vitamin D treatment, particularly in individuals deficient in vitamin D, have yielded conflicting outcomes. Despite the lack of definitive results in large trials and meta-analyses, More investigation is required to fully understand the intricate interplay between vitamin D, calcium homeostasis, and cardiovascular health (25).

Phospholipase A2 Associated with Lipoproteins

Phospholipase A2 (PLA2), an enzyme superfamily, plays a vital role in hydrolyzing phospholipids to release essential fatty acids involved in signaling inflammation and energy production. Lipoprotein-associated PLA2 (Lp-PLA2), a member of Group VII of the PLA2 superfamily, is associated with both LDL and HDL in the bloodstream. While initially identified as platelet-activating factor acetyl-hydrolase, Lp-PLA2 is implicated in plaque development, accelerating atherosclerosis, and forming necrotic cores. Elevated levels of Lp-PLA2 have been independently linked to increased risks of stroke and coronary artery disease (CAD). Studies utilizing mouse models suggest that reducing the expression of Group VII PLA2 genes decreases atherosclerosis burden and inflammation, indicating that Lp-PLA2 could be a potential therapeutic target (25). However, clinical studies investigating the use of darapladib, the most advanced Lp-PLA2 inhibitor, did not demonstrate significant benefits for patients with stable CAD or ACS. Despite challenges in translating preclinical potential into successful clinical trials, the role of Lp-PLA2 as a cardiovascular risk marker remains significant (26).

ACS Genetics: The Various RNAs

The biology of the heart relies significantly on microRNAs (miRNAs), the dysregulation of which has been linked to several illnesses, such as CAD. Certain cardiac miRNAs, such as miR-133a and miR-499, hold promise as biomarkers for myocardial infarction (MI), enhancing diagnostic accuracy. MiRNAs exhibit a complex interplay with atherosclerosis, impacting processes such as inflammation, smooth muscle cell homeostasis, and endothelial senescence. Conversely, miRNAs associated with inflammation, like miR-181c and miR-362, may heighten plaque susceptibility. However, caution is warranted in interpreting miRNA research due to potential biases in sample processing, platform selection, and a lack of standardization (27). Cellular functions are significantly influenced by long non-coding RNAs (lncRNAs) in cardiovascular disorders, with dysregulated lncRNAs detected in patient plasma samples and cardiac tissue following myocardial infarction (MI), suggesting potential diagnostic utility. Nevertheless, comprehensive research and standardization efforts are necessary to establish lncRNAs as reliable diagnostic biomarkers (28). Certain circRNAs, such as circ-tetratricopeptide

repeat domain 3 (circ-Ttc3) and Cdr1as (CiRS-7), play regulatory roles in myocardial infarction (MI), influencing processes like cell death, mitosis, and apoptosis. However, due to the limited understanding of circRNA production and function, their clinical application remains challenging, necessitating further research. Nonetheless, emerging evidence suggests that circRNAs could serve as promising therapeutic targets by aiding in myocardial recovery post-MI (29).

CONCLUSION

In conclusion, the landscape of research in acute coronary syndrome (ACS) has witnessed significant strides in understanding the complex interplay of various factors contributing to its pathogenesis and progression. The field is still developing, with new actors like long non-coding RNAs (lncRNAs) and circular RNAs (circRNAs) replacing more established indicators like cholesterol and plaque composition. Despite advancements in therapeutic interventions and diagnostic tools, challenges persist in translating promising pre-clinical findings into consistent clinical benefits. The intricate web of genetic, metabolic, and inflammatory pathways involved in ACS underscores the need for comprehensive and personalized approaches to patient care. As we delve deeper into the molecular intricacies of ACS, the pursuit of innovative strategies and a deeper understanding of the multifaceted nature of this cardiovascular condition will be critical for improving patient outcomes and addressing the global burden of cardiovascular diseases.

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Review Article

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MYTHS AND FACTS OF STABLE ANGINA

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ABSTRACT

Stable angina, characterized by chest pain from decreased blood flow to the heart, is a typical sign of CAD. Stable angina is a common illness, but there are many misconceptions about it, including its origins, symptoms, and available treatments. The purpose of this review is to dispel these myths and offer factual data to enhance our comprehension and treatment of stable angina. Although epicardial coronary stenoses account for over half of angina cases, the symptoms can also be caused by other conditions such microvascular dysfunction or spasms in the epicardial arteries. For people with stable angina, a variety of drugs have been demonstrated to enhance their quality of life and long-term results. Only when the best medical therapies are unable to effectively control the symptoms are revascularization techniques taken into consideration.

KEYWORDS: Angina, CAD, Anxiety, Oxygen, Heart rate.

INTRODUCTION

Angina, which frequently results in feelings of discomfort, pressure, or tightness in the chest, can happen when the heart doesn't obtain enough oxygen. It's critical to realize that angina is a warning indication of a more serious problem rather than an illness in and of itself. Ischemia basically occurs when there is insufficient oxygen-rich blood in a portion of the heart muscle, usually as a result of constricted or blocked coronary arteries. Angina can mimic a heart attack and is frequently linked to coronary heart disease even though it is not a dangerous for life condition in and of itself. It's critical to see a healthcare provider if you suffer from abrupt, chronic angina that doesn't go away with rest or medicine. Angina comes in a variety of forms, including (1).

Stable Angina: When the heart must work harder than normal, such during exercise, stable angina develops. This kind often lasts five minutes or less and has a consistent rhythm. Although the soreness usually goes away with rest or therapy, it might last for months or even years.

Unstable Angina: Even while you're at rest, this kind of angina can strike without warning and without warning. It is mostly brought on by atherosclerosis, A medical disorder marked by the accumulation of plaque, which impedes the heart's functionality in pumping blood. The soreness, which frequently becomes worse over time and lasts longer than five minutes, may continue even after rest or medicine. Since unstable angina might be a warning of an imminent heart attack, anybody suffering abrupt angina should get medical help right once.

Coronary microvascular disease (MVD): The smaller coronary arteries are impacted by coronary microvascular disease (MVD), which is associated with microvascular angina. People may also have sleep issues, exhaustion, poor energy, and shortness of breath in addition to chest discomfort. Microvascular angina usually persists for 10 minutes or more, in contrast to stable angina.

Prinzmetal Angina: Also referred to as variant angina, this uncommon form of the condition frequently manifests while at rest, especially in the early morning or during night. It is brought on by coronary artery spasms, which can be brought on by a number of things, including stress, certain drugs, smoking, cocaine usage, and cold exposure. Despite being a chronic illness, medicines can successfully manage it.

Signs and Symptoms: Angina can cause a variety of chest pains, most typically beginning below the breastbone. Pain, tightness, weight, pressure, squeezing, or scorching are some examples of these

feelings. Other parts of the body, including the throat, back, arms, shoulders, neck, mouth, and teeth, may also experience discomfort. Other symptoms include be weakness, perspiration, heartburn, indigestion, cramps, and nausea and dyspnea. The kind of angina determines how long these symptoms last.

Women's Symptoms: Angina can strike anybody and is frequently brought on by coronary heart disease (CHD) or myocardial infarction (MVD). However, women may have distinct symptoms since MVD is more prevalent among them. Women may experience nausea, vomiting, exhaustion, shortness of breath, and stomach pain in addition to chest pain. It's crucial to keep in mind that cardiovascular disease is the primary cause of mortality for American women, and it disproportionately affects African American women (2).

Risk Factors: Stress, heavy drinking, and recreational drug usage can all cause angina, exposure to smoking-related particle pollution at work, for example, very little action A poor diet caused cholesterol levels to rise. Being overweight or obese For women over the age of 55 and males over the age of 45, hereditary factors are responsible for diseases such as anemia, metabolic syndrome, diabetes, low blood pressure, and heart disease. certain medical procedures and treatments.

Stable Angina

Angina's stability Brief episodes of chest discomfort, tightness, pressure, or squeezing are indicative of stable angina. Frequently, stable angina serves as an indicator of coronary heart disease, wherein obstructed arteries prevent adequate blood flow to the heart. The discomfort experienced is attributed to ischemia, which refers to a reduction in blood supply to the cardiac muscle. Individuals may feel pain during exercise or stressful events, although such episodes generally resolve rapidly. This condition is also known as angina pectoris. Angina discomfort may indicate the imminence of a heart attack (3).

In the context of coronary heart disease, stable angina (SA) is a prevalent clinical feature that affects between 2–4% of persons in western European nations. Angina has a substantial influence on quality of life (QoL) in people with cardiovascular disease (4-5) and is inversely connected with the number of angina episodes (6). SA still significantly reduces many people's quality of life and causes significant impairment, despite improvements in interventional cardiology and several successful pharmacological therapies (7). Due to the difficulty in diagnosing angina, clinical decisions rely mostly on the physician's assessment of the symptom load (8). Regretfully, opinions among medical professionals on the severity of the disease and how it affects patients' quality of life frequently diverge (9). A significant portion of patients, even those who have angina often (≥ once a week or daily), are believed to have angina that is successfully managed by general practitioners (GPs), according to CADENCE study (7). In a cross-sectional observational research, Quintar discovered that 43.3% of participants did not report having angina symptoms. Physicians reported significantly fewer anginal episodes, whereas patients with more accurate diagnoses had significantly greater rates of revascularization, hospitalizations, diagnostic testing, and drug escalation (10). These findings imply that the doctor and the patient disagree on the severity of the symptoms, which might negatively impact clinical therapy and the patient's quality of life. Experts may take into account a number of factors when assessing how the sickness affects certain people. Despite the fact that women experienced a more severe kind of angina than men, doctors were unable to distinguish any differences between the diseases of men and women (9).

Signs of Angina Pectoris or Stable Angina: Chest pain, often characterized as a squeezing or pressing sensation, is the main sign of stable angina. Some people feel as though their chest is full, while others feel as though it is tight or uncomfortable. Although every person's experience is unique, the pain is usually very temporary. The chest may remain the site of the discomfort during an episode, thus, the sensation of pain may propagate to the arms, shoulders, jaw, and neck areas. Fatigue, light-headedness, dyspnea, fast breathing, nausea, palpitations, sweating, and anxiety are other symptoms that may coexist with stable angina. These episodes frequently happen while you're exerting yourself or doing things like climbing stairs. They are more often in the morning, however they can occur at any time. Since the symptoms tend to follow a predictable pattern, individuals with stable angina may find that future episodes are less alarming once they have experienced them before. (4-5, 11)

Coronary heart disease: Because they share certain risk factors, stable angina and coronary heart disease (CHD) are closely linked conditions. One important underlying issue that fuels these symptoms is atherosclerosis. The condition known as atherosclerosis is marked by the buildup of plaque within the arteries, leading to their constriction. This plaque, which is made up of fats, cholesterol, and other substances, inhibits blood flow by adhering to the artery walls. Both stable and unstable angina can be caused by blood clots that develop in these constricted arteries. These clots can reduce the amount of blood that reaches the heart by blocking the artery entirely or

partially. Coronary heart disorder (CHD) and stable angina are caused by a number of risk factors, such as an elevated level of LDL (bad) cholesterol, a deficit of high-density lipoprotein, or HDL, cholesterol, smoking, obesity, diabetes, hypertension, and a family history of heart disease (6, 12-13).

Reasons for Angina Pectoris and Its Impact: Angina pectoris, which leads to myocardial ischemia, the two potential causes of this imbalance are either an increase in oxygen demand or a reduction in the flow of oxygen (due to decreased coronary blood flow, anemia, or other conditions that impair the blood's ability to carry oxygen). Because atherosclerotic coronary plaque narrows the arterial lumen, it lowers coronary reserve and increases the oxygen demand on the heart, making it the most common cause of this imbalance. Sometimes, even when there are no noticeable coronary blockages on an angiography, people may nevertheless have ischemic symptoms and tests that show ischemia. Abnormalities in the coronary circulation, such as microvascular malfunction in the heart or vasospastic angina, may be the cause of this (14- 15).

Heart attacks and other acute coronary syndromes are frequently brought on by an abrupt reduction in blood flow, which happens when an atherosclerotic plaque ruptures or coronary thrombosis causes a blood clot to develop in the artery (16). Numerous techniques, such as revascularization procedures, lifestyle changes, and medications that can assist manage symptoms and improve long-term results, can be used to treat chronic stable angina.

Commonly Held Myths and the Truth about Angina

A condition known as angina, which is a condition marked by chest pain or discomfort that results from a reduction in blood circulation to the heart muscles. It usually means that coronary artery disease or another heart issue is present. Unfortunately, a lot of misconceptions exist around angina that can cause miscommunications and unnecessary stress. In order to provide accurate information and promote a better understanding of angina, we shall dispel some of the most common misconceptions about the condition in this blog post.

Myth 1: A heart attack is the same as angina.

Fact: Although chest pain is a common feature of both angina and heart attacks, they are two different illnesses. Angina is a momentary pain or discomfort brought on by the heart muscles not receiving enough oxygen-rich blood flow. In contrast, a heart attack happens when the heart's blood supply is totally cut off, permanently harming the heart muscle. Angina is not the same as a heart attack, even if it may be a sign of heart issues.

Myth 2: Angina always signals a heart attack is about to happen.

Fact: Angina can be brought on by coronary artery disease as well as other underlying heart disorders. However, angina is not necessarily a sign that a heart attack is imminent.

Myth 3: Angina is only a problem for the elderly.

Fact: Angina is often thought to primarily affect older adults; however, it can also impact younger individuals. Numerous factors, including smoking habits, increased cholesterol, diabetes, obesity, hypertension, and a family carrier with heart disease, can lead to the early development of this condition.

Myth 4: Severe chest pain is a constant symptom of angina.

Fact: Chest discomfort is a frequent symptom of angina, though its kind and severity might vary. Some people may sense a pressure-like sensation, while others may have pain in their back, shoulders, arms, jaw, or neck. Shortness of breath, nausea, fatigue, and dizziness are other signs of angina. It is vital to acknowledge that not all chest pain corresponds to angina, and any form of chest discomfort warrants immediate evaluation by a healthcare provider.

Myth 5: Angina is a trivial health concern.

Fact: Angina must not be dismissed as a minor problem. It is indicative of a serious underlying heart condition that, if neglected, could have dire consequences. The occurrence of angina suggests that there is not enough oxygen reaching the heart, thereby elevating the risk of a heart attack or other complications. Early identification, suitable treatment, and In order to effectively manage angina and reduce the risk of developing heart disease in the future, lifestyle changes are essential (17).

The Prospects for Individuals with Chronic Angina: For those with stable angina, the prognosis may differ even if the annual mortality rate may be close to 3.2%. Among the factors influencing the long-term prognosis are comorbidities, exercise tolerance or capacity, Systolic performance of the left ventricle and the degree of severity associated with coronary artery disease (CAD) (18).

The therapeutic use of nitrates, beta-blockers, and calcium: channel blockers has been established as effective in the treatment of angina. Beta-blockers and calcium channel blockers also demonstrate comparable efficacy to nitrates in the management of this condition (19). Oral nitroglycerin spray and sublingual nitroglycerin tablets can reduce the risk of MI and

increase exercise tolerance due to their rapid absorption. One of the most frequent side effects of nitrate use is headache, which can get so intense that the medication must be stopped (20). Letting extended periods of time pass without nitrate to reduce nitrate levels prior to the subsequent dosage might help avoid tachyphylaxis, or tolerance to continuous nitrate consumption (21-22).

Because of its negative effects and propensity for tachyphylaxis, long-acting nitrates are presently considered second-line therapy, per guidelines. In the 1970s, beta-blockers (BB) were first used to treat angina and hypertension in the UK (23-24). In individuals diagnosed with stable angina, beta-blockers showed no significant effect on mortality or the occurrence of myocardial infarction. Conversely, in heart failure patients with diminished ejection fraction and a recent myocardial infarction, these medications may lead to reductions in both mortality and morbidity (25) Because of their side effects and propensity for tachyphylaxis, long-acting nitrates are currently considered second-line therapy, per the guidelines. BBs were initially used to treat angina and hypertension in the UK in the 1970s (26).

Nicorandil, Trimetazidine, Allopurinol, Ranolazine, and Ivabradine

As an adenosine-sensitive potassium channel opener that incorporates a nitrate element, Nicorandil contributes to the enhancement of coronary blood flow and serves as a preventive agent against coronary artery spasms. Its clinical approval in Japan and various European countries has been substantiated by numerous trials involving patients with stable angina (27). However, because placebo-controlled trials have not shown that it is effective in treating angina, it is not approved for use in the US or Australia. It is used in Europe either in conjunction with other antianginals or as a substitute for nitrates (28). A piperazine derivative called ranolazine works well when taken orally (29), Studies conducted on animals have provided insights that suggest a reduction in the targeted variables intracellular calcium excess by inhibiting late sodium inward current following ischemia (30). When compared to a placebo, ranolazine is equally efficacious as atenolol in treating ischemia and angina (31-32).

Further, it slows the onset of exercise-induced MI and increases treadmill walking duration for angina patients (33). Ranolazine has not, nonetheless, been demonstrated to be helpful in treating ladies with microvascular angina when contrasted with a placebo (34).

Ivabradine inhibits the sinoatrial node current, which lowers heart rate. Because ivabradine's effects are less pronounced at lower heart rates, bradycardia is less prevalent among its users. Because it is use-dependent, greater heart rates are where its effects are most noticeable (35). In contrast to atenolol alone or other BBs, studies have demonstrated that ivabradine, when administered in conjunction with atenolol, considerably enhances exercise duration and lowers angina frequency without inducing severe bradycardia (36). Nevertheless, individuals with severe symptoms may still have symptomatic bradycardia as a side effect of combination treatment. In individuals with stable angina without heart failure, However, in a subset of people with severe angina, it did not function as effectively as a placebo (37).

Antianginal Combination Therapy: Mono therapy often performs as well as combination therapy comprising two or more medications when given at the appropriate dosage (35). There aren't many well-designed studies that show using one class of antianginal drugs together is better than taking another (38). Combining CCB or a long-acting nitrate with BB therapy is often beneficial since it reduces MI, improves exercise tolerance, and decreases the incidence of angina (37). It has been shown that BB and ivabradine function effectively together for patients whose heart rates are higher than 60 BPM, despite safety concerns (35). Prolonged release ranolazine functions effectively either by itself or in combination with BB or CCB, as was previously noted. Additionally, it has been shown that trimetazidine functions effectively when combined with earlier antianginal drugs (39).

DISCUSSION

One prominent symptom of coronary artery disease is stable angina, which arises when the heart muscle lacks adequate oxygenated blood owing to the reduction in the diameter of coronary arteries. Patients frequently report chest pain or discomfort that may radiate to the arms, shoulders, neck, or jaw. The determination of a diagnosis is accomplished through a careful examination of the patient's medical history, an exhaustive physical examination, and the administration of specific diagnostic tests, electrocardiograms (ECGs) and stress tests. Treatment approaches often include lifestyle adjustments. The best treatment for coronary heart disease is a comprehensive strategy that lowers the risk of thrombosis and stops the development of atherosclerosis. The latest ISCHEMIA study revealed that just 41% of patients met all basic goals, demonstrating our continued poor success rate in optimizing risk factor reduction in those with acute heart failure who are stable. Success rates are probably far lower outside of the exacting setting of clinical trials.

More funds and incentives should be set aside for better secondary prevention as a stronger emphasis on reaching preventative objectives in patients with CHD would significantly affect patient outcomes and hospitalization rates. According to the ISCHEMIA study, revascularization is ineffective until angina becomes intolerable even with OMT, Even a tiny percentage of high-risk individuals with a significant ischemia load do not benefit from revascularization. Since patients with severe heart failure, unprotected left main disease, and agonizing angina were not included in ISCHEMIA, our evaluation may have been designed to identify individuals needing revascularization in addition to an initial OMT approach (16, 12-13).

An arterial circulation-affecting systemic illness that is more severe in localized places is called atherosclerosis. The existing framework for ischemia testing may no longer be relevant from an imaging perspective. Findings from recent studies such as COURAGE, PROMISE, SCOT-HEART, and ISCHEMIA indicate that anatomical imaging is more effective than functional testing for assessing inducible myocardial ischemia in the risk evaluation and treatment of patients with suspected or confirmed coronary heart disease (CHD). A considerable amount of evidence suggests that the extent of atherosclerotic disease plays a more pivotal role in the risk of CHD than the degree of inducible ischemia itself. In the PROMISE study, nonobstructive CHD was detected in 55% of participants, and this condition accounted for 77% of cardiovascular deaths and myocardial infarctions during follow-up. This presents a significant opportunity to address the condition early in a substantial population with undetected CHD, (14-15, 40).

CONCLUSION

To sum up, people with stable angina are still at high risk even with a number of advancements in treatment. In example, a worse quality of life and more hospitalizations result from inadequate management of angina symptoms. It has been shown that some medications can improve prognosis and lower the risk of serious adverse cardiovascular events. However, because to their varied effects and behaviors, antianginal drugs enhance quality of life without overtly improving prognosis. Comprehending the truths and misconceptions surrounding stable angina is essential for effective CAD therapy and prevention. By clearing up misunderstandings and sharing correct information, medical professionals may better educate patients and enhance results. The burden of stable angina and its associated repercussions must be reduced, and this requires more research and patient education.

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Review Article

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CONCEPT AND REQUIREMENTS OF ESTABLISHING GREEN LABORATORIES: SCOPING REVIEW

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ABSTRACT

Green laboratories are innovative research environments designed to prioritize sustainability and environmental stewardship. These facilities aim to minimize ecological footprints by integrating energy-efficient designs, resource conservation, waste reduction, and fostering a culture of sustainability. This review examines the core principles of green laboratories and outlines the requirements for their development. It delves into advancements in infrastructure, operational strategies, cultural transformations, and technological solutions. Furthermore, challenges such as high initial costs, resistance to change, and regulatory complexities are explored. Highlighting success stories and providing a forward-looking perspective, this review aspires to guide global efforts in adopting sustainable research practices and catalyze a paradigm shift toward environmentally conscious science (1-3).

KEYWORDS: Sustainable Practices, Laboratory Sustainability, Energy Efficiency, Waste Reduction, Green Building Standards

INTRODUCTION

In the face of increasing environmental concerns, institutions worldwide are under mounting pressure to integrate sustainability into their operations. Scientific laboratories, which are known for their high energy consumption, resource use, and waste generation, present a unique challenge in this transition. Traditional laboratory practices often involve extensive energy use, reliance on hazardous chemicals, and significant waste production, making the need for sustainable alternatives critical. (4). As demand grows for environmentally responsible practices across industries, green laboratories emerge as a key solution, aiming to align scientific research excellence with ecological sustainability. Green laboratories are designed to reduce their environmental footprint while maintaining the integrity and innovation of scientific work. The shift toward greener practices in research environments is not just a matter of compliance with environmental standards but also a proactive effort to support broader global sustainability goals (5). In this context, green laboratories seek to meet the United Nations Sustainable Development Goals (SDGs), particularly those related to responsible consumption, climate action, and sustainable innovation. By adopting green building standards, energy-efficient technologies, and eco-friendly materials, laboratories contribute to the achievement of SDGs while ensuring continued scientific progress (6-7). This review will explore the key elements required to establish green laboratories, including essential infrastructure improvements, operational shifts, and cultural changes. It will focus on the transformative strategies that can drive sustainability in laboratory settings and outline the steps institutions can take to harmonize their research activities with ecological responsibility.

METHODOLOGY

A scoping review methodology was employed to systematically explore the existing literature on the topic of green laboratories. This approach was chosen due to its ability to comprehensively map the available evidence across diverse sources and identify key themes related to sustainable practices in laboratory environments.

DATA SOURCES

The review encompassed a wide range of sources to

ensure a thorough and diverse perspective:

Peer-Reviewed Journals: Academic research articles were selected from high-impact journals in environmental science, sustainability, and laboratory management.

Government Publications: Reports and guidelines issued by government agencies on laboratory sustainability were included to assess regulatory frameworks and policy recommendations.

Institutional Guidelines: Documentation from universities, research institutions, and laboratory networks, including internal sustainability strategies and green certification guidelines, were examined for best practices.

Case Studies: Real-world examples of laboratories that have successfully implemented green practices were incorporated to illustrate practical applications of sustainable strategies.

SEARCH STRATEGY

Comprehensive literature searches were conducted across multiple databases to ensure extensive coverage of the topic: PubMed, Web of Science, Scopus, Gray Literature: Additional sources were gathered from sustainability-focused organizations, including reports from non-governmental organizations (NGOs), industry white papers, and conference proceedings .Search terms used included combinations of keywords such as "green laboratory," "sustainable laboratory practices," "energy efficiency in laboratories," "waste reduction," and "environmental impact of research labs."

SELECTION CRITERIA

Articles were selected based on their **relevance to key themes**, including:

Sustainable Practices: Emphasis on energy conservation, waste management, water efficiency, and green chemistry in laboratory settings.

Infrastructure and Design: Focus on the physical environment, such as green building standards, energy-efficient lab equipment, and renewable energy solutions.

Policy and Regulations: Insights into institutional and governmental policies that drive or hinder the adoption of green laboratory practices.

Inclusion criteria were set to prioritize studies that offered detailed descriptions of laboratory interventions or strategies that have led to measurable improvements in sustainability.

DATA EXTRACTION AND ANALYSIS

Key data was extracted regarding the types of green practices adopted, the infrastructure changes implemented, and the impact on both environmental outcomes and research efficiency. Thematic analysis was conducted to identify recurring patterns and insights across the literature, with an emphasis on strategies, barriers, and best practices for creating sustainable laboratory environments. (8-10).

DEFINING GREEN LABORATORIES

Green laboratories are research environments designed to minimize their environmental footprint while maintaining or enhancing research quality and efficiency. These laboratories integrate a range of environmentally sustainable practices aimed at reducing resource consumption, waste generation, and energy use. The primary objective is to create a balance between scientific innovation and environmental responsibility, ensuring that laboratory activities contribute positively to both scientific progress and sustainability

1. Energy Efficiency

Energy consumption in laboratories is significantly higher than in traditional office spaces due to equipment and ventilation requirements. Green laboratories adopt multiple strategies to reduce energy use, including:

Advanced HVAC Systems: Modern heating, ventilation, and air conditioning systems with energy recovery ventilators (ERVs) and variable air volume (VAV) systems minimize energy waste while maintaining precise environmental controls.

High-Efficiency Equipment: Laboratories prioritize energy-efficient appliances, from ultra-low temperature freezers to LED lighting. ENERGY STAR-certified equipment is often used.

Renewable Energy Integration: Solar panels, wind turbines, and geothermal systems power laboratories sustainably, reducing dependency on fossil fuels.

Passive Solar Design: Buildings are designed to maximize natural light and heat during colder months and prevent overheating during warmer periods.

Smart Grid Technologies: Integrating laboratories with smart grids allows real-time energy monitoring and dynamic load management, ensuring energy is used only when needed. (11).

2. Water Conservation

Laboratories employ innovative approaches to minimize water consumption, especially since many processes rely heavily on water:

Efficient Fixtures: Low-flow faucets, dual-flush toilets, and water-efficient autoclaves significantly reduce water usage.

Rainwater Harvesting: Capturing and storing rainwater is a common practice, with water treated and used for non-potable applications like cooling towers and irrigation.

Closed-Loop Water Systems: These systems reuse water in cooling and cleaning processes, minimizing the need for fresh water inputs.

Process Optimization: For instance, water-saving techniques in chromatography and synthesis processes reduce water dependency in chemical laboratories. (12)

3. Waste Minimization

Laboratories produce various waste types, including chemical, biological, and electronic waste. Green laboratories emphasize:

Comprehensive Waste Segregation: Clear labelling and disposal protocols ensure proper segregation of hazardous, non-hazardous, and recyclable waste.

Safe Disposal Mechanisms: Collaborations with certified waste management companies ensure hazardous materials are disposed of without harming the environment.

Recycling Programs: Recycling materials like glass, plastics, and metals is integral, supported by innovative processes like solvent recovery systems.

Reduction of Single-Use Plastics: Many laboratories transition to reusable materials for pipette tips, test tubes, and containers. (13).

4. Chemical Management

Green chemistry principles underpin sustainable laboratory practices:

Hazardous Substance Reduction: Laboratories use alternative reagents and materials with lower environmental impacts, such as replacing traditional solvents with ionic liquids or biodegradable solvents.

Green Synthesis Pathways: Reaction pathways are designed to minimize waste and maximize atom economy.

On-Site Neutralization: Hazardous chemicals are neutralized or treated before disposal, reducing environmental contamination risks. (14).

5. Sustainable Procurement

Laboratories consider the entire lifecycle of equipment and materials to reduce their carbon footprint:

Lifecycle Analysis (LCA): This analysis evaluates environmental impacts from sourcing raw materials to manufacturing, distribution, usage, and disposal.

Eco-Friendly Supplies: Preference is given to products with certifications like LEED, ENERGY STAR, or FSC.

Vendor Partnerships: Laboratories collaborate with suppliers committed to sustainability, such as those offering take-back programs for used equipment.

Digitalization: Transitioning to electronic records reduces paper usage and waste. (15).

6. Cultural Adaptation

Green laboratories are only as effective as the people who use them. Establishing a culture of sustainability involves:

Training Programs: Educating researchers and staff on green practices, such as energy-saving protocols and safe disposal methods.

Incentive Systems: Recognizing and rewarding individuals or teams who implement effective sustainability measures.

Behavioural Change: Campaigns to encourage simple actions, such as turning off unused equipment or proper waste disposal.

Collaborative Efforts: Green lab committees ensure consistent implementation of sustainability initiatives. (16).

REQUIREMENTS FOR ESTABLISHING GREEN LABORATORIES

INFRASTRUCTURE AND DESIGN

Energy-Efficient Structures:

Alignment with Green Building Standards: Laboratories should meet recognized certifications such as **LEED (Leadership in Energy and Environmental Design)**, which promote sustainable site development, energy efficiency, water conservation, and environmental quality. LEED standards include using sustainable materials and integrating renewable energy solutions to achieve net-zero energy buildings. (17).

Passive Solar Design and Advanced Insulation: Structures should incorporate **passive solar heating** to leverage natural sunlight during colder months and shading mechanisms for cooling. High-performance insulation materials reduce energy losses and improve HVAC efficiency. (18).

OPTIMIZED VENTILATION:

Energy Recovery Ventilators (ERVs): These systems recover heat or cooling energy from exhaust air and use it to condition incoming fresh air, minimizing the energy needed for heating or cooling. (19).

Demand-Controlled Ventilation (DCV): Advanced

ventilation systems adjust airflow based on laboratory occupancy and activity levels, ensuring energy efficiency while maintaining air quality and safety. (20).

Sustainable Lighting:

LED Lighting: High-efficiency LED lights consume significantly less energy and have a longer lifespan compared to traditional lighting systems, reducing overall energy consumption and maintenance costs. (21).

Maximizing Natural Daylighting: Using strategically placed windows, skylights, and reflective surfaces to maximize daylight reduces reliance on artificial lighting.

Motion-Sensor Technology: Implementing sensors ensures that lights are only active when spaces are occupied, preventing unnecessary energy usage. (22).

Integrated Waste Management:

Facilities for Waste Segregation: Laboratory spaces should include dedicated zones for segregating general, recyclable, and hazardous waste to streamline waste management and disposal processes. Clear labelling and protocols ensure compliance. (23).

Sterilization Systems for Biohazard Waste: Autoclaves and advanced sterilization units can treat biohazardous waste on-site, reducing the need for external transportation and mitigating contamination risks. (24).

OPERATIONAL PRACTICES

1. Energy Management

Efficient energy use is critical for minimizing the environmental impact of laboratories.

Smart Meters: Smart meters track energy usage in real time, enabling laboratories to identify inefficiencies and optimize energy consumption. For example, identifying peak usage times can help reschedule non-essential energy-intensive activities. (25).

Strategic Scheduling of Operations: Activities such as running high-energy equipment (e.g., autoclaves or centrifuges) can be scheduled during off-peak hours to reduce energy demands and costs. Automating systems to shut down equipment when not in use further minimizes waste. (26).

2. Chemical Handling

Reducing chemical waste and minimizing hazardous exposure are pivotal aspects of sustainable laboratory management.

Centralized Inventories: Maintaining centralized chemical databases helps avoid duplicate purchases, ensuring optimal use of existing stocks and reducing waste due to expired chemicals. (27).

Microscale Experiments: Conducting experiments on a smaller scale reduces the amount of chemicals used, thereby decreasing waste production and exposure risks. This is particularly effective for teaching laboratories and initial experimental phases. (28).

3. Sustainable Procurement

Integrating sustainability into purchasing decisions ensures laboratories have a lower environmental footprint.

Collaboration with Eco-Conscious Suppliers: Partnering with suppliers committed to sustainability, such as those offering reusable or recyclable packaging, supports the green initiative. Vendor take-back programs for end-of-life equipment also reduce landfill contributions. (29).

Lifecycle Evaluation of Equipment and Materials: Considering the environmental impact of materials and equipment from production through disposal helps prioritize purchases that are energy-efficient, durable, and recyclable (30).

4. Water Efficiency

Water conservation is essential in laboratories, where many processes rely heavily on water.

Recycling Water Through Closed-Loop Cooling Systems: Closed-loop systems reuse water in cooling applications, drastically reducing freshwater requirements. These systems are particularly effective for equipment like chillers or cooling baths. (31).

Retrofitting Laboratory Equipment: Retrofitting older equipment, such as autoclaves, with water-saving technologies maintains operational efficiency while reducing water use. Low-flow fixtures and automated shutoff systems further enhance water conservation efforts. (32).

CULTURAL AND BEHAVIOURAL SHIFTS

1. Education and Training

Creating a culture of sustainability begins with knowledge dissemination and active participation.

Workshops on Sustainable Laboratory Practices: Regular workshops educate staff and researchers on the principles of sustainability, such as waste minimization, energy conservation, and chemical handling. Hands-on training ensures the adoption of best practices. (33).

Embedding Sustainability into Research and Curricula: Incorporating sustainability concepts into research design and academic programs fosters an

early commitment to eco-friendly practices among students and researchers. This includes designing experiments with minimal resource usage. (34).

2. Recognition Programs

Recognition and rewards encourage laboratories to commit to sustainability initiatives.

Incentivizing Sustainability Achievements: Laboratories achieving measurable goals-such as energy reduction or waste minimization-can be rewarded through grants, certifications, or public recognition. (35).

Green Certification Programs: Programs like **LEED** or My Green Lab Certification assess and validate laboratory efforts, creating a benchmark for others to follow. (36).

3. Collaborative Engagement

Fostering collaboration ensures a cohesive approach to sustainability across institutions.

Partnerships Among Stakeholders: Collaboration between researchers, facility managers, and sustainability advocates aligns operational strategies with environmental goals. (37).

Exchange of Best Practices: Platforms that facilitate knowledge sharing-such as conferences, forums, or online communities-help institutions implement proven sustainable solutions effectively. (38).

TECHNOLOGICAL ADVANCEMENTS

1. Digital Innovations:

Laboratory Information Management Systems (LIMS): Streamlining workflows with LIMS reduces reliance on paper documentation and enables efficient data tracking and resource allocation. (39).

Internet of Things (IoT): IoT-enabled devices monitor and control laboratory equipment remotely, optimizing energy use, maintenance, and operational efficiency. (40).

2. Green Chemistry:

Eco-Friendly Catalysts and Reagents: Transitioning to non-toxic, biodegradable reagents minimizes the environmental impact of chemical reactions. (41).

Processes Leveraging Renewable Resources: Incorporating materials like bio-based polymers and plant-derived chemicals supports the shift toward renewable resources in research and production. (42).

3.Renewable Energy Solutions:

Integration of Renewable Energy: Laboratories can adopt solar panels, wind turbines, or geothermal systems to power operations. Energy storage systems, such as batteries, ensure reliability even during off-peak renewable generation times. (43).

Challenges in Establishing Green Laboratories

1. Financial Barriers:

High Upfront Costs: Sustainable infrastructure and cutting-edge technologies often require significant initial investments. Balancing these costs with the long-term benefits of reduced operational expenses is a common hurdle. (44).

Justifying Costs to Stakeholders: Institutions must provide compelling cost-benefit analyses to gain stakeholder buy-in for sustainability projects. (45).

2. Behavioural Resistance:

Overcoming Reluctance to Change: Resistance among laboratory personnel stems from a lack of awareness or fear of disrupting established workflows. Tailored training and clear communication help mitigate these concerns. (46).

Building a Sustainability Culture: Sustained efforts are needed to embed green practices into daily operations, ensuring long-term adherence. (47).

3. Regulatory Hurdles:

Non-Aligning Policies: Existing regulations may not prioritize sustainability or may create additional compliance burdens. Institutions need to advocate for policy changes aligned with green initiatives. (48).

Aligning with Standards: Institutions must navigate local and national environmental laws while maintaining operational flexibility. (49).

4. Technological Constraints:

Adapting Existing Equipment: Retrofitting older equipment to meet sustainability standards can be expensive or technically challenging. (50)

Scaling Technologies: Ensuring that new sustainable technologies can meet the diverse and high-demand needs of laboratories remains a significant challenge. (51).

Case Studies

Academic Institution

An academic institution embarked on a comprehensive initiative to enhance the sustainability of its laboratories. Recognizing the high energy demands and waste generation typical of laboratory environments, the institution implemented targeted measures to address these challenges.

Key Initiatives

1. Energy-Efficient Retrofitting: The laboratories were upgraded with LED lighting systems, which consume significantly less energy

compared to traditional fluorescent or incandescent lights. Demand -Controlled Ventilation Systems were installed to optimize airflow based on occupancy and activity levels. This adjustment improved HVAC efficiency while maintaining safety standards for researchers and staff.

2. **Training for Sustainable Practices:** Regular workshops and interactive training sessions were organized to promote awareness and adoption of sustainable laboratory practices. Researchers were trained on techniques such as waste minimization, proper waste segregation, and reducing chemical usage during experiments.

3. **Integration of Green Policies:** The institution developed policies that embedded sustainability into daily laboratory operations, including guidelines for energy and resource conservation.

OUTCOMES

Energy Reduction: The retrofitting measures resulted in a 30% decrease in electricity consumption across laboratory facilities.

Waste Minimization: Improved waste segregation and recycling programs led to a 25% reduction in non-recyclable waste output.

Enhanced Sustainability Culture: Training sessions created a culture of responsibility, with faculty and students actively contributing to sustainability goals.

Pharmaceutical Industry

A leading pharmaceutical company recognized the environmental and economic impact of traditional laboratory practices. To address this, the firm implemented green chemistry techniques aimed at reducing hazardous waste, optimizing reaction efficiency, and promoting the use of sustainable materials.

Key Initiatives

1. **Optimizing Reaction Conditions:** Reaction parameters such as temperature, pressure, and catalyst use were refined to enhance energy efficiency and minimize unnecessary resource use. Computational modeling tools were employed to identify optimal reaction pathways, further reducing trial-and-error experiments.

2. **Reducing Solvent Use:** The firm transitioned from traditional organic solvents to environmentally benign alternatives, such as water or bio-based solvents, where applicable. Recycling systems for solvents were introduced, enabling the recovery and reuse of materials in multiple reaction cycles.

3. **Adoption of Atom Economy Principles:** Processes were restructured to maximize the incorporation of raw materials into the final product, reducing byproducts and waste. (54)(

Outcomes

Sustainability Impact: The implementation of green chemistry principles reduced the firm's hazardous waste output by 40%, significantly decreasing the environmental burden.

Cost Reduction: Solvent recycling and improved reaction efficiency lowered operational costs by 15%, showcasing the financial benefits of sustainable practices.

Industry Recognition: The company received accolades for its commitment to sustainability, enhancing its reputation among stakeholders and clients.)(55).

Government Research Facility

A prominent national research laboratory, recognizing its significant environmental footprint, initiated a comprehensive sustainability program. The laboratory focused on integrating renewable energy systems and implementing advanced waste management strategies to align with national environmental goals.

Key Initiatives

1. **Installation of Renewable Energy Systems:** The facility deployed solar photovoltaic panels to generate clean electricity, supplemented by a geothermal heating and cooling system to reduce reliance on fossil fuels. Energy storage systems, including advanced batteries, were incorporated to ensure uninterrupted power supply during peak research activities.

2. **Robust Waste Diversion Program:** A multi-stream recycling system was established to segregate paper, plastics, metals, and electronic waste effectively. An on-site waste treatment facility was introduced, allowing for the safe disposal of hazardous materials while recovering reusable components. Organic waste was composted to support landscaping and community agricultural projects.

3. **Energy Monitoring and Optimization:** IoT-based energy management tools were installed to monitor real-time energy use, identifying opportunities for further efficiency improvements. (56)

Outcomes

Ecological Benefits: The renewable energy systems offset over 40% of the facility's total energy requirements, reducing carbon emissions significantly. Waste diversion efforts achieved a 50% reduction in landfill contributions, minimizing the

facility's overall environmental impact.

Operational Efficiency: The combination of renewable energy and optimized waste management led to a 20% decrease in annual operational costs, showcasing the economic advantages of sustainable practices.

Community and Industry Leadership: The laboratory's success inspired similar facilities to adopt comparable sustainability initiatives, cementing its role as an industry leader in green practices.)(57).

Future Directions

1. Standardizing Sustainability Metrics

Developing Universal Standards: Establish globally recognized sustainability metrics tailored to laboratory environments, encompassing energy usage, water conservation, waste reduction, and carbon emissions. Encourage the adoption of frameworks like ISO 14001 (Environmental Management Systems) and ISO 50001 (Energy Management) to create consistent benchmarks.

Real-Time Monitoring and Reporting: Integrate advanced energy and resource tracking tools to enable real-time monitoring of sustainability performance. Develop centralized platforms for institutions to share data, compare metrics, and identify improvement areas.

Outcome Tracking: Use standardized methods to measure progress toward institutional and global sustainability goals, such as net-zero emissions or zero waste targets. (58)

2. Exploring Emerging Technologies

AI and Automation: Utilize artificial intelligence for optimizing laboratory workflows, such as adjusting HVAC systems based on real-time occupancy or predicting maintenance needs to prevent equipment inefficiencies. Implement robotics to handle hazardous materials, reducing risks while minimizing resource wastage.

Advanced Recycling and Reuse Systems: Invest in on-site technologies for recycling solvents, chemicals, and plastics to create closed-loop systems within laboratories.

Innovative Materials: Explore the use of sustainable materials for laboratory equipment, such as biodegradable plastics or reusable alternatives to single-use items. Develop and adopt green reagents and bio-based chemicals to minimize hazardous waste. (59)

3. Fostering Global Collaborations

International Knowledge Sharing: Create global networks of academic, industrial, and governmental laboratories to exchange best practices, sustainability innovations, and case studies. Host conferences and webinars focused on advancing green laboratory technologies and methodologies.

Joint Research Initiatives: Encourage collaborative research projects aimed at addressing global challenges, such as sustainable energy solutions, water conservation methods, and eco-friendly chemical processes.

Funding and Policy Advocacy: Advocate for international funding mechanisms to support sustainability transitions in under-resourced laboratories. Align laboratory sustainability initiatives with United Nations Sustainable Development Goals (SDGs) to ensure broad alignment with global environmental priorities. (60)

CONCLUSION

Green laboratories play a pivotal role in integrating scientific innovation with environmental stewardship. By adopting sustainable practices, laboratories can significantly reduce their ecological footprint without compromising the quality and impact of scientific research.

Through a holistic approach encompassing:

1. **Sustainable Infrastructure and Design**: Energy-efficient buildings, advanced waste management systems, and the integration of renewable energy sources reduce operational costs while enhancing the sustainability of laboratory spaces.

2. **Technological Advancements**: The use of green chemistry, digital innovations like LIMS, and renewable energy systems not only reduce the environmental burden but also enhance laboratory efficiency, lowering costs and fostering innovation.

3. **Cultural Shifts and Education**: Embedding sustainability into the core of laboratory culture, through training programs and incentivizing sustainable practices, ensures that research teams actively engage in environmentally responsible behaviour.

4. **Collaborative and Global Engagement**: Partnerships between academic, industrial, and governmental institutions, alongside the standardization of sustainability metrics, will help propagate green laboratory practices worldwide.

The ongoing evolution of sustainable practices in laboratories demands a commitment to continuous innovation, collaboration, and data-driven strategies. This review highlights the crucial need for integrating

sustainability into all facets of scientific research, emphasizing that green laboratories are not just an environmentally responsible choice, but also a critical step toward shaping the future of scientific discovery. (61).

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Review Article

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ARTIFICIAL INTELLIGENCE IN PATHOLOGY: PRESENT AND FUTURE

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ABSTRACT

Artificial intelligence is the future and its use in pathology can create a tremendous impact on health care in different aspects.Its use is being initiated in the field of pathology and is on the rise with a increasing acceptance.Pathology services will undergo a paradigm shift due to the implementation of computational pathology and the use of tools based on AI, which would increase the effectiveness and would be able to satisfy the demands of the precision medicine age. Moving AI models from research to clinical applications has been sluggish, notstanding their success. There may be too much distance and neglect between the clinical setting and self-contained research. The merge of AI technologies into pathology has significantly impacted diagnostic precision and speed. Digital pathology platforms equipped with machine learning algorithms enable pathologists to analyze large volumes of histological images with enhanced accuracy. These systems have demonstrated remarkable capabilities in identifying subtle morphological features indicative of various diseases such as cancerous lesions or infectious conditions. Moreover, AI-driven image analysis tools can assist pathologists in differentiating between benign and malignant tumors by quantifying cellular characteristics beyond human visual perception.

Furthermore, AI-powered predictive models have the potential to refine prognostic assessments based on pathological findings. By leveraging vast datasets encompassing clinical outcomes and molecular profiles associated with specific diseases or tissue alterations, these algorithms can generate more tailored predictions regarding disease progression or treatment responsiveness. Through this approach,pathologists can offer more precise guidance on patient management while harnessing valuable insights from diverse sources for optimizing therapeutic intervention.The convergence of advanced image recognition techniques,virtual microscopy,and genomics data analysis could enable comprehensive profiling of individual disease phenotypes at an unprecedented level.In conclusion,AI technologies have already begun reshaping the landscapeof modern pathologypracticesthrough improved diagnostic capabilities,enriched prognostic insights,and envisaged pathways towards personalized healthcare delivery.The seamless integrationofAI-driven solutionsinto daily laboratory workflowswill undeniably propelpathologyintoa new era marked by heightened efficiencyand unparalleled precisionin diagnosticsand therapeuticsupport.

KEYWORDS: AI in pathology, digital pathology, machine learning algorithms, diagnostic accuracy, prognostic prediction.

INTRODUCTION

Traditionally pathology laboratories have been using automated analyzers and tissue processors, manual and automated staining techniques and manual to automated reporting methods (1). But with the advent of technology involving digitalized whole slide image (WSI), quite interest for pathologists has been generated worldwide (2).However still some robust workflow-related algorithms including automated information triage, AI assisted WSI annotations and readings along with quality assurance and control are being continuously studied and integrated into the system (3). Another advancement in AI is using image based diagnosis and its integration with predictive outcome, prognosis and treatment has generated interest in application of AI in daily practice (1-2).Convulational neural networks are the most commonly used image-based algorithms in AI (5). With the help of digitalized pathology WSI as input, a correlation can be done between the diagnosis, prognosis and treatment outcomes in patients (6). These algorithms establish connections between certain parameters and labels of interest, such patient survival or responsiveness to adjuvant/neoadjuvant therapy, as well as pathologist diagnoses and underlying molecular characteristics (7). AI has also been shown to improve accordance between practicing pathologists in a number of points, such as the

assessment anisokaryosis,degree of atypia, mitosis, and proliferation index (8). In the interim, these algorithms may be able to provide not only the visual evaluation of the important histology markers, but also detect subtle patterns that are missed by human eye, such as the cancer microenvironment (9). By integrating information from many different features, AI is able to make broad diagnoses. In order to provide potentially helpful insights about the progress of the disease, the prognosis of patients, or the possibility that a patient might respond to treatment, it may then link these qualities with additional patient-related data (10). As a result, AI technology can be used to improve the quality and quantity of reporting system overall, reducing turn around time for reporting, and objectively assess morphological elements. AI-assisted reporting of certain traits or lesions would also enable pathologists to focus on challenging cases, which will help them manage the increasing demands of their work (11). Currently many AI techniques are being in Pathology which are summarized in Table1.

Current AI Techniqes	Applications in Pathology
1. Convolutional Neural Networks (CNNs)	CNNs are in depth learning algorithm that are frequently applied to image analysis in pathology. They are ideal for tasks like tissue segmentation and cell classification because of their ability to recognize patterns and characteristics within images.
2. Generative Adversarial Networks (GANs):	Generator and discriminator neural networks, which make up GANs, collaborate to create new synthetic data by using training samples. GANs can be used in pathology to enhance pre-existing datasets or produce realistic tissue samples.
3. Reinforcement Learning:	Using this method, an AI agent is trained via trial and error to maximize rewards in a specific environment. Reinforcement learning could be used in pathology to improve treatment suggestions based on patient results and histology data.
4. Transfer Learning:	Utilizing expertise from one job or area to enhance performance on a similar task or domain with sparser data is known as transfer learning. By applying knowledge from comparable datasets, transfer learning can enhance the precision of illness classification models in the context of pathology.
5. Natural Language Processing (NLP):	In pathology, NLP approaches are utilized to process clinical notes, reports, and other textual data in order to extract pertinent facts regarding patient outcomes and illness diagnosis.

Table 1: Current AI Techniques and applications in Pathology

Following are the potential uses of AI in pathology along with future challenges in its implementation and uses:

1. **Algorithms for independent reporting:**

Potential use: These comprise AI systems that are capable of diagnosing patients without the need for pathologists' involvement. Examples include automated screening algorithms that are able to recognize normal tissue and generate automated reports on cases that meet the given criterias (e.g., biopsy from gallbladder, appendix, colon , gastric and other organs with normal morphology) (13).

Challenges: Though this seems like the simplest work, there are certain things to keep in mind, like further checks in circumstances where there are discrepancies. When creating these algorithms, the developers ought to take into account the diverse ranges of normal tissue to prevent overlooking some microcarcinoma or carcinomas in situ that can be overlooked in the screening process (14-15).

2. Tools for assisting in diagnosis:

Potential use: These comprise algorithms that evaluate one or more characteristics of the slides, such as the type, extent, and grade of the tumour (2,16)

Challenges: To make a diagnosis, pathologists usually evaluate several features and aggregate them all. The way that these single-feature diagnostic algorithms are integrated into the diagnostic process and how easily pathologists may use them should be of great concern to those who develop them. These AI algorithms' additional value will depend on several factors, such as the features to be evaluated, how quickly the findings will be available, and how easily the integrated algorithms may be used (15,17).

3. Automated measurement of particular characteristics:

Potential use: The automated evaluation of immunohistochemistry (IHC) staining of receptors along with their percentage of staining, intensity and other parameters for scoring in breast carcinoma has attracted a lot of interest. Attempts have also been made to simultaneously predict biomarkers involved in carcinoma breast directly from H&E slides recently (18). These algorithms also need to consider the cost-savings aspect and the extent to which the objectivity and accuracy of AI-assisted assessment adds value for clinical application. AI systems that are able to predict the expression of IHC markers from H&E results are very promising (19).

Challenges: In some circumstances, pathologists use auxiliary tests—IHC, most commonly—to aid in the patient's diagnosis. Selecting which IHC markers to employ is a decision that is made in part by the pathologist. The diagnosis on H and E , the morphology of tumour is correlated with the IHC expression of positive and negative expression of receptors, their pattern of involvement and intensity and percentage before a final diagnosis is rendered. An AI algorithm based only on H&E is unlikely to diagnose such diagnostically challenging cases (18,20). Additionally, sufficient evidence of the effectiveness of the specific targeted therapy that the AI techniques are meant to address must be present before these tools may be implemented in clinical practice.

4. Applications for prognosis and prediction

Potential uses: One of the most important useful and promosing applications of AI in pathology is the predicting the prognosis and outcome of patient along with response of treatment based on morphological features (21). Although the morphology, architecture, pattern, stromal features, atypical mitosis, necrosis and presence of lymphovascular /neurovascular invasion of tumor cells are associated with numerous variables, image-based artificial intelligence (AI) techniques can provide a completely novel categorization system based on treatment result and response. Additionally, they have the ability to connect a subset of characteristics from a wide range of characteristics pertaining to the pattern, architecture, stromal features, and presence of lymphovascular/neurovascular invasion of tumor cells (22). Additionally, they are able to associate each of these characteristics with specific clinically outcome goals, like the probability of metastasis, recurrence and response to treatment.

Challenges: There is a paucicity of research which establish a direct correlation between pathology images and its corresponding genetic profiles, tumour microenvironment and related prognosis along with treatment response to chemo and radiotherapy, despite some well studies pathological features including tumour grade, stage and subtypes. Also its quite diffucult to integrate various morphological parameters and microenvironment patterns into a single prediction score or index (15, 22- 23).

5. Combining genetic and genomic characteristics of patients

Potential use: AI technologies are being studied to correlate patient tumor genetic and genomic profiles with their morphological characteristics which would be helpful for understanding the underlying pathophysiology of the development of cancer along with choosing a targeted therapy (24-25).

Challenges: A considerable knowledge on the utility of the Next Generation Sequencing must be acquired before the algorithms can be applied for diagnosis. Also it is quite difficult to integrate such massive-scale genomic and genetic data such as next-generation sequencing (NGS) data with the imaging data and thus to establish any relation between them whatsoever. Even if such intergration of genomics with imaging is done , further developing and refining of such data for each lesion and individual tumour would pose a considerable challenge (20, 26).

6. Efficiency of the pathology workflow

Potential Uses: Use if AI can decrease largely preanalytics, analytic and post analytic errors increasing the overall turn around time . Also it can enhance the existing quality assurance and quality control programmes (27). This can be done by integrating the pathology workflow of a lab with the laboratory information management systems (LIMS) and Digital pathology image management system .Artificial intelligence algorithms are capable of detecting a wide range of defects on scanned slides including any processing fault, under and overstaining, staining quality , fixations artefacts and those tissue representation on the slide which add to the quality control. AI can triage cases on the basis of urgency and prioritise examination of such critical cases on priority, thus helping in the workflow management.Also it can eliminate the requirement for duplicate reporting of patients with subjective diagnoses (25-28).

7. AI in pathology training and education

Artificial Intelligence (AI) tools have the potential to enhance the education of the trainees , post graduates and also practicing pathologists. This can be done by labelling, automatic annotations and other interactive options that would provide a more practical and faster

method of learning . Also this can be used as a addition to the primary reporting of post graduates and making differential diagnosis of similar lesions. Also the undergraduates can be taught in a similar way. Since the scanned images can be uploaded to the software and can be assessed from anywhere remotely, this would further enhance the learning experience as it could be accessed from anywhere and anytime, even on mobile phones and help in dynamic learning (29).

Challenges: A multidisciplinary approach must be taken to build clinically practical and useful AI applications, with input from other stakeholders like surgeons and oncologists in addition to AI researchers and pathologists(28-29). It is important to take into account the detrimental effects of unreasonably high expectations for technology on its clinical application and utilization, as well as the trade-off between technology's performance and its practical benefits (2,5).

Future of AI and Word of Caution:

When sponsoring AI-based projects, healthcare institutions ought to take into account the technologies' clinical usefulness in addition to their analytical capabilities. The whole benefits of the algorithms, including their costs, hazards, and additional value when compared to current practice, are measured by the clinical utility (3,7). The evaluation of an algorithm involves comparing its predictions on a held-out set to a reference standard. As a result, a comprehensive strategy that takes into account all relevant factors is needed, including the algorithms' intended use case, algorithm performance evaluation, platforms that will be used in the future and present, the possible environment in which AI tools will be processed ,integrated and used, and any potential therapeutic benefits. The most reliable way to get this degree of confidence is usually through randomized control studies, which are difficult to conduct in the field of diagnostic pathology. To get accurate results, retrospective cohorts with superior data collection could be employed cautiously (11,23,29).

The usefulness and additional value of the suggested AI technologies, as well as any potential interruption to the current workflow, are other factors that must be taken into account. Regarding added value specifically, it is noteworthy that in addition to these algorithms' ability to integrate complex image-based data with genomic, radiological, and other clinical data, it is crucial to promote the use of these algorithms in routine clinical practice by measuring the number of diagnostic components they contain. (13,15,19). Artificial intelligence (AI) technologies can only be useful in clinical practice if they are built to function in areas where the highest need exists, such screening typical cases, detecting situations that require two reports, or elements where several components need to be evaluated simultaneously. The best and most beneficial use of this technology will be facilitated by these kinds of applications. Long-term storage is costly for most hospitals because WSIs demand hundreds of terabytes of space. Because of current guidelines requiring the storage time of glass slides for a longer time , expenses of storing diagnostic materials is increased (18, 23-24). Furthermore, AI systems will need access to radiography, WSI, genomic, and in situ hybridization images in order to support the multimodal use case. This will complicate the integration of these disparate data sources (5,7).

CONCLUSION

The implementation of AI technologies connected to pathology and computational pathology can be viewed as a gigantic shift that will alter the management of diagnostic services and enable them to fulfil the demands of the precision medicine era while also increasing their efficiency. The creation of pathology-based AI tools necessitates input from various allied branches of medicinal and surgery with majorly involvement of pathologists in order to improve the sustainability and implementation of these technologically advanced applications. Artificial intelligence (AI) can further optimize process streamlining. Enhancing the pathology service workflow's efficiency, having trainee and junior pathologists report, having pathologists report on time, using cost-effective diagnostic and prognostic/predictive algorithms, producing multidimensional pathology report outputs, and merging with genomic/genetic data. The future of precision oncology will benefit from this combination, which may lead to more individualized treatment regimens.

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Review Article

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STUDY OF PERCEPTION OF SENSITIVITY TOWARDS PATIENTS' CONDITION AMONG ALLIED HEALTH CARE UNDERGRADUATE STUDENTS USING PHOTOGRAPHY

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ABSTRACT

This project has been chosen to assess the insights of the students grounded on their sensitivity and perception towards the patients through a qualitative analysis. This research aims to employ photography under cultural activities parameter of the above concept to study the perception and the sensitivity of undergraduate students of Allied Health Sciences. Photographs can be found in almost every element of contemporary living. Pictures are used in magazines, periodicals, ads, billboards, broadcast, and the World Wide Web as a medium of communications and record. In this study participants were showed photographs of the patients in different situations and were asked to frame a write-up of 100 words based on their feelings, emotions, sentiments, empathetic outlook, imagination, professional viewpoint and thoughts. The data collection was based on the stratified random sampling method and was further analyzed using thematic analysis technique. Thematic Analysis can be used to investigate respondents' perceptions, experiences, standpoints, behavioral patterns, and approaches, including the influences and socio - cultural operations that impacts and frame specific circumstances in a clear, rolling as well as in a clandestine style.This paper studies how personal and social mores emphasizes the regulations that guide specific strategies, and perform the subjective and shared fabrication of explanation and the illustration of individual or community objects or experiences in specific writings for a particular scenario. Medical humanities (MH) are defined as "a collaborative and increasingly global enterprise that relies on the aesthetic and cognitive qualities of many domains such as literature, artwork, creative arts, theater, cinema, philosophy, morally acceptable judgment, and legacy in achieving medical education objectives." There is a huge urgency for a "compassionate" general practitioner who can utilize this empirical data and talents for every affected person while also possessing professionalism, interpretive competence, and intuition. This research aims to employ photography under cultural activities parameter of the above concept to study the perception and the sensitivity of undergraduate students of Allied Health Sciences. Photographs can be found in almost every element of contemporary living. Pictures are used in magazines, periodicals, advertisements, billboards, broadcast, and the World Wide Web as a medium of communications and record. This paper studies how personal and social mores emphasize the regulations that guide specific strategies, and perform the subjective and shared fabrication of explanation and the illustration of individual or community objects or experiences in specific writings for a particular scenario. In this study participants were showed photographs of the patients in different situations and were asked to frame a write-up. The data collection was based on the stratified random sampling method and was further analyzed using thematic analysis technique. Data coding and reduction was done, and the codes which were derived were: perception, experience, standpoint, behavioural patterns, approaches and socio-cultural framework.

KEYWORDS: Patient-Doctor interaction, Diagnostic Interview, Sensitivity ensuring patient wellbeing, Problem resolution, Communication Barrier.

INTRODUCTION

Aesthetics can be one of the means to study and evaluate their orientation towards the profession they are about to get in. The idea of aesthetic expression is one of the most essential aspects of the psychology of art and creative aesthetic appeal; however, it is also one of the most nebulous and inadequately described22. Orientation can be defined as the evaluation/assessment of individual's perception, experience, standpoint, behavioural patterns, approach and sociocultural framework towards their profession. In a broad sense, aesthetic expression can be thought of as a unique mental state that is fundamentally different from the way people think about day-to-day life. Cupchik and Winston (1996) say that sensory feeling is the result of a mental activity in which a person focuses on an object and pushes away other thoughts and feelings, even ones that are less important6. In an identical vein, artistic encounter was described by Ognjenovi (1997) as a unique type of psychological topic in association with a specific object that powerfully occupies the consciousness of the particular topic, overshadowing all other neighboring spheres as well as occurrences. Aesthetic circumstances and subjects of aesthetic involvement are described as being substantially distinctive from commonplace conditions and objects that are used in daily life in both of these descriptions2 & 24.

The medical humanities can facilitate healthcare providers understand problems from different vantage points, such as the visual arts, philosophy, literature, sociology or maybe psychology and history1. The term "medical humanities" is not universally agreed upon, but it frequently refers to an engineered standpoint that pulls on the expressive and erudite epistemological attributes of specialties like ethnography, art, medical ethics, theatrics or screenplay, cultural legacy, literary works, electronica, metaphysics, behavioral science, and social science3,7&18. Despite several efforts to describe the word "medical humanities," theoretical frameworks often fall into one of four main categories: pragmatic, inherent, analytical, and philosophical. Therefore, the intrinsic (or non-instrumental) justification is concerned with the possibility for curricula that incorporates a humanistic outlook to have a coherent benefit. As opposed to the pragmatic (or realistic) reasoning, this places more emphasis on information, abilities, and perspectives explicitly relevant to clinical settings (e.g., communications, compassion, storytelling ability and many more).13,17,19&26 Skill, instruction, and investigation in medicine are largely focused on treating specific individuals, and as each person is composed up of interwoven cognitive, economic, spiritual, and physiological components, societal and cultural factors also invariably have an impact on the health-care workers4. It is critical for the medical humanities community to identify the requirement for verifiable evidence of its efficacy in an age of result-oriented education and to also defend the cost of its implementation8. According to research, the integration of the medical humanities in Allied Health Science students' curriculum has positive effects on coping skills, improved sensitivity, intercultural skills, mental flexibility, collaboration, rationality, listening, interaction and empathy building.9 & 28 It is suggested that the decrease in empathy that has been seen in medical trainees can be fought with individual or group reflection. This will allow learners to make the transition from "the apprehension of altering their behaviours to transforming their particular sense of self, which means that they will propagate away from "executing the duties of treatment to demonstrating the qualities of a healthcare practitioner," and "from the continual procedure of developing themselves to the merged sense of 'being' a medical professional.(15,19)

According to the findings of Lindberg (2012), there are significant discrepancies between opinions of adequate job readiness and the perspectives of an exceptionally skilled professional. While clinical expertise and aptitudes are recognized as vital in job preparation, they were lacking in the views of the extremely proficient and practical doctor. Fundamental characteristics such as desire, inquisitiveness, willingness to collaborate, friendliness, competence, and reflectiveness, on the other hand, typified assessments of highly outstanding medical practitioners. These characteristics were also acknowledged as developing before or "beside" the official medical education curriculum21.

These days, medical humanities are an upcoming area which needs focus to develop further for employment of photography or paintings as the tool of analysis to study patient experience by engaging the students in the whole process of understanding and evaluating photographs or paintings to decode the perception and experience of patients16. The process involves giving photographs of doctor-patient interaction to students and asking them to evaluate and analyze them on set parameters to understand the over-all experience of the patients14. They learn practically what is happening in the environment of the hospital and how their patients respond to the atmosphere and behavior offered to them. Photo-analysis, also described as photograph evaluation, is the exploration of images to gather several forms of information, such as analyzing the content classification of almost everything that can be pictured. The method used by quarries and

tanneries discern dispersed information have altered is primarily a result of photo-analysis technologies. Photographic analysis is a popular tool that can be used to involve the students and create awareness among them to study key factors practically through which they can ensure the wellbeing of their patients by understanding and analyzing the neglected areas of patient experience12 & 23.

Methodology of employing Photography to study Patient Experience

This paper discusses a novel pedagogical method in which undergraduate students of Allied Health Sciences were given photographs to understand patient experience. The students are given direction by their curriculum that they should be able to understand the importance of the psychophysical condition of patients. They should be able to inculcate an understanding of patient and doctor behavioral patterns to assess and also evaluate and control the hazards related to perception, experiences, standpoint, behavior patterns, approaches and socio-cultural framework which are a part of doctor-patient relationship. The practical handling of patients is very important which relies on the student's ability to understand what the patient is experiencing at the hospital during his treatment. The students need to be taught through new tools of pedagogy in which they are made to study the above parameters through patient experience. One of the methods is to study the experience and wellbeing of the patients and their interaction with the doctors who are handling them, through photography as the tool of pedagogy to decipher behavioral patterns and the lacunas therein. One such method of pedagogy is the Medical Humanities approach, which comprises the following characteristics:

1. They use methods, concepts, and content from one or more of the humanities disciplines to investigate illness, pain, disability, suffering, healing, therapeutic relationships, and other aspects of medicine and health care practice.
2. They employ these methods, concepts, and content in teaching health professions students how to better understand and critically reflect on their professions with the intention of becoming more self-aware and humane practitioners.
3. Their activities are interdisciplinary in theory and practice and necessarily nurture collaboration among scholars, healers, and patients27.

The methodology involved studying the psychophysical condition of the patients and also by studying the empathy and compassion of the doctors towards them through active listening by doctors and content analysis of the written description by the students of the doctor-patient photographs given to them for analysis. The students were given the following questions while they viewed the photographs:

Q1. What do you see in the picture?

Q2. How do you feel about the participants?

Q3. What are your comments about the relationship that is visible among the participants?

The students produced a write-up based on one of the following photographs, to practically understand the doctor patient relationship, experience and behavior patterns in the respective photograph selected by them for analysis:

The photographs were displayed on the projector screen in front of 50 Undergraduate students of Allied Health Sciences. Before starting the analysis, the students were given instruction by the faculty that they should analyze any one of Photographs labeled as 1,2,3in order to study the experience of the patients in relation to their interaction which was visible in the said photograph which displayed patient-doctor interaction.

- A key finding of the present analysis enabled many themes out of the write-ups which were given by the samples. Various categories were jotted which included the 'perception', 'experience', 'standpoint', 'behavioural patterns', 'approaches' and 'sociocultural framework' under which 5 themes were derived on which mainly student had their orientation towards the patients.
- Theme 1 was 'Content Listening' which means that students believed that Patient-Doctor interaction' is an essential element. The statements like 'doctor understands the patient's symptoms' or 'patient is comfortably telling about his symptoms to the doctor' justifies the theme of 'Content Listening'. Content listening by doctors can improve the diagnosis. Passive listening by doctors can be hazardous towards the evaluation of actual patient condition.
- Theme 2 'Importance of Diagnostic Interview', which means that according to the students taking case study/ case history before the process of prognosis is fundamental and primary. Without proper diagnostic interview neither doctor can properly diagnose nor can prognosis be performed aptly, which will not lead to patient's healing. The statement from the write-ups which justifies this theme is 'doctors asked the history of the disease from the patient' or 'doctor asked about the previous encounters of the symptoms'.

- Theme 3 'Sensitivity among the doctors', this theme gives an understanding to the students that they have an idea about the profession they are soon going to be in and they have compassion and empathy. Students have sensitivity towards the patient's condition and they wish to treat them and enhance their wellbeing. The statements like 'prescribing the medicine and precautions to get rid of her problems' or 'doctor is ensuring the patient, that nothing serious has happened and he will calm down'. The understanding of the student at the subconscious level and determination of sensitivity towards the patient shows his belief in calming them down and therefore ensuring their wellness.
- Theme 4 'Problem Resolution', explains that students as doctors to believe in solving the problems faced by the patients. They want to address all the problems reported by the patient.
- Theme 5 delves into the nuances of passive listening. Listening to the patient actively will not only lead to better patient engagement, but also, better diagnosis after listening to the patient's immediate symptoms and health concerns.
- Theme 6 stems from the present sociocultural framework of Indian society. Being a 'high tradition culture', a gender divide exists, due to which there is a communication gap between the male doctor and female patient and vice-versa. These gaps need to be bridged to facilitate uninterrupted flow of communication.

S. No.	Framework	Identified Themes	Intentions Expressed by the students	Conclusion
1.	Perception	Sensitivity ensuring patient wellbeing	1. Doctor ensuring patient wellbeing. 2. "Doctor is looking calm as if nothing serious happened to the patient. Ensuring wellbeing	New perception of analysis of patients through the lens of aesthetics alongside practical learning and experience of the medical profession.
2.	Experience	Problem resolution	1. Patient is comfortable with the doctor- "telling her problem without any fear or hesitation"	The problem resolution is done through realization of the confluence of humanities and the medical profession and recognition of the same by students.
3.	Standpoint	Doctor faces many barriers in assessing patient condition	No barriers should be there between doctor and patients. Doctors should not be ignorant towards patient condition Doctor is approachable	The students realize that the doctors will diagnose the conditions better if they are closer to patients if they discover the importance of human condition.
4.	Behavioral patterns	Patient doctor interaction	-"Doctor is listening to patient's problem very carefully." T-"There is no barrier between the patient and doctor and patient is comfortable".	Content Listening by Doctors can improvise the diagnostics. Passive Listening by doctors is hazardous towards evaluation of actual patient condition.
5.	Approaches	Diagnostic Interview and Planning Prognosis	Passive Listening "Doctor was not diagnosing the issue properly." doctor asked the history of the patient" "genuine approach"	Casual Approach by doctors can lead to errors in diagnosis and displays a lack of professional attitudes.
6.	Sociocultural Framework	It does not matter. "she is treating gently and calmly"	"Patient is not able to tell her problem and doctor is writing his prescriptions".	Culture/ Gender oriented Cultural Framework- Female patient-male doctor-gender concerns are brought to the fore. The crisis of gender divide deters actual diagnosis due to gaps in communication because of gender and cultural barrier.

Table 1: Thematic Study of Patient-doctor Interaction

CONCLUSION

This emphatic exhortation to health care providers to welcome the "corner where arts and health sciences intersects" unveils both the already well-known humane and also a most newly understood imaginative or "artistic" side of the therapeutic interaction. This acknowledgement is aplaud able insofar as it flows, but by concentrating on desensitizing health personnel, researchers incur the danger of omitting the potential that the mingling of art and medical science may alter the very essence of clinical professional development9. Such conceptualizations are generally regarded as the medical humanities: a "multiplicative" outlook, in which a biomedicine that is largely unmodified is toned down in practice by the sensitive healthcare professional; and a "unified" perception, in which the phenomenon, objectives, and skillset of medical field itself are considered to be molded by the comprehension and alleviation of human physiological distress. This increasingly grandiose viewpoint requires that, if essential, the concise description of medicine be reevaluated in order to bring the experienced dimension of distress within their purview.

Instead of being seen as a collection of free spins to a primarily technical notion of medicine, the medical humanities can be seen as endemic to health care curriculum and profession. To assist Allied Health Sciences students' professional growth, medical training has underlined the significance of including medical humanities sessions within the curricula20. After years of becoming accustomed to the idiosyncrasies, errors, and conflicts of the patients' lamentable lives, the only thing that remains is a professional separation. It is at the intersection of art and medicine that medical professionals are able to reaffix them to the human condition and reawaken the feelings that inspire or frighten their sufferers. Every interaction that a healthcare provider has with a client involves not only a professional but also a philosophical and creative component5 & 11. The recognition of this creative self among the Allied Health Students is going to recreate a new perspective towards the examination and analysis of the patients10&25. This new angle of making the students sensitive towards aesthetics will add a humane dimension to the simple and practical examination of patients which lacks the human traits of empathy and sensitivity. This would make the medical professionals aware of the confluence of medicine and humanities to recognize the sufferings of their patients and their conditions while they would diminish the professional separation between the disciplines for achievement of the higher goal, which is inculcating a perception of sensitivity towards patient condition(29).

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Review Article

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THE GENETICS OF *CYP* GENE VARIANTS IN ASSOCIATION WITH POLYCYSTIC OVARY SYNDROME: A NARRATIVE REVIEW

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ABSTRACT

A multifactorial endocrinal condition, polycystic ovarian syndrome (PCOS) is typified by lack of ovulation, hyperandrogenism, and polycystic ovary shape. Although the exact dysfunctional physiology of PCOS is unknown, genetic and environmental factors, and disruption of the hypothalamic-pituitary-ovarian axis are the main causes of this condition. Hyperandrogenism, which manifests clinically as hirsutism, acne, and alopecia, is the hallmark of PCOS. The overproduction of androgen by the ovaries and adrenal glands results in hyperandrogenism. Women with PCOS have neuroendocrine system anomalies, including increased gonadotropin-releasing hormone pulse frequency and pituitary stimulation that produces more luteinizing hormone than follicle-stimulating hormone. When there is a relative deficiency in FSH, follicular growth is hampered, whereas excess LH increases ovarian androgen production. The LH imbalance: FSH promotes the growth of ovarian theca cells, which in turn increases steroidogenesis and ultimately results in hyperandrogenism in women with PCOS. Aberrant steroidogenesis has been linked to a number of genetic variables. The steroidogenic P450s gene variants that are involved in steroidogenesis are thought to be crucial in the generation of androgens in PCOS. By modulating their expression either up or down, CYP gene polymorphisms can exacerbate the hyperandrogenic phenotype in PCOS-affected women, hence raising androgen levels even higher. Further research is necessary to support this concept.

KEYWORDS: PCOS, Hyperandrogenism, CYP, CYP11, CYP17, CYP19.

INTRODUCTION

One of the most well-known hormonal problems is Polycystic Ovary Syndrome (PCOS). Affects 4% to 12% of women globally who are of conception age (1). Between 4% and 20% of people worldwide are thought to have PCOS (2). For women who are of generative stage, it is one of the most widely recognized endocrine dysfunctions (3). Significantly more Indian women than any other have PCOS. The combined commonness of PCOS was practically 10% when using the Rotterdam and Androgen Excess Society (AES) criteria; though, it was only 5.8% when utilising the National Institutes of Health (NIH) standards. (4). PCOS is a highly common conceptive endocrine condition that includes oligomenorrhea, polycystic ovaries, anovulatory infertility, hyperandrogenism, insulin blockage or hyperinsulinemia, and an increased risk of several metabolic illnesses (5). The overproduction of androgens in the ovaries that causes PCOS can result in major health problems such insulin resistance, obesity, endometrial cancer (6). The development and consequences of PCOS are significantly influenced by hyperandrogenism. Excess androgen may produce follicular dysplasia, the primary cause of anovulation, according to recent research (7). The disorder known as hyperandrogenism is characterised by a higher-than-normal level of androgens, or male hormones, in females. One of the primary side effects of PCOS is ovarian and extraovarian hyperandrogenism (8). Testosterone levels in PCOS patients will be significantly greater than average. The values of Sex steroid-binding protein (SSBP), androstenedione, dehydroepiandrosterone (DHEA), androgen, and SHBG are typically used to diagnose hyperandrogenism (9). High ovarian androgen levels are thought to be a classic sign of hyperandrogenism in PCOS, which impairs follicular maturation. This is because high androgen levels can negatively affect follicular growth, resulting in atresia. Although the ovaries are normally remembered to be the essential wellspring of androgen overabundance in PCOS,

research has shown that 20-30% of PCOS people additionally have raised adrenal androgen levels (10).

Because genetic factors predispose individuals to unusually high androgen production in ovarian tissue, they are also supposed to have a significant part in the progress of this condition. Here, we go over recent and past gene-associated discoveries in relation to the progress of knowledge about it. We are therefore providing an indication of the clinical consequences, role of cytochrome P450 (*CYP)* and its genetic part that intricate in the synthesis of biologically active steroid on hyperandrogenism, in PCOS patients.

Hyperandrogenism with PCOS

Ovulatory malfunctional, polycystic ovary morphology, and experimental or biological hyperandrogenism are two irregularities required for the finding of PCOS (11). Excessive androgen production in PCOS is caused by dysregulation of steroidogenesis in the theca cells as a result of both intra- and extraovarian causes (12). Adrenal hyperandrogenism is also caused by abnormal folliculogenesis, deregulation of a potential steroidogenesis gene, and increased peripheral cortisol metabolism (13). Hyperandrogenisms can also result from luteinizing hormone (LH) -stimulated theca cells, as shown in Figure 1; which are aromatized to oestrogen by follicular stimulating hormone (FSH) stimulated granulosa cells. This environmental change may result in anovulation and the polycystic ovarian stage (14).

Clinical features of hyperandrogenism

PCOS is characterised by hyperandrogenaemia, a biological trait. Acne, androgenic alopecia, as well as hirsutism, is the term for the masculine pattern of terminal hair on the body. This is among the primary features of it. Between 60 to 80% of PCOS-afflicted women have hirsutism (15). PCOS and hirsutism is linked to higher amounts of free testosterone in the blood and dihydrotestosterone, which is a more active form of testosterone. The furthermost dependable and constant sign for assessing experimental raised androgen levels is hirsutism. (16). The furthermost characteristic symptom of hyperandrogenism is acne vulgaris. It is more common in some ethnic groups than others; Indo-Asian women have been found to have the greatest frequency, while Pacific Islanders have the lowest. Pilosebaceous gland irritation is the cause of acne. Higher testosterone stimulates the generation of more powerful dihydrotestosterone, which promotes aberrant desquamation in follicular epithelial cells. Acne typically appears on face but can also appear on the back, chest, and shoulders (17). One more sign of the raised level of androgens that affects PCOS is alopecia, sometimes known as male pattern baldness. It is typified by miniaturisation, in which the terminal hair on the scalp region gradually changes into fewer, finer vellus hair by elevated testosterone levels, which cause male pattern of baldness (19).

Biochemical aspect of hyperandrogenism

The elevated levels of testosterone as well as other determined markers of hyperandrogenism, like luteinizing hormone (LH), free testosterone (FT), and FAI. There are two types of testosterones free and attached to proteins like albumin and SHBG. Normally, because there is less follicular stimulating hormone in the blood, only 1% of testosterone is released as free testosterone. The remaining 80% of androgen is bound to sex steroid binding protein, and 19% is bound to albumin (20).

Cytochrome P450

The production of a gene super-family, which presently has several members in species that produce CYPs, a family of haemoproteins that includes bacteria, vegetation, and wildlife. Approximately 40 distinct CYPs are found in humans, also they are essential because they catalyse processes in the biogenesis of steroid hormones, the oxidation of unsaturated fatty acids to intracellular messengers, the metabolism of drugs, fat-soluble vitamins, environmental pollutants, and other xenobiotics. Numerous different steroids are biosynthesised by cytochrome P450 systems, which also acting a part in the biogenesis of steroid hormones (21). The steroidogenic acute regulatory protein (StAR) facilitates the rate-limiting transport of cholesterol into the mitochondria, which is the first step in steroidogenesis. Pregnenolone, the initial precursor in the steroidogenic cascade, is produced there (22). As demonstrated in Figure 1 CYP11A1 (cholesterol side chain cleavage cytochrome P450), CYP17 (17a-hydroxylase), and CYP11B1 (113-hydroxylase cytochrome P450 or P450113) are among the up to six P450s involved in the multi-step pathways that produce steroid hormones. The sole distinction between CYP19 (aromatase cytochrome P450 or P450arom) and CYP11B2 (aldosterone synthase cytochrome P450) is that the genes are printed in italic. While glucocorticoids, mineralocorticoids, and androgens are predominantly produced by the adrenal gland, the gonads are the primary source of production for sex hormones, including oestrogens and testosterone. Two very thoroughly associated enzymes, CYP11B1 and CYP11B2, carry out the last steps in the production of cortisol, the primary glucocorticoid in humans, and aldosterone, the primary mineralocorticoid in humans. (23).

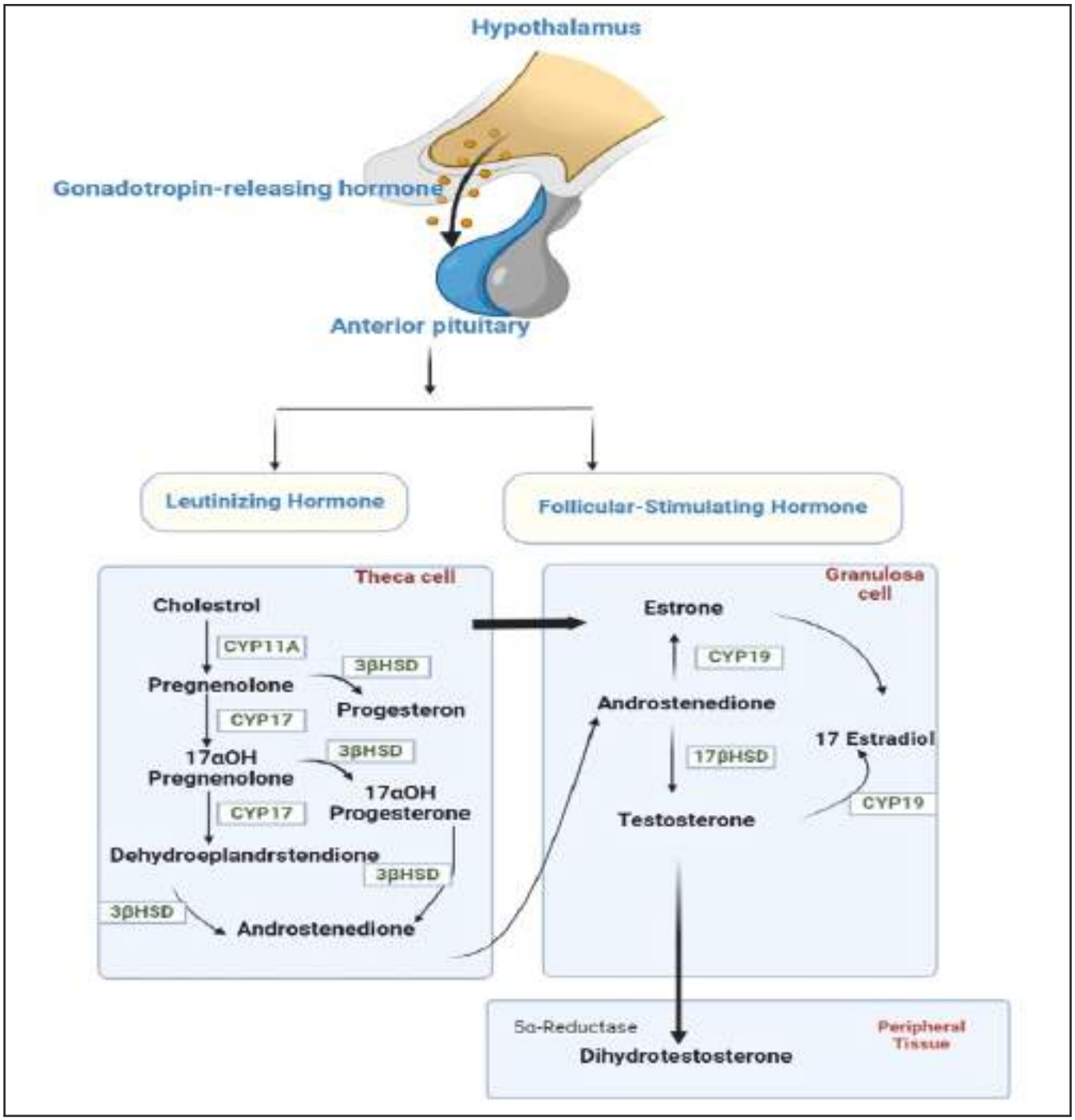

Fig. 1: Hypothalamic-pituitary-ovarian axis and Steroidogenesis (23)

Ovarian and Adrenal Steroidogenesis in PCOS

Excess androgens are thought to originate from the ovary as a result of dysregulated steroidogenesis, as describe in Figure 2. The key component of PCOS is hyperandrogenism. The hypothalamic-pituitary-gonadal axis, that affects steroidogenesis, is dysfunctional in patients. Steroidogenic dysregulation of theca cells in the ovaries increases the levels of circulating androgens. Furthermore, a hormonal imbalance results in an early disruption of follicular growth, which leads to infertility, polycystic ovaries, chronic anovulation, and amenorrhoea. Elevated levels of adrenal androgens, such as DHEA and androstenedione, have been seen in females with PCOS, as the ovaries are the core basis of androgen excess in the condition (24).

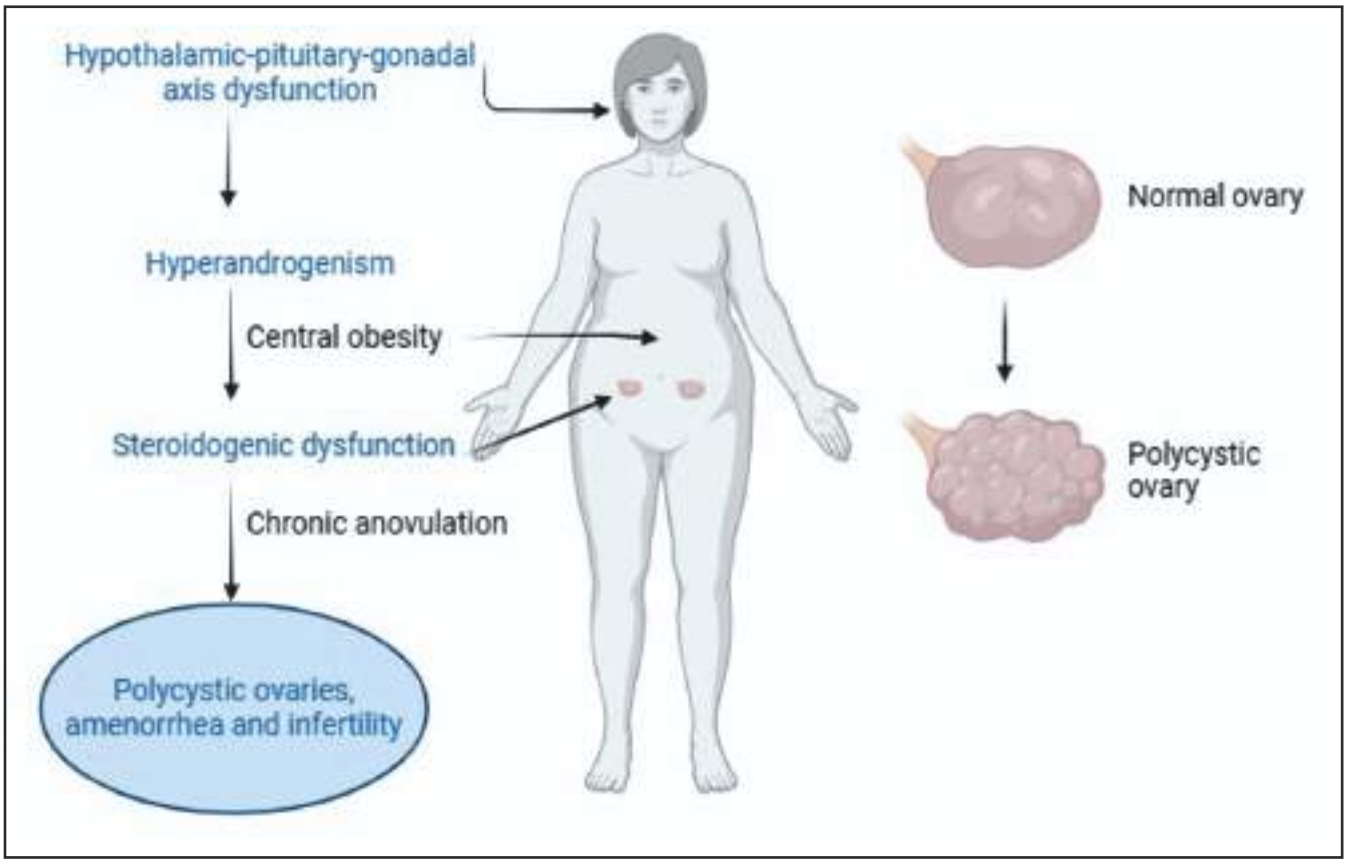

Fig. 2: Pathway that involved in the Pathophysiology of PCOS (24)

Major Genes Associated with Ovarian and Adrenal Steroidogenesis

The very usual endocrine disorder related with PCOS is an increased androgen level so, the hyperandrogenic state in PCOS is linked to heterogeneity in clinical features and genetic variants, suggesting the potential involvement of anomalies related to the steroidogenic pathway. PCOS candidates are thought to be genes that encode for enzymes implicated in the steroidogenesis. The most thoroughly researched genes among them are *CYP11, CYP17,* and *CYP19.*

CYP11

The most important phase in the synthesis of steroid hormones is catalysed by the cytochrome side-chain cleavage enzyme and it is encoded by the CYP11 gene, which is found at 15q24. This enzyme act as the rate-limiting in the alteration of cholesterol to progesterone (25). With ten exons and nine introns, it is about 30 kb long. In the synthesis of steroid hormones, its code for the cytochrome P450 superfamily enzyme cholesterol side-chain cleavage (P450 scc), which catalyses the first rate-limiting step in the conversion of cholesterol to pregnenolone and is found in the inner membrane of the mitochondria (26). This is mostly expressed in organs that are steroidogenic, such as the placenta, gonads, and adrenal cortex. Genetic variations in *CYP11A1* alter its expression, leading to certain hormone-related illnesses such as polycystic ovarian syndrome, endometrial cancer, breast cancer, and prostate cancer (27). It is hypothesised that variations in this gene show a crucial part in controlling the expression of *CYP11A1* through transcriptional up- or down-regulation, which results in increased or decreased androgen production (28). Numerous polymorphism investigations concerning the *CYP11* gene in relation to PCOS have been conducted. Numerous studies as shown in Table 1; have documented the correlation between a microsatellite polymorphism (TTTTA) in the *CYP11A1* promoter region and modified gene expression observed in PCOS. A strong correlation was found between PCOS risk and the *CYP11A1* penta nucleated repeat polymorphism in a study conducted by Reddy KR et al. (2014) (29). Shan B. et al. (2016) demonstrated a substantial correlation with PCOS in their study, which is consistent with our findings. The risk of developing PCOS was 2.5 times higher for those with the heterozygous genotype (30). Additional research

(Abdel-Mageed W S. et al.) (31) demonstrated the possible impact of *CYP11A1* gene single nucleotide polymorphisms (SNP) in various populations. On the other hand, (tttta)n polymorphism is not correlated with the presence of hirsutism in a study of Chinese women (32).

CYP17

The endoplasmic reticulum-resident enzyme cytochrome P450 17α-hydroxylase-17, 20-lyase is encoded by this gene, which is located on chromosome 10q24–q25. The hydroxylase and lyase activities of this bio-catalyst are important in the making of steroid hormones. Pregnenolone and progesterone are converted to 17-hydroxypregnenolone and 17-hydroxyprogesterone, respectively, by its 17αhydroxylase and 17αlyase activities. These steroids are then converted to dehydroepiandrosterone and 4-androstenedione (33). The hydroxylase and lyase activities of this enzyme are important in the production of steroid hormones. Its 17αhydroxylase and 17αlyase activities change progesterone and pregnenolone into 17-hydroxyprogesterone and 17-hydroxypregnenolone, respectively, and then these steroids are converted to 4-androstenedione and dehydroepiandrosterone (34). The ovarian hyperandrogenism linked with PCOS is believed to be caused in part by dysregulated P450 CYP17 enzyme (35). Ovarian hyperandrogenism linked with PCOS is believed to be caused in part by dysregulated P450 CYP17 enzyme (36). Single nucleotide polymorphism rs743572 of *CYP17* has been linked in the past to PCOS and related phenotypes (37). Diamanti-Kandarakis et al. reported similar findings in Greek patients, demonstrating a markedly elevated occurrence of C alleles of the *CYP17* gene in PCOS (38). Additionally, research by Pusalkar et al. conducted a study in which they come with a result that in PCOS the occurrence of the C alleles of the *CYP17* gene was higher (39). Moreover, there are some studies also that were not thought to be a chief influence in the progress of PCOS (40).

CYP19

The enzyme P450 aromatase is encoded by the CYP19 gene, which is located at 15p21. The enzyme compound is composed of cytochrome P450 reductase, cytochrome P450 aromatase, and nicotinamide adenine dinucleotide phosphate. It is the catalyst that turns androgens into oestrogen. Numerous patients with hyperandrogenism have been observed to have diminished aromatase activity (41). This enzyme may be crucial in the emergence of hyperandrogenism since it catalyses the last stage of oestrogen biosynthesis, which converts testosterone and androstenedione into estradiol and estrone, respectively. Research has shown that women with PCOS have low amounts of aromatase in the granulosa cells that are derived from medium-sized follicles (42). This enzyme may be crucial in the emergence of hyperandrogenism since it catalyses the last stage of oestrogen biosynthesis, which converts testosterone and androstenedione into estradiol and estrone, respectively. Low levels of aromatase have been observed in granulosa cells derived from medium-sized follicles in PCOS (43).

GENE	SNPs	ORIGIN	SAMPLE NUMBER	KINSHIP	REFERENCE
CYP11	(tttta)n	South India	267 cases 275 controls	Yes	[29]
	rs4887139 *rs48866595*	China	285 cases 299 controls	Yes	[30]
	rs4077582	Egypt	53 cases 53 controls	Yes	[31]
	rs11632698 *rs4077582* *rs4887139*	North India	270 cases 270 controls	Yes	[32]
CYP17	*rs743572*	Pakistan	204 cases 100 controls	Yes	[33]
	34 T/C SNP	Greece	50 cases 50 controls	Yes	[34]

Table 1: The contribution of different CYP gene SNPs in PCOS with different ethnicity

		Indian	100 cases 100 controls	Yes	[35]
		Indian	60 cases 54 controls	No	[36]
		Caucasian	287 cases 187 controls	No	[37]
CYP19	*rs2414096*	Chinese	785 cases 297 controls	Yes	[20]
		Indian	249 cases 257 controls	Yes	[29]
		Egyptian	30 cases 30 controls	Yes	[44]
		Pakistan	204 cases 100 controls	Yes	[45]
		Kashmir	396 cases 306 controls	Yes	[46]

Cont. Table 1: The contribution of different CYP gene SNPs in PCOS with different ethnicity

A different study conducted in Egypt came to the conclusion that in PCOS women with hyperandrogenism, *rs2414096* of the *CYP19* gene is linked to decreased aromatase action (44). Accordingly, a same study has been done on the same SNP that concluded with strongly association (45). Additionally, several researches on a different polymorphism, *rs2470152* in the *CYP19* gene, revealed that heterozygous TC genotype was linked to higher testosterone levels and a lower E2/T ratio but had no effect on PCOS risk. This finding suggested that the polymorphism had a function in controlling aromatase activity (46).

CONCLUSION

The prevalence of PCOS has considerably grown in recent decades. We give an outline of the capability of *CYP* gene varieties in hyperandrogenism in this review. The deregulation of bio-catalyst participated in the steroidogenic production pathway and the enlargement of theca cells in the ovaries, are factors contributing to the rise in androgen. GnRH rhythm rate rises leads a result of increasing androgens because they block the hypothalamic-pituitary axis' negative feedback loop. A rise in LH causes the ovaries' theca cells to proliferate quickly, which in turn increases their ability to produce steroids and, ultimately, androgens. The bio-catalyst participated in steroid metabolism are encoded by genes including *CYP11, CYP17* and *CYP19*, which have been well investigated and are supposed to potential contenders for roles in the causing PCOS. These genes are overexpressed in the ovary, which leads to elevated testosterone, androstenedione, and 17-hydroxyprogesterone production. Additionally, the action of aromatase is lowered, which additional upregulates the production of androgens. Numerous research has examined the correlation between various genetic variations of these steroidogenesis-related genes and PCOS. By also upregulating or downregulating the expression, *CYP* gene polymorphisms can exacerbate the hyperandrogenic phenotype in PCOS-affected women, hence raising androgen levels even higher.

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Review Article

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TAURINE'S CRUCIAL FUNCTION IN METABOLIC DISEASES

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ABSTRACT

The cluster of risk factors for metabolic syndrome, which includes several diseases like cardiac disease, hypertension, obesity and diabetes, has emerged as a major issue in public health. The majority of mammalian tissues contain taurine, an amino acid that contains sulphur. Although it is possible to produce taurine internally, dietary sources are still the most important. Researchers discovered that taurine has many biological functions, such as reducing blood pressure, protecting cells from ischemia-reperfusion damage, and influencing intracellular calcium concentration. It also has antioxidant, antiatherogenic, and other beneficial benefits. Taurine has effective action to metabolic syndrome, including lowering triglycerides to avoid obesity, according to a lot of research. In this review, we will briefly describe the how taurine in preventing metabolic syndrome, as well as its favourable effects on cardiac, obesity, hyperlipidaemia, diabetes mellitus, and other disorders.

KEYWORDS: Taurine, Metabolic disease, Diabetes, Hypertension, Atherosclerosis.

INTRODUCTION

In recent times, there has been a significant amount of study and public attention focused on the increasing prevalence of metabolic syndrome, which is also referred to as insulin resistance syndrome. There are a number of risk factors for heart attacks that are included in the metabolic syndrome. These risk factors include obesity, insulin resistance, dyslipidaemia, and hypertension. Different clinical criteria for this condition have been created by a variety of expert bodies; however, they are all in agreement that you should take all of these variables into consideration simultaneously(1).

A person is considered to have metabolic syndrome if they have increased BMI value with altered lipid profile, elevated blood pressure, and elevated fasting plasma glucose. Metabolic syndrome is known to raise the chance of getting type 2 diabetes by five times, as well as cardiovascular events by around two times, all-cause mortality by about 1.5 times, and type 2 diabetes by about 1.5 times(2,3).

Almost all mammalian tissues, including the heart, retina, liver, muscles, and platelets, contain the conditionally necessary amino acid taurine (2-aminoethanesulfonic acid), which is abundant in seafood. Before the discovery that preterm newborns given formula could not maintain normal plasma or urinary taurine levels in 1975, it was thought to be a non-essential nutrient for humans. Low taurine levels were also linked to a number of clinical diseases, such as cardiomyopathy, retinal degeneration, growth retardation, and others, according to in vivo investigations. Among taurine's several documented biological and physiological functions are its anti-oxidant and anti-inflammatory qualities, as well as its ability to regulate osmoregulation, stabilise membranes, and modulate cellular calcium levels(4,5).

TAURINE DEMONSTRATED IN CLINICAL AND ANIMAL RESEARCH TYPE 1 DIABETIC MELLITUS

In the various published reports it was found that taurine can help with type 1 diabetes,. who were taking insulin had improved glucose metabolism after 30 days of taking taurine supplements (0.5 g twice daily) (6). Both streptozotocin and alloxan destroy pancreatic beta cells, which is a common complication of type 1 diabetes, and taurine may protect them (5,7).

MECHANISMS OF TAURINE IN HYPOGLYCEMIA

A clinical investigation was conducted on men who were overweight but did not have diabetes. Various

studies reveals, insulin resistance and heparin through the intravenous route, may damage the pancreatic cells while , after a course of therapy consisting of three microgram of taurine per day for a period of two weeks reverse these mechanism (8). In another study on rodent was observed that 2% taurine for a period of thirty days provide better results. Taurine administration resulted in decreased levels of glucose in the blood of mice, and a tyrosine insulin receptor protein phosphorylation in skeletal muscle and liver and regulate the insulin level and stimulation.–(9,10).

IMPACT OF TAURINE ON OBESITY

Nowadays it was found that taurine provide very important and beneficial role in the treatment of obesity, both in animals and in people. In a study conducted in 2004 in a group of approximately 30 people, it was found that, students who did not have diabetes mellitus and had a body mass index (BMI) of 25.0 and who were given taurine, while the other group consisted of fifteen individuals who were given a placebo. Very interesting results they found that in body weight, triglycerides (TG), were decreased significantly in the group that was given either 3 microgram of taurine or a placebo orally at regular intervals for a period of seven weeks. With regard to the prevention of cardiovascular disease in those who are overweight or obese, the data suggest that taurine has the potential to be a game-changer. According to the findings of a study that involved 243 healthy teenage females, researchers discovered that individuals whose urinary taurine excretion was higher had considerably lower serum triglyceride levels than those whose excretion was lower. A diet that is high in taurine may be able to improve serum lipid profile, according to this evidence (12).

ANTIOXIDATION

By promoting insulin resistance and pancreatic β cell dysfunction, oxidative stress adds to the pathophysiology of diabetes, which is caused by the increased production of reactive oxygen species (ROS). The reactive oxygen species and imbalance between oxidant and antioxidant environment inside the cellular system mainly responsible for the Initiation of diabetes (13). Animal models for familial hypercholesterolemia in humans, including apoE-deficient mice and Watanabe heritable hyperlipidemic (WHHL) rabbits, have shown that taurine can inhibit lipid peroxidation. Because of its antioxidant capabilities, taurine improves beta cell dysfunction. Evidence suggests that taurine's antioxidant benefits are mediated through mitochondrial pathways, as it has been demonstrated to reduce mitochondrial superoxide generation in mice. By decreasing taurine levels in mitochondria, in vitro investigations have examined the molecular pathways underlying this action. When mitochondrial taurine synthesis drops, the amount of ND5 and ND6, proteins encoded by mitochondria, drops as well, rendering Complexes I and III useless.(14).

NEUROINFLAMMATION MODULATION

Inflammation in the neurological system can be mitigated by taurine, according to research. Taurine significantly enhanced functional recovery after traumatic brain injury (TBI) in the penumbral region while reducing water content and accumulation of glial fibrillary acidic proteins (15). In a combined study it was found that a week of taurine treatment a significant notable decrease in the levels of various cytokines, Intracellular inflammatory factors, monocyte chemotactic protein-1, and vascular endothelial growth factor (VEGF) (16). Taurine treatment effectively reduced the severity of neuronal damage in serious brain injuries and traumatic brain injury by decreasing cerebral oedema, increasing astrocyte activity, and proinflammatory cytokines. In STZ- and Mn-induced animals, taurine therapy restored choline acetyltransferase and acetylcholinesterase activity, which are important for acetylcholine regulation. Regarding the cholinergic signaling system and Aβ-mediated neurotoxicity, taurine shielded the retinal neurones of chicks in vitro. Glutamate receptors are not involved in the action, however taurine's neuroprotective properties have blocked picrotoxin, a GABAA receptor antagonist. (17).

Beyond the Alzheimer's disease (AD) model, researchers have investigated taurine's neuroprotective benefits in PD models in both cells and animals. Taurine demonstrated a protective effect when tested against neurotoxicity caused by rotenone(16).

THE POTENTIAL OF TAURINE IN COMBATING ATHEROGENESIS

Atherosclerosis, impacting more than 60 million individuals in the United States, has undergone extensive research over the past sixty years. While low-density lipoproteins (LDL) are recognised for their role in plaque development within the arterial wall, oxidised LDL can significantly worsen this process. Rats with high cholesterol that were administered taurine (15 g/kg/day) for a duration of five weeks exhibited a 37% decrease in plasma LDL, a 32% decrease in total cholesterol, and a 43% decrease in triglyceride (TG) levels in comparison to control rats that were fed the same diet without taurine (12,18) Additionally, rats that were provided with a high taurine diet, when compared to those on a cholesterol-

free diet, exhibited a notable reduction in plasma levels of LDL, total cholesterol, and triglycerides. A 43% reduction in hepatic triglycerides and a 77% increase in free fatty acids in the liver were noted. Platelet activation, adhesion, and aggregation at locations of vascular endothelial disruption due to atherosclerosis are critical processes in the formation of arterial thrombus. The influence of taurine on platelet agreeability has been proposed to be substantial. Platelets obtained from taurine-depleted cats exhibited a sensitivity to aggregation that was twice that of platelets from cats supplemented with taurine(19).

ANTI-INFLAMMATORY

Type 1 diabetes, in which pancreatic beta cells die due to inflammatory processes, and type 2 diabetes, in which macrophages migrate into adipose tissue, are both thought to be rooted in inflammation. The anti-inflammatory taurine chloramine is produced when taurine reacts with hypochlorous acid. An important part of inflammatory pathways, taurine chloramine reduced the activity of NF-kB and reduced levels of monocyte chemoattractant protein 1 (MCP-1), in addition to inhibiting TNF-alpha release the prospective mechanism behind it that they directly damage the beta cells or inhibiting ulk-1, beclin-1 macrophage activity in type 2 diabetes. (20,21).While no direct anti-inflammatory role of taurine directly found with taurine treatment in in vivo study on mice.

ARTERIAL PRESSURE

Many research have examined taurine's antihypertensive effects. After 7 days of 6 g taurine, young borderline hypertensive' systolic and diastolic blood pressure dropped significantly. Tibetans were studied for taurine's hypotensive effects. After 2 months of ingesting 3 g of taurine daily, systolic and diastolic blood pressures dropped dramatically. Taurine has been tested for its hypotensive effects in rats with spontaneous hypertension (SHR), deoxycorticosterone acetate (DOCA), and high-fructose diets (22). The hypotensive effects of taurine are linked to renin-angiotensin-aldosterone system. This is the primary pathways which directly involved hypertension conditions. One of the many medications used to manage hypertension is angiotensin II, a crucial hormone in the RAAS. Experimental evidence suggests that taurine can inhibit angiotensin II activity in cell cultures(23).

CONCLUSION

In the conclusion we found that, taurine has been demonstrated to treat metabolic syndrome and diabetes in animals. This study also provide a broad idea regarding the various metabolic pathways and signalling molecules were bused to modulate and regulate the general metabolism of our human body as well as rodent system, and may be beneficial in the treatment of diabetes, obesity, hypertension and cardiac disease. Unfortunately, clinical trial data is lacking. More research is needed to improve clinical studies. This will shed light on taurine as a nutritional supplement for metabolic syndrome and diabetes prevention.

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Review Article

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NATURAL AGENTS IN THE MODULATION OF METABOLIC SYNDROME

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ABSTRACT

Metabolic syndrome or syndrome X is a profound health issue across the world and a recognized risk elements for both atherosclerosis-related as well as non-atherosclerotic cardiovascular disease. There was remarkable variation in the definition and diagnostic parameters for metabolic syndrome, which represents a chronological advancement in perception about this ailment. Several triggers leading to the primary cause of persistent inflammation variables for metabolic syndrome are pathophysiological. Finding a reliable alternative medication that is ecological and spared from adverse effects, therefore will be a helpful tool in the battle counter to metabolic syndrome. In this set of circumstances, consuming functional foods or making the supposition that natural bioactive compounds (NBCs) exist might have an advantageous effect on controlling body mass, glucose metabolism, and hypertension, as well as endothelial destruction, enhancing lipid profiles, reducing inflammation, and reducing oxidative stress. NBCs like EGCG, curcumin, polyphenols, allicin, barberine, quercetin, hydroxytyrosol, resveratrol etc. shows activity against the risk factors for metabolic syndrome. This review emphasizes the latent activities of NBCs in the modulation of metabolic syndrome, its associates risk determinants, as well as in their prevention.

KEYWORDS: Metabolic Syndrome, Natural bioactive agents, Obesity, Insulin Resistance, Dyslipidemia, Cardiovascular diseases.

INTRODUCTION

The incidence of chronic degenerative non-communicable diseases (CDNCDs) has increase drastically during the past century. This is due to the population's average life expectancy increasing as well as the proliferation of risk factors for unhealthy lifestyles like smoking, drinking too much alcohol, being sedentary, and having poor dietary habits. The metabolic syndrome, one of the most prominent CDNCDs (1).

Obesity, hypercholesteremia, or insulin resistance all are contributory factors to the metabolic syndrome. It begins by identifying individuals who have a higher vulnerability to acquiring type 2 diabetes mellitus and atherosclerotic CVD. Secondly, by considering the interrelationships among the different elements of the metabolic syndrome, we may be able to comprehending the pathophysiology integrating them to the increased probability of heart disease. Thirdly, it contributes to making it more feasible to conduct epidemiological and clinical research on pharmacological, dietary, and preventative treatment methods (2). It's crucial to correctly diagnose patients so that lifestyle and risk factor modifications can be made to improve the disease's outcomes. Metabolic syndrome can be diagnosed whether one or more of its symptoms like abdominal visceral fat, hypertension, impaired insulin sensitivity, and hypercholesteremia are present (3).

Epidemiology of Metabolic Syndrome: Metabolic syndrome is a worldwide issue. Abdominal obesity is allied with the higher probability of metabolic syndrome. Based on several variables, such as gender, ethnic group, age and the criteria used for diagnosis, the disease's prevalence differs throughout various nations and locations. As people age, their risk of developing metabolic syndrome rises. Less than 10% of young adults in their 20s and 40% of seniors in their 60s are affected by metabolic syndrome. The condition can affect schoolchildren, and some of them may even possess more than two of its symptoms (central obesity, insulin resistance, hypertension and dyslipidemia). More than 45 million adult Americans, or more than one-fifth of the population, are affected by metabolic syndrome in the US (4). Depend upon global epidemiological studies, the frequency rate of metabolic syndrome is approximately estimated in

between 20% and 45%, with a roughly increment of 53% by 2035.

Pathophysiology of Syndrome X or Metabolic Syndrome: Abdominal obesity and insulin resistance have been identified as the primary pathophysiologic abnormalities underlying the metabolic syndrome. Since these two risk factors are intricately linked to one another, it is impossible to say which is more important for Metabolic Syndrome etiology and progression. Furthermore, contributing factors like age, ethnicity/race, food, physical inactivity, dysregulation of cytokines originating from adipose tissue, genetics, inflammation, abnormalities in hormone levels, and medications further complicate the pathophysiology of metabolic syndrome (5).

An increased concentration of the adipose tissue in abdominal area has been related to an elevated incidence of insulin resistance, T2DM, and CVD. (6, 7). Endocrine roles of adipose tissue, is further categorized into two kinds of adipose tissue i.e. brown adipose tissue and white adipose tissue, regulates a number of metabolic pathways that, if changed, might result in a dysfunctional glucose and lipid metabolism (8). Protein 4 (FABP4) that binds fatty acids, adiponectin, leptin, hydroxyl fatty acids (FAHFAs) that are ester of fatty acids and palmitoleate are other substances secreted by WAT that have an impact on the hepatic tissue, skeletal muscles, brain, and pancreas. Because it facilitates the emission of cytokines that are associated with inflammation in the blood, which involve interleukin-6, interleukin-8, and tumor necrosis factor-α, only the previous one is associated with the cardiovascular morbidity, (8, 9,10). In fact, IR, T2DM, metabolic, and CV disorders can be spurred on by the pro-inflammatory chemicals secreted from adipose tissue (11-12). Many researches have indicated that some cytokines that caused inflammation, such as interlukin-1 and interlukin-18, are present in metabolic syndrome and are crucial for the advancement of the atheromatous plaques.

The pathophysiology of metabolic syndrome is significantly influenced by elevated concentration of mono and diacylglycerols in the blood, caused by insulin resistance. Insulin inhibits hepatic gluconeogenesis and lipolysis while elevating the absorption of glucose in muscle and the liver. However, adipose tissue has impaired insulin's capacity to conquer lipolysis during impaired insulin sensitivity, which leads to the transmission of free fatty acid levels to rise and stimulate to reduce antilipolytic effect of insulin (13). Protein kinase is not activated by the muscled due to the presence of FFAs, which results in the less absorption of glucose. They enhance the liver's ability to activate protein kinase, which promotes the gluconeogenesis and lipogenesis. In order to maintain euglycemia, a hyper-insulinemic condition is created overall. The compensation eventually fails, and insulin secretion declines. The pancreas' beta cells are likewise lipotoxic to FFAs, which results in less insulin production.

Accelerated action of sympathetic nervous system (SNS), and the salt reabsorption in the kidneys are additional processes. Because insulin resistance raises serum viscosity, it increases the risk of CVD, inducing a prothrombotic condition, and activating a pro-inflammatory cytokine from adipose tissue (14). An increase levels of FFAs result in more production of apolipoprotein B by the liver, as well as increase synthesis of triglyceride. The lowering in HDL-cholesterol and intensify in low density lipoprotein-cholesterol are the indirect consequences of changes in the lipid metabolism in liver (15).

Research Methodology: The electronic databases Pubmed, Scopus, Google Scholar were searched for the paper (original or review papers) through August 2023. The terms "metabolic syndrome," "natural bioactive compounds," "metabolic changes," "endothelial distruction," "lipid profile," "inflammation," "oxidative stress," "polyphenols" and "alternative medicine" were used. Additionally, we only incorporated English-language papers. Each and every reference were manually selected for the article.

Potential effect of Natural Agents or Bioactive Compounds in modulation of the Metabolic Syndrome

The initial therapeutic strategy implemented in the case of metabolic syndrome is dietary and lifestyle advancement. The therapeutic management of metabolic syndrome comorbidities can actually be aided by a better dietary regime, including a decrease in caloric consumption in cases of overweight and obesity, also a decrease in salt, saturated fats, cholesterol, and simple carbohydrates (16). Other associated factors of metabolic syndrome can be regulated by the dietary modifications; for example, dyslipidemia, hyperglycaemia, and hypertension have been identified to be improved by a minimal consumption of sodium, cholesterol, saturated fatty acids, and simple carbohydrates. Diets with a excessive and a very low-fat substance aggravate atherogenic dyslipidemia; as a result, it's typically advised to consume 25–35% of daily calories as fat.

Metabolic syndrome does not have a single medication that is effective, and the polypharmacy and low

compliance that result from the present pharmacotherapy and related comorbidities make it difficult for patients to take multiple medications for a prolonged duration. Since their impact is unknown what the long-term cardiovascular results and compliance will be, considerable concern in using the naturally available bioactive compounds to decrease the vulnerability and progression of the metabolic syndrome.

Natural bioactive agents have been shown positive impact on managing obesity and a decrease in visceral obesity in various clinical investigations. Catechins and its derivatives are among of the most extensively researched bioactive compounds for their potential anti-obesity activity. As it turns out, these bioactive molecules appear to have two main ways of reducing body weight: raising energy expenditure by activating the sympathetic nervous system, which enhances lipid oxidation, especially in adipose tissue; and lowering intestinal lipid content, which helps people consume less calories (18).

Epigallocatechin gallate (EGCG) is a natural biologically active agent abundantly occur in a green tea. According to an array of clinical studies (19-22), EGCG consumption is linked to a remarkable decrease in abdominal obesity, BMI, and intra-abdominal fat. These activities have frequently been investigated in relation to caffeine use, which appears to work in combination with EGCG to reduce body weight (23). It seems that EGCG can increase AMPK activity. AMP-activated protein kinase (AMPK) contributes to decreased fat production, increased fat breakdown, and improved insulin sensitivity, all of which leads to reduced body weight. Coffee contains a significant amount of chlorogenic acid, which appears to work by modulating the PPAR, the receptor in charge of lipid metabolism, it can also help intercept the buildup of visceral fat and uncontrolled body weight (24, 25).

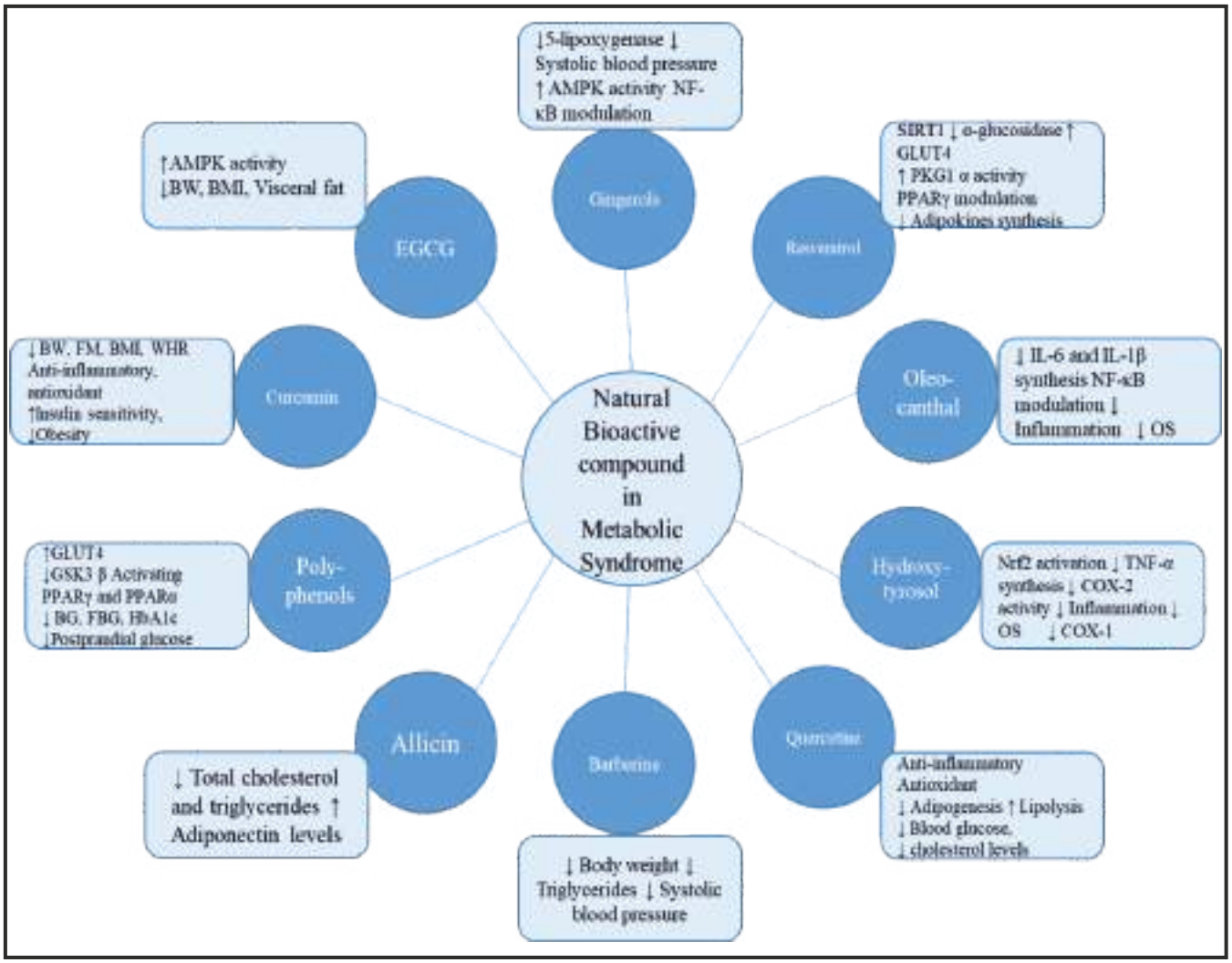

Fig. 1: The Impact of Naturally Occurring Bioactive agents on the Metabolic Syndrome

MUFAs, PUFAs, fibre, folate, calcium, magnesium, and potassium are all present in nuts, making them useful foods. Their impact on body weight management appears to be brought about by a rise in satiety (26-28).

In addition, nuts are an excellent food source for managing metabolic syndrome because they have a favorable impact on the modulation of lipid and glucose metabolism (29). Further research has determined the role the curcumin, the naturally occurring phenol found in *Curcuma longa*, plays an important role in managing pathways related with obesity. In addition to the low-calorie diet, curcumin use accelerates weight loss, resulting in decreased FM%, BMI, and body circumferences. (30-32).

Turmeric, one of the NBCs, that have been constantly investigated for its anti-inflammatory, anti-diabetic and antioxidant characteristics, and it come into sight to have a significant regulatory role on diabetes and insulin resistance. Curcumin is one of the important natural bioactive agents that shows anti-inflammatory, antioxidant and have modulatory activities on T2DM and insulin resistance (33, 34). Additionally, the anti-inflammatory and anti-lipolytic activities of its antihyperglycemic role have been linked to a decrease in circulation of fatty free acids (FFAs) levels and TNF-α, respectively (35-37).

Natural Bioactive Compounds	**Source**	**Pathways**	**References**
EGCG (Epigallocatechin gallate)	Green Tea (*Camellia sinensis*)	↑Enhance AMPK activity ↓Body Weight, BMI and Visceral fat	21, 22
Curcumin	*Curcuma longa*	↓Adipocytes differentiation ↑ Preadipocytes apoptosis ↓Body Weight, BMI and Waist Hip Ratio Anti-inflammatory, antioxidant ↓Leptin, ↑adiponectin ↑Insulin sensitivity, ↓Obesity	32, 63, 64
Polyphenols	Cinnamon (*Cinnamomum zeylanicum*)	Antithrombotic activity, Anti-inflammatory, ↑Insulin sensitivity ↑GLUT4 ↓ Blood Glucose, Fasting blood sugar, HbA1c ↓PP glucose levels ↑ Insulin sensitivity TRPA1 activation ↑ Vasorelaxation ↓GSK3 β Activating PPARγ and PPARα	65, 66-68
Allicin	Garlic *(Allium sativum)*	Increase Anti-inflammatory and Antioxidant activities, Decrease Hypercholesteremia and Triglycerides levels and increase Adiponectin levels	39, 70
Barberine	*Rhizoma coptidis*	Increase Insulin sensitivity, decrease Systolic blood pressure, ↓ Body weight and Triglycerides	47
Quercetin	Onions *(Allium cepa)*, Grapes, Red wine	↓ Adipogenesis ↑ Lipolysis ↓ Blood glucose, ↓ cholesterol levels Modulation of PPARγ increases the activity of AMPK ↓ Obesity ↑ GSH synthesis Catalase, and increase GSH peroxidase modulation of SOD activities Decrease Inflammation	56,71
Olive Oil (Extra Virgin)	Olive *(Olea europaea)*	Increase activity of eNOS Increase synthesis of NO and NF-κB Decrease Oxidative Stress and Endothelial damage Decrease Blood Pressure	72-75,45, 76, 77
Hydroxytyrosol		Decrease activity of Nrf2 Decrease synthesis of TNF-α Reduced activity of COX-2 & COX-1 and OS Decrease inflammation	

Table 1: Natural Bioactive Compound in the modulation of Metabolic Syndrome

Oleocanthal		Reduce synthesis of interlukin-6 and interlukin-1β and decrease activity of NF-κB Decrease Inflammation and oxidative stress Decrease COX-2 and iNOS	
Gingerols, Shogaols, Parasols	Ginger *(Zingiber officinale)*	Increase anti-inflammatory activities Reduce Cyclooxygenase-2, and 5-lipoxygenase activity Decrease systolic blood pressure Increase activity of AMPK and NF-κB modulation Reduce Endothelial damage and BP	78-80
Resveratrol	Grapes *(Vitus vinifera)*	↓ Adipogenesis ↑ Lipolysis ↓Insulin resistance, ↓Body mass index Increase activation of SIRT1 and AMPK Decrease activity of α-glucosidase ↑ GLUT4 ↑ PKG1 α activity PPARγ modulation ↓ Adipokines synthesis ↓ Inflammation ↑ PKG1 α activity ↓ OS ↓ BP	81-83, 54, 84-85
Charantin	Bitter gourd *(Momordica charantia)*	↓ Blood Glucose level ↓Serum Cholesterol levels	89, 90
Swertiamarin	Chota-chiretta *(Enicostemma littorale)*	↓ Fasting blood glucose, HbA1c, ↓TC, LDL, triglycerides ↑ Plasma insulin, HDL	91, 92
Gymnemic acid	Gurmar *(Gymnema sylvestre)*	↑ MIN 6 ↓ Hyperglycemic effect	93, 94
Garcinol, Hydroxycitric acid, Anthocyanins	Kokum *(Garcinia indica)*	Antidiabetic effect, Cardioprotective effect, Anti-obesity activity ↑ SREBP1c, SREBP2c	95
Tannins, Flavonoids Proanthocyanidin	Rose mallow *(Hibiscus rosasinensis)*	↑ Ratio of TC/HDL ↑ Ratio of LDL/HDL Anti-diabetic activity	96
Gallic acid, Ellagic acid, E mblicanin A & B	Amla *(Emblica officinalis)*	Cardio protective activity ↓ ChREBP expression ↓ FAS and HMGCR	97-98

Cont. Table 1: Natural Bioactive Compound in the modulation of Metabolic Syndrome

Another bioactive compound, Allicin which is found in garlic (*Allium sativum*), have medicinal properties as it possesses antioxidant and antithrombotic properties. Different studies shows that garlic improves insulin sensitivity and also lowers total cholesterol and triglyceride levels (38, 39). Berries like strawberries, red fruits, blackberries, blueberries, or raspberries contain natural bioactive agents, including anthocyanins and flavonoids (40). Since lipotoxicity is reduced, it would seem that anthocyanins are responsible for their hypoglycemic activities. However, anthocyanins function by activating AMPK, which increases the amount of GLUT4 transporters, increases the absorption of glucose, and inhibits gluconeogenesis. In addition, PPAR, CPT1A (carnitine palmitoyltransferase-1A) and acyl-coA oxidase are the genes that modulate the hepatic lipid metabolism by the influence of AMPK (41-42). Additionally, it appears that anthocyanins stimulate the secretion of the GLP-1, which in turn stimulates the release of insulin.

Olives are abundant in natural polyphenolic substances like as oleuropein, hydroxytyrosol, and tyrosol, which

have a number of beneficial properties. Extra virgin olive oil (EVOO) has been recently gained a scientific attention, as it contains free radical scavenging quality and anti-inflammatory characteristics. The anti-inflammatory and antioxidant qualities of the polyphenols hydroxytyrosol and oleocanthal aid in delaying the onset of chronic degenerative non-communicable diseases (CDNCDs). The stimulation of Nrf2, a factor contributing in the production of phase two enzymes which are involved in detoxification, is one way by which hydroxytyrosol might appear to execute the body's endogenous defences (43). Both in vivo and in vitro investigations have demonstrated that hydroxytyrosol suppresses the activity of cyclooxygenases (COX)-2 and increases the generation of cytokines that promote inflammation, including TNF-α (44). Oleocanthal exhibited a primary anti-inflammatory effect comparable to that of ibuprofen (an anti-inflammatory medication) because of its capacity to prevent the activation of COX-1 and COX-2 enzymes, which in turn contributes to the production of inflammatory prostaglandins in a dose-related approach. Preadipocytes expression of genes linked to inflammation can be altered by oleocanthal. As a matter of fact, the research contends that oleocanthal appears to reduce NF-κB activation, which reacts to incendiary response and controls the synthesis of cytokines and adipokines (45, 46). By the regulation inflammatory reactions at the adipose tissue level, as suggested by this research, oleocanthal may be able to reduce the persistent low-level inflammatory condition of obesity-related illnesses and metabolic syndrome.

The plant *Rhizoma coptidis* Insulin sensitivity, lipid levels, and body weight all improve when berberine is administered. Equivalent to thiazolidinediones and metformin, berberine acts by downregulating lipogenesis- related genes and activating genes involved in energy utilisation. Berberine also has an insulin-sensitizing effect that is mediated through adipocyte pivoting of the adenosine monophosphate-associated protein kinase. Research on humans with metabolic syndrome has demonstrated a decrease in lipid levels, waist circumference, together with systolic blood pressure, particularly in females (47-49).

Quercetin being demonstrated to have an anti-inflammatory and free radical scavenging characteristics (50-51). 60 participants in an in vivo trial found that an 8-week treatment of 500 mg/day of quercetin substantial reduced levels of IL6 and C-reactive protein (CRP).

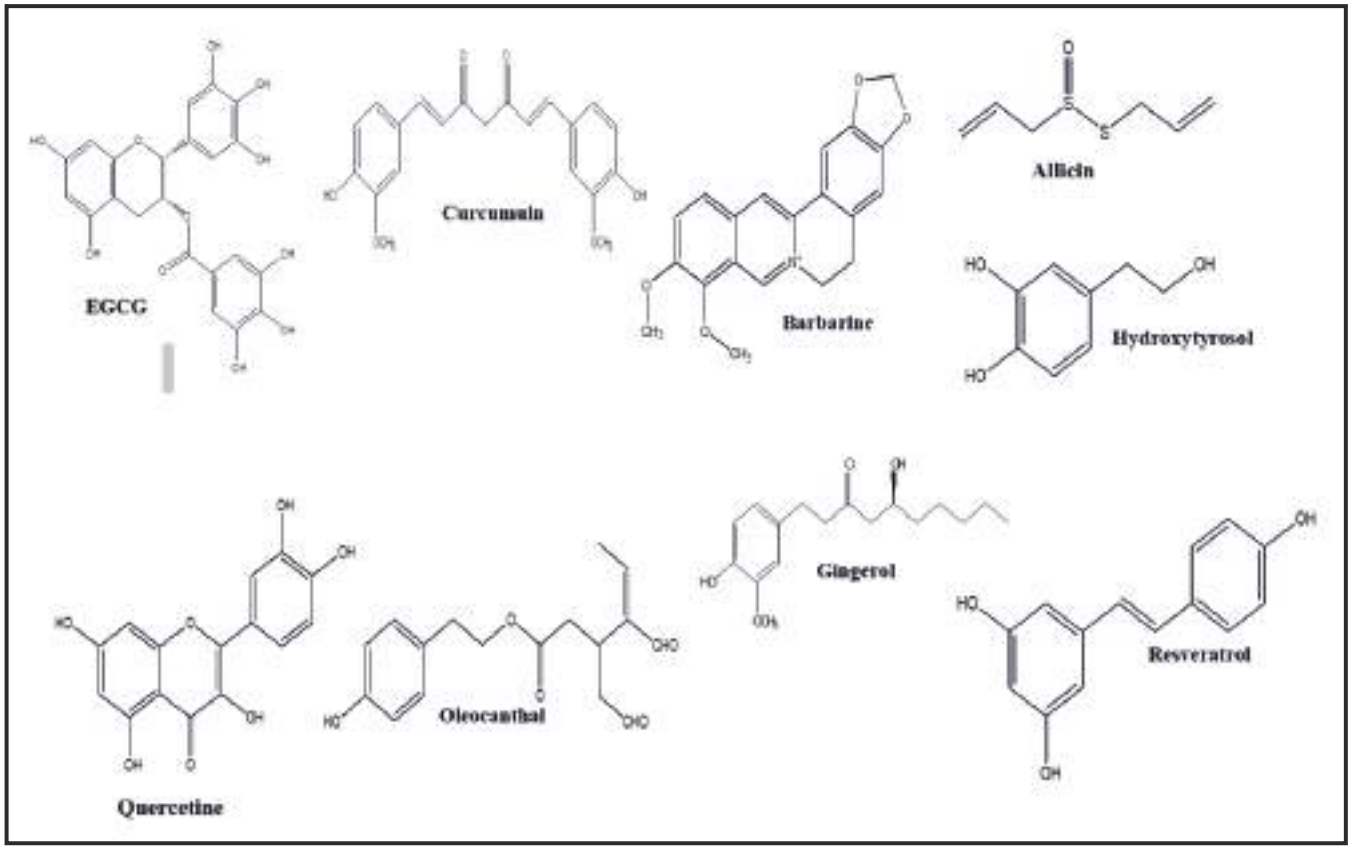

Fig. 2: Structure of Bioactive compound in the modulation of Metabolic Syndrome

Additionally, quercetin appears to decrease the gene expression for inducible nitric oxide synthase (iNOS) and COX-2 (52). Quercetin may strengthen the body's barriers system against free radicals by encouraging the production of glutathione (GSH), regulating the catalase gene expression, superoxide dismutase (SOD), and GSH peroxidase (53).

A polyphenol, resveratrol (3,5,4′-trihydroxystilbene), is derived from natural herbs notably in grapes, dry fruits or nuts as well as its derivatives like wine. It is a sirtuin pathway activator, that controls a number of cellular processes including metabolism, oxidation, along with aging. It has benefit in reducing adipogenesis and promoting lipolysis via a variety of methods and also prevents cyclooxygenase, with the resulting antioxidant activity (54). Investigations on individuals suffering from NAFLD and IR have produced encouraging findings (55). In fact, the investigations on the application of resveratrol in individuals with metabolic syndrome has revealed that it increases insulin sensitivity, glucose tolerance, total weight, and body mass index. Additionally, resveratrol has antioxidant properties that counteract reactive oxygen and nitrogen species (56-57).

Numerous epidemiological studies have looked closely at omega-3 polyunsaturated fatty acids (PUFAs), especially in regards to their preventive impact on metabolic syndrome-related symptoms (58). Eicosapentaenoic acid and docosahexaenoic acid are two particular PUFAs that are rich in fish oils and have drawn a lot of attention, leading to important preventive recommendations for society (59).

Sulforaphane is another phytochemical that comes from the Brassica family, which includes broccoli. Because of its antioxidant and anti-inflammatory qualities, it has been shown to offer potential therapeutic benefits for metabolic syndrome. It has been demonstrated to offer protection against a range of illnesses, conditions like type 2 diabetes mellitus, hyperlipidemia, and hypertension— each of which is significant contributory factors for the metabolic syndrome (60- 62).

The relevance of the polyherbal formulation's application in Metabolic Syndrome:

Approximately 80% of Asians, based upon estimates from the World Health Organization (WHO), receive their primary medical care from complementary and alternative medicine., partly due to the fact that the majority of population in developing countries can hardly afford basic health services. Metabolic syndrome has numerous etiologies; hence no single therapy can reverse the condition. Lifestyle modifications are the core component of risk-adverse persons' prevention and management. Those with high levels of risk determinanats, on the other hand, are the recipients of pharmaceutical treatment directed at managing individual symptoms (86).

The underlying mechanisms that allow for the synergistic therapeutic effect of polyherbal formulations include the modulation of the different targets or same targets in different mechanisms, which when combined increase activities; the modulation of transporters and enzymes to enhance the bioavailability of oral drugs; neutralization of detrimental effects; and the circumvention of drug resistance mechanisms (87). Multiple chemical constituents in only one herb or in combination with other herbs exhibit synergism, suggesting that these constituents may be useful as therapeutics for a range of disease targets. This is thought to be more logical and effective in treating diseases with multiple targets and serves as the foundation for polyherbal therapy (88).

CONCLUSION

As a consequence of stress, the synthesis of superoxides, abnormalities in lipid metabolism, and rises in impaired insulin sensitivity, the intricate nature of the metabolic syndrome is becoming more and more pronounced every day. The primary form of treatment and prevention for metabolic syndrome is regarded as changing one's lifestyle worldwide because pharmaceutical therapy is not a complete solution.

It is unquestionably obvious that natural bioactive agents play a beneficial contribution in the medical oversight of syndrome X and its associated concomitant conditions. In actuality, their hypothesis presents a number of positive outcomes, particularly over a long period of time, including body weight management, improved carbohydrate and lipid metabolisms, blood pressure management, endothelium protection, and eventually the reduction in oxidative stress and a persistent low-grade inflammatory state. Even though the possible advantages to health of several natural bioactive agents which have been already received extensive research, more clinical studies with larger population are still required to fully understand the unique mechanisms of action that can be used to regulate metabolic pathways. In order to achieve the positive benefits outlined in the research, it is required to develop worldwide norms for a natural bioactive compound's minimum effective dose and their period of assumption.

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Case Report

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UTERINE LIPOLEIOMYOMA : A RARE CASE REPORT

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ABSTRACT

Uterine lipoleiomyoma and pure lipomas are both benign tumors of fatty tissue. They are uncommon, with a reported incidence of only 0.03% to 0.25%. Pure cervical lipomas are especially rare. While MRI can sometimes help identify the fatty nature of these tumors before surgery, most are diagnosed after surgery by examining the tissue under a microscope. Despite several proposed theories, the exact origin and development of these tumors remain a mystery. Uterine lipoleiomyomas are a specific type of uterine leiomyoma (fibroids) distinguished by the presence of fatty tissue. They have the potential to continue growing even after menopause. We present the case of a patient diagnosed with a uterine lipoleiomyoma through ultrasound and CECT imaging, which was later confirmed through tissue analysis. Currently, surgical intervention remains the primary treatment approach for managing lipoleiomyomas.

KEYWORDS: Lipoleiomyoma, Smooth muscle, Histogenesis, Fibroids.

INTRODUCTION

Uterine lipomas, first identified by Lobstein in 1816, fall into two distinct categories: "pure lipomas," consisting solely of fatty tissue, and "mixed lipomas," which also contain muscle tissue (1). Lipoleiomyomas, composed of both fatty tissue and smooth muscle cells (SMCs), are often categorized as "mixed lipomas", were first described in 1965 (2). This distinct type of tumor was characterized by its composition of diverse proportions of fatty tissue and SMCs (2-3). A uterine lipoleiomyoma is an uncommon variation of the more prevalent uterine leiomyoma (4). Lipoleiomyomas are rare, benign tumors characterized by a mixture of mature fat cells (adipocytes) and SMCs.

The initial research by Willén et al. in 1978 estimated that lipoleiomyomas occur in roughly 0.03% to 0.2% of all uterine leiomyomas (3), a more recent study by Akbulut et al. in 2014 suggested a notably higher incidence of 2.9% (5). This latter study also found that over 80% of lipoleiomyomas occurred in women who have gone through menopause, with an average age of 55.5 years (5). Furthermore, lipoleiomyoma has been identified as the predominant variant in postmenopausal women with uterine leiomyomas, accounting for 85.7% of cases in one study (6).

The patients in the study were either parous (had given birth) or nulliparous (had not given birth), but none were pregnant at the time (5). With the increasing global population and the aging demographic, the number of lipoleiomyoma cases is expected to rise, though the condition itself rarely leads to death.

The origin of lipoleiomyomas remains a subject of investigation, but it is hypothesized that these tumors arise through one of two potential pathways: the first involves the direct transformation of existing SMCs within the uterus, whereby these cells undergo a phenotypic change and begin to accumulate fatty tissue. The second proposed pathway involves the differentiation of multipotent mesenchymal cells, which possess the capacity to develop into various cell types, into adipocytes (fat cells) within the uterine tissue (7). Additionally, decreasing estrogen levels following menopause seem to be a significant contributing factor (7). The development of a lipoleiomyoma could occur **concurrently** with the formation of a leiomyoma (8), through the fatty transformation of an existing leiomyoma (9), or as a new growth within the uterine muscle layer (myometrium).

Even though numerous theories have been proposed regarding the origin and development of these tumors, their exact histogenesis remains elusive (10). The

significance of these uterine wall lesions lies in the potential for concurrent malignancies in the ovaries, fallopian tubes, or uterus. Additionally, patients with these lesions may also present with other metabolic disorders and abnormal estrogen levels (11).

This report aims to present a case of uterine lipoleiomyoma, detailing the patient's journey from initial symptoms and presentation through diagnosis and subsequent management.

CASE REPORT

A 42-year-old woman visited the surgery department due to abdominal lump, discomfort, and pain. She did not report any burning sensation while urinating, vaginal discharge, vaginal bleeding, difficulty urinating, changes in bowel habits, or general symptoms of illness. Additionally, There was no reported history of cancer within the family. Upon physical assessment, a 10x10cm lump was detected in her pelvic region. Her medical history was otherwise largely unremarkable. An abdominal and pelvic ultrasound revealed a large, hyper-echoic mass measuring 10.7x13.2x11.1cm in the pelvic cavity, extending above the navel. The imaging also showed an enlarged uterus with a thickened endometrium, fibroids, and an enlarged cervix.

A Contrast-Enhanced Computed Tomography (CECT) scan of the abdomen endorsed a large, varied mass in the pelvic area, displacing the uterus forward and compressing its lower right side. The mass measured approximately 156x148mm. The imaging also showed swelling in the right kidney due to a blocked ureter. Routine blood tests, including HbA1c (for diabetes) and CA125 (a tumor marker), were normal. The patient had a surgical procedure to remove her uterus, both fallopian tubes, and ovaries. The pathology report after surgery described the removed uterus as measuring 6.5x5.5x5cm, with the cervix appearing to have been surgically removed.

Upon cutting, the uterus revealed a grayish-white surface with a fibroid measuring 4cm in diameter. The endometrial cavity was narrow. A large growth, measuring 15x13x7cm, was attached to the uterus. When cut, it showed a grayish-white surface with areas of bleeding. Both ovaries and fallopian tubes appeared normal when examined.

Under the microscope, the tumor was found to be made up of bundles of smooth muscle fibers mixed with mature fat cells. The SMCs tested positive for vimentin and desmin, while the fat cells were positive for estrogen receptor (ER), and progesterone receptor (PR).

Fig. 1: Gross Appearance

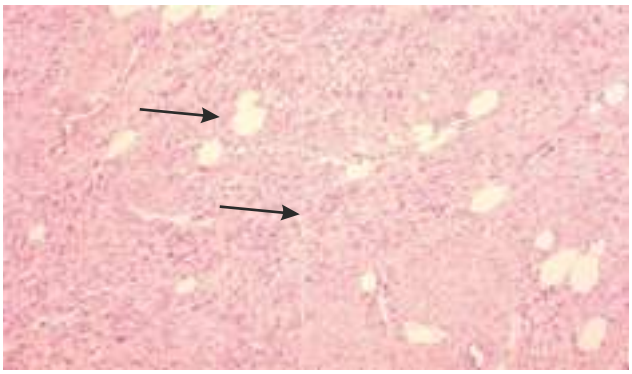

Fig. 2: Smooth Muscle Cells Proliferation Admixed with Mature Adipocytes in Lipoleimyoma (H&E 10X)

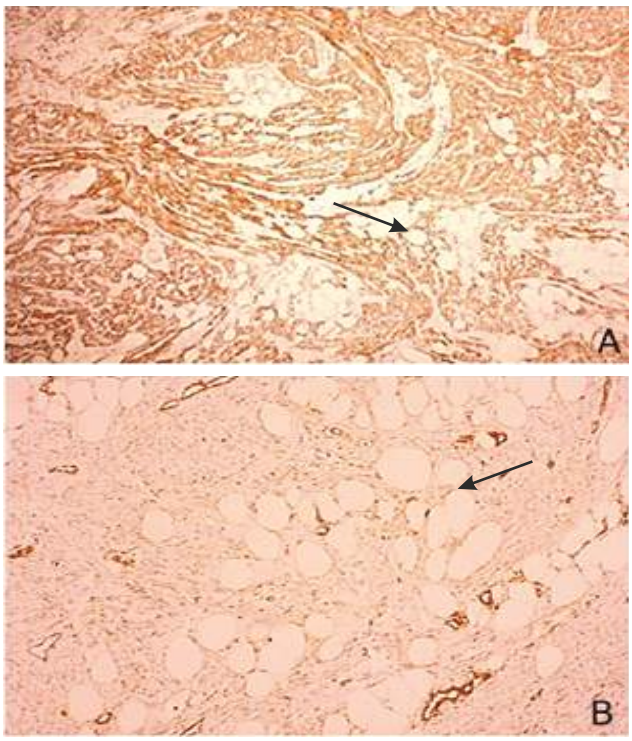

Fig. 3: (A) Desmin Positive A (4X) (B) Vimentin Positive (10X)

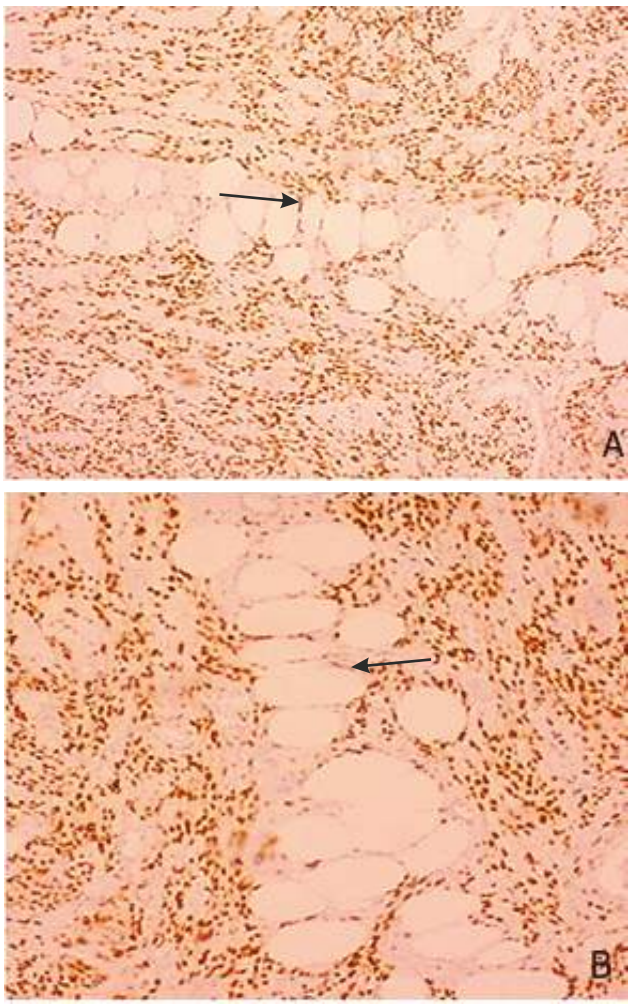

Fig. 4: (A) PR positive (10X) (B) ER positive (10X)

DISCUSSION

Lipoleiomyomas are a type of uterine fibroid that contain fatty tissue. They are usually discovered incidentally and most often affect postmenopausal women. Uterine lipoleiomyoma, a non-cancerous growth composed of fat cells within the uterus, is uncommon, accounting for only 0.35% of uterine myomatous tumors (12). It is typically found in the women after menopause and often presents similarly to uterine leiomyomas (12).

Lipoleiomyomas, while generally benign, can cause complications due to their size and pressure on surrounding structures. As they primarily occur in women over 50, fertility is usually not a concern. The choice of treatment for a uterine lipoma is influenced by factors such as the tumor's size, any associated symptoms experienced by the patient, and their general health condition.

For asymptomatic patients with a suspected lipoleiomyoma, management may be similar to that for conventional leiomyomas, often involving observation only. However, because a definitive diagnosis cannot be made before surgery, a needle biopsy guided by ultrasound can be crucial for confirming the diagnosis.

Under a microscope, these tumors show a mix of SMCs, mature adipocytes, and fibrous tissue. This composition likely results from the transformation of SMCs within leiomyomas into mature adipocytes (13).

While lipoleiomyomas are primarily found in the uterus, they have also been identified in other pelvic locations like the cervix, broad ligament, retroperitoneum, and ovary (14). The differential diagnosis for fatty pelvic masses in females includes benign cystic ovarian teratomas, other lipomatous ovarian tumors, pelvic lipomas, and liposarcomas in addition to uterine lipoleiomyomas (14-15). Lipoleiomyomas are widely considered benign tumors that do not impact mortality rates (15).

Although histopathological analysis provides the definitive diagnosis, radiological investigations are crucial for pre-operative identification and localization of lipoleiomyomas. Additionally, immunohistochemical (IHC) studies have contributed significantly to our understanding of their intricate origin. Mignogna et al. reported that fat cells in these tumors react with vimentin, desmin, and SMA antibodies, supporting the theory of smooth muscle cells transforming directly into fat cells. In our case, mature adipocytes also showed immunoreactivity with vimentin and desmin (16). Similar findings were observed in a study by Sharma and Mandal (17). Cytogenetic studies of uterine lipoleiomyoma further suggest that their development is similar to that of typical leiomyomas (17).

Researchers suggest that elevated estrogen levels, often associated with metabolic disorders like hyperlipidemia, hypothyroidism, diabetes mellitus, postmenopausal lipid changes, and pregnancy-related toxemia, may contribute to lipoleiomyoma development (17-18). These estrogen elevations, along with menopause-related lipid metabolism changes, could be key factors, as patients often present with conditions like hypothyroidism, hyperlipidemia, and diabetes (19-20).

Lipoleiomyomas frequently affect postmenopausal women (19-22), who may experience no symptoms or present with symptoms resembling those of uterine leiomyomas, including vaginal bleeding, pain in abdomen, abdominal lump and increased urinary frequency. These tumors typically show up as single,

enlarged masses of different sizes, most often found in the main part of the uterus. However, they have also been seen in the cervix, broad ligament, area behind the abdomen (retroperitoneum), and ovaries (23).

Asymptomatic uterine lipoleiomyomas, being benign, can often be managed conservatively. Accurate diagnosis and differentiation from other adipocytic pelvic tumors are crucial to avoid unnecessary surgical intervention (24). Treatment generally depends on the patient's the size of the mass and symptoms. In symptomatic patients with large lipoleiomyomas, medical management with pain medications and hormone therapy may help alleviate symptoms.

In this case study, the patient was a 43-year-old woman with no notable medical history or lab results suggesting any metabolic disorders. While a few studies have reported coexisting gynecological malignancies in patients with lipoleiomyomas (18, 25), our patient underwent a total hysterectomy and no evidence of gynecological malignancy was found.

CONCLUSION

Lipoleiomyoma, an elusive and benign uterine tumor, often masquerades as its more common counterpart, the leiomyoma, making clinical distinction a formidable challenge. However, the discerning eye can suspect its presence in postmenopausal women presenting with a distinctive hyperechoic uterine lesion framed by a hypoechoic rim. The final verdict, however, rests solely with the pathologist's microscope. This case report underscores the rarity of this entity, particularly its manifestation at a relatively young age, adding a compelling layer to the existing medical literature.

PATIENT CONSENT

Prior to initiating this report, we secured written informed consent from the patient for the publication of their case details.

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Case Report

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A CASE OF MIXED INFILTRATING (LOBULAR AND DUCTAL) BREAST CARCINOMA IN A PREVIOUSLY DIAGNOSED PATIENT OF UDH

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ABSTRACT

Introduction: Breast carcinoma has a heterogenous clinical and pathological presentation. Here is a female of 41 years, with a clear-cut, painless mass of the left breast for three years. Her radiology consisted of an USG which had an evidence of heterogeneously hypoechoic space occupying lesion in left breast with evidence of few ipsilateral, sub-centimetric, lymph nodes in left axilla (BIRADS ¾). Her tru-cut biopsy had earlier showed Usual Ductal Hyperplasia (UDH) but her excisional biopsy revealed 'Infiltrating Mixed (Lobular+Ductal) Carcinoma with Usual Ductal Hyperplasia'. Thus, a Modified Radical Mastectomy (MRM) was done under General Anesthesia and the specimen was sent to our histopathology laboratory which revealed Invasive Carcinoma with Mixed Lobular and Ductal features; Lymph nodes, left, axillary dissection: 17/17 positive. Nottingham Grade III (3+3+3=9). Discussion: Diagnosing cases of DCIS is not an issue but the problem arises in differentiating benign intraductal lesions from invasive carcinoma. Conclusion: To the best of our understanding, this is a rare presentation case where there is transformation from benign intraductal lesion into mixed invasive (ductal and lobular) carcinoma.

KEYWORDS: Breast carcinoma, UDH, Mixed, Infiltrating, Lobular, Ductal.

INTRODUCTION

Ductal hyperplasia is a proliferative condition that histologically is an increase in the cellularity of the underlying ductal epithelium. The resting epithelium is a monolayer of cuboidal to columnar epithelial cells with supporting myoepithelial cells, any increase in this two-layer configuration cellularity constitutes hyperplasia. That ductal hyperplasia which is not atypical is known as "usual," "regular" or "ordinary" (1).

Invasive ductal carcinoma, NOS includes a histologically different group of tumors that may express, some or more characteristics of the specific types of breast carcinoma and doesn't include the individual tumors (2). Examples of this are invasive ductal carcinomas having limited foci consisting of tubular or medullary or papillary or mucinous differentiation. When in a needle core biopsy a mixed growth pattern is present, the diagnosis is descriptive, and the final classification is made using the excisional biopsy.

CASE REPORT

A 41year old presented to the surgery OPD and she had complaints of swelling in left breast for 3 years. On local examination, a swelling of size 6x4cm was noted which was firm with irregular surface. Nipple areola complex was normal. Her general as well as systemic examination were within due limits, and all her hematological as well as biochemical investigations were within due limits. Her radiology examination was done and the ultrasonography showed evidence of a hypoechoic heterogeneous space occupying lesion (SOL) of 2.8x2.6x1.4cm showing minimal internal vascularity noted in 2o' clock to 4o' clock position of left breast with evidence of few ipsilateral, sub-centimetric, lymph nodes in left axilla (BIRADS ¾). Her trucut biopsy showed Usual Ductal Hyperplasia and excisional biopsy revealed 'Infiltrating Mixed (Lobular+Ductal) Carcinoma-Left breast with Usual Ductal Hyperplasia. Thus, a Modified Radical Mastectomy was done under General Anesthesia and her specimen was sent to our histopathological laboratory at Era's Lucknow Medical College for further processing.

Gross examination

Received 2 labelled vials.

Vial 1- Labelled as MRM specimen (left breast), some part of Pectoralis major and level I, II lymph node.

The left MRM specimen comprising of Nipple Areola

Complex and axillary tail, partially covered with skin all together measuring 22x12x4cm at our histopathology department. The outer surface was seen to be gray-white to gray-brown and smooth with attached fat. The cut surface had a gray-white to gray-brown along with solid areas. Nipple Areola Complex separately measures 2.5x1.5cm. Skin separately measures 16.5x7cm. Tumor measures 9x7x3cm. Resection margin measures: Superior margin- 3cm, Base- 0.5cm, Medial margin- 4cm, Inferior margin- 2cm, Lateral margin- 9cm. Largest lymph node measures 2x1cm. Representative sections were taken from the specimen and then the histological tissue was processed and routine H&E staining was conducted. (Fig.1).

Vial 2- Level III lymph node

Nine lymph nodes identified grossly. Largest measured 2.2x1cm and smallest measuring 0.5x0.5cm. cut surface shows gray-white, solid areas with few gray brown hemorrhagic areas. Representative sections were taken from the specimen and then the tissue processing and routine H&E staining was conducted.

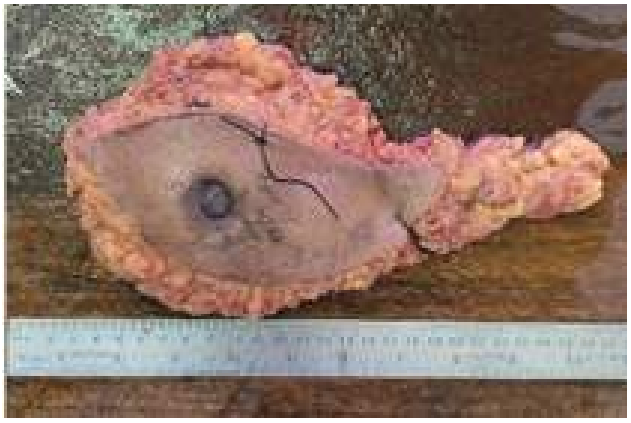

Fig. 1: Gross examination of MRM-Vial 1

Fig. 2: Cut surface of the Gross Specimen received

Fig. 3: Vial 2 Lymph nodes

Microscopy

Section from tissues reveled tumor cells which were arranged in single files, cords and scattered cells and these cells are dyscohesive, small, monomorphic having, round nuclei and scant cytoplasm.

Also seen were infiltrating nests and sheets of atypical cells at places forming tubules.

These atypical cells had large moderately pleomorphic hyperchromatic nuclei with prominent nuclei, increased nucleocytoplasmic ratio and amphophilic cytoplasm.

Few mitotic figures also seen with surrounding fibro-collagenous stroma showing infiltration with chronic inflammatory infiltrate which comprised of lymphocytes and plasma cells.

The microscopy also revealed areas of comedo necrosis and lympho-vascular invasion with few foci of hyperplasia of cohesive epithelial cells having uniform nucleus and moderate amount of eosinophilic cytoplasm.

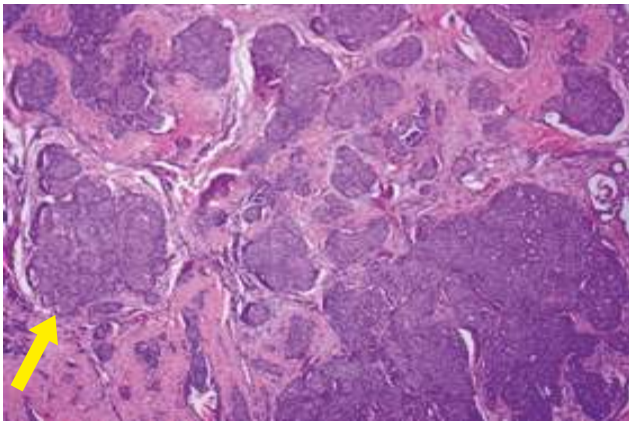

Fig. 4: Usual Ductal Hyperplasia H&E(40x)

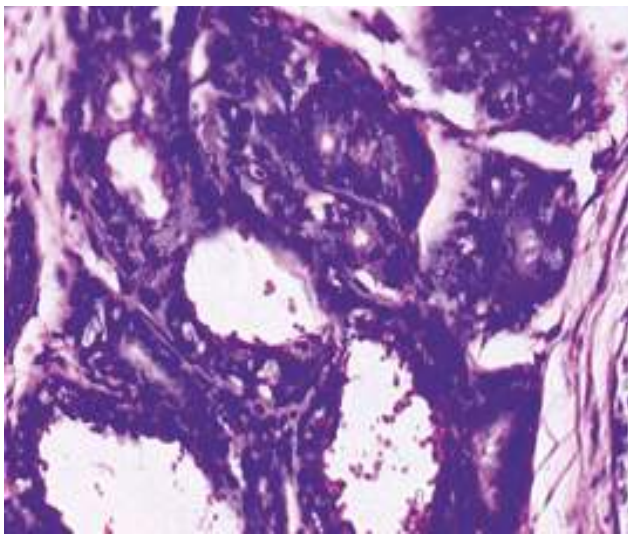

Fig. 5: Ductal Carcinoma Breast H&E (400x)

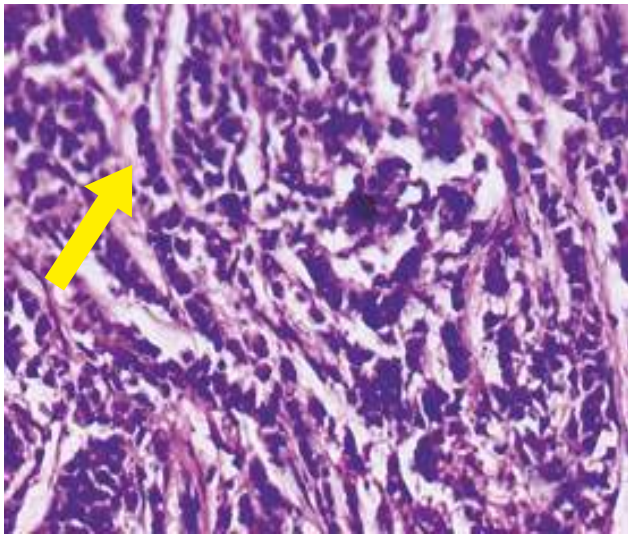

Fig. 6: Lobular Carcinoma Breast (100x)

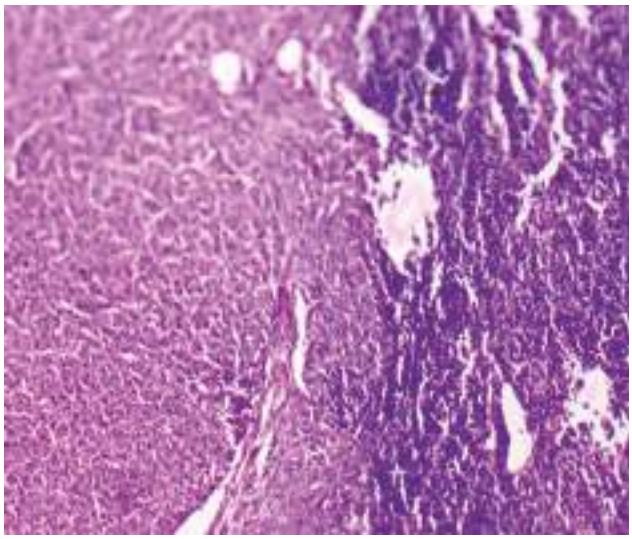

Fig. 7: Lymph Node Metastasis H&E (100x)

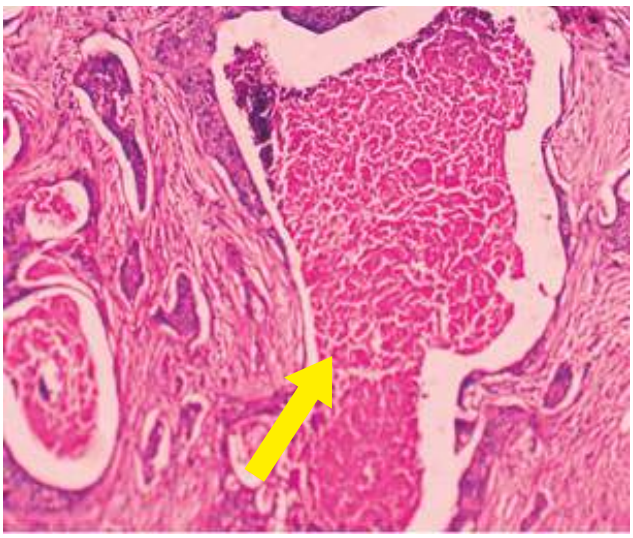

Fig. 8: Comedo Necerosis (10x) H&E

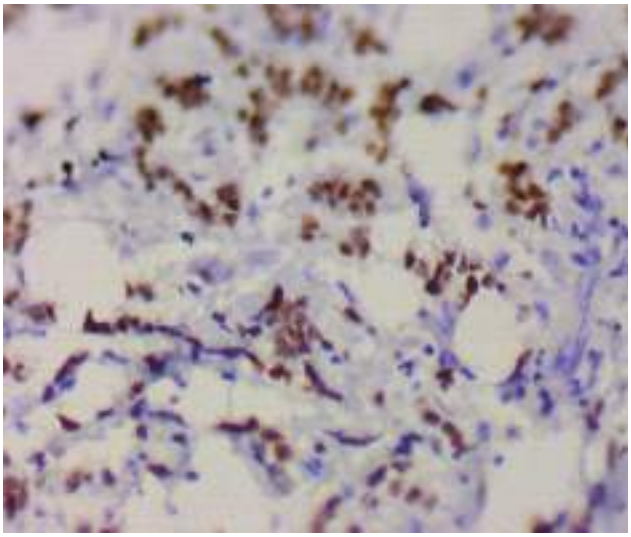

Fig. 9: ER Positive (400x)

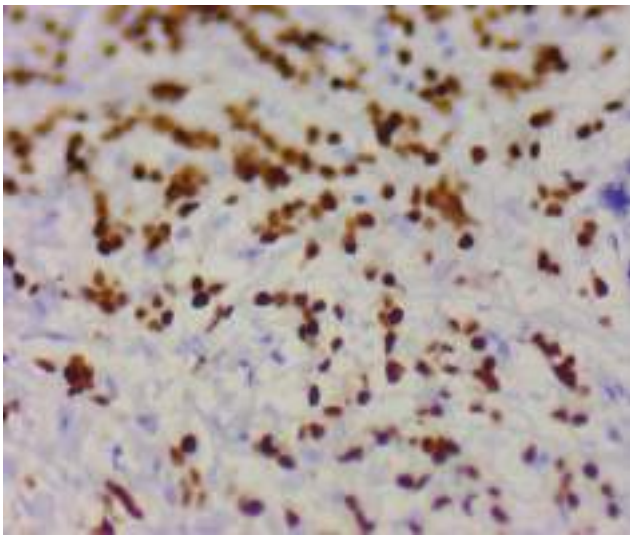

Fig. 10: PR Positive (400x)

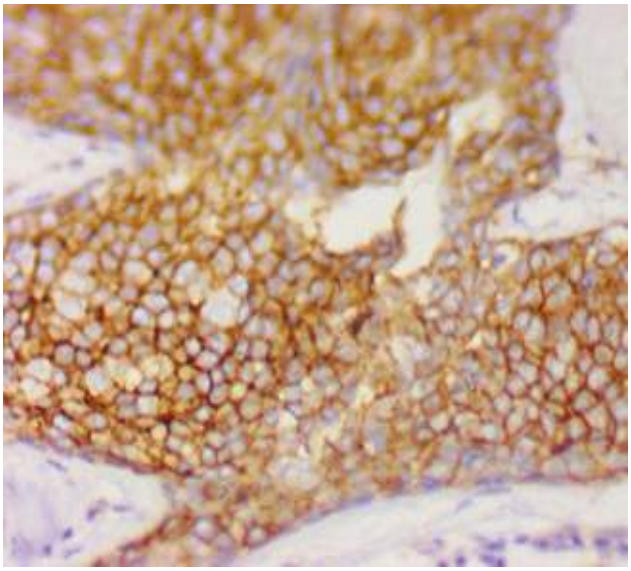

Fig. 11: HER2neu Positive (400x)

DISCUSSION

The WHO Working Group uses *the term Usual ductal hyperplasia* (UDH). The features which direct towards a benign lesion are- oval and normochromatic nuclei, scant or none mitotic activity, eosinophilic cytoplasm, with complete or incomplete apocrine metaplasia, along with the presence of foamy macrophages and absence of necrosis. The intercellular lumina of UDH are irregularity in size and shape (elongation rather than rounding), and location rather than regular in all of the three parameters that are seen in the cribriform pattern having ductal carcinoma in situ (DCIS), seen both at the lumen as well as the proliferating epithelial cells.

Breast atypical hyperplasia (AH), includes a proliferating disease of breast having atypia that may include Atypical Ductal Hyperplasia (ADH) along with Atypical Lobular Hyperplasia (ALH) of breast, and can be associated with an increased risk of development of carcinoma (3-5).

Breast tumours have two morphological distinct groups: tumors having characterstic growth patterns, and tumors having none of the special defining features (invasive carcinoma of no special type (IC-NST), or invasive ductal carcinoma (IDC) (6). 3 to 5 % of these breast tumors can have both lobular along with ductal histology, and can be divided as mixed ductal–lobular carcinoma (MDL). This is said if the ductal morphology part is composed of at least 10% of the tumor cells and the lobular morphology part is composed of more than equal to fifty percent (6-7). It was seen that ILC and mixed cancers had much more probability of having low-grade tumor, with estrogen-positivity, and with progesterone-positivity tumors and were diagnosed at later point of the disease in comparison with females with IDC (5). When mixed tumors were compared with purely IDC, mixed tumours evidenced to have an association with low grade, ER positivity and lower frequency for the development of distant metastases. On comparing mixed tumors to pure ILC, mixed tumours have been shown to have an association with higher grade and positive LN metastasis and also for the development of regional metastasis (8).

CONCLUSION

Diagnosing cases of DCIS is not an issue but the problem arises in differentiating benign intraductal lesions from invasive carcinoma. As per our best understanding, this is a rare presentation case where there is transformation from benign intraductal lesion into mixed invasive (ductal and lobular) carcinoma.

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Case Report

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SURGICAL APPROACH TO A LARGE DENTIGEROUS CYST AND ASSOCIATED IMPACTED TEETH:INSIGHTS FROM A CLINICAL CASE

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ABSTRACT

Cysts in the oral and maxillofacial regions are common, accounting for about 20% of all lesions in oral and maxillofacial pathology. Diagnosing cysts within the jaw bones are particularly accounts for second most cyst of jaw typically occur in the age group 2- to 30 years and a definitive diagnosis usually requires histological examination of the cyst, along with clinical and radiological assessments. Here a case report of thirteen-year-old girl with painless enlargement over her lower front teeth, diagnosed with a dentigerous cyst, who successfully underwent enucleation was explained.

KEYWORDS: Dentigerous Cyst, REE (reduced Enamel Epithelium), Impacted Teeth, Enucleation, Aspiration.

INTRODUCTION

Dentigerous cyst is lined by epithelium that encircles the crown of an impacted or unerupted tooth (1). Dentigerous cyst accounts for about 25% of all tooth related cystic lesions. It is a benign, slow growing and developmental in origin. These develops when fluid accumulates in the middle of REE and unerupted tooth's crown. Normally, the follicular space measures three-four mm; if this space is greater than five mm, a dentigerous cyst is suspected (2). Dentigerous cysts generally do not cause pain or discomfort unless they become secondarily infected, and are often found incidentally on radiographs. On radiographs, these cysts appear as unilocular well defined radiolucent areas with sclerotic margins, typically around an unerupted/impacted tooth (3). Dentigerous cysts occurs as either solitary or numerous in cases with Gardner's syndrome, basal cell nevus syndrome and Cleidocranial dysplasia (3).

CASE REPORT

A thirteen years old female patient presented to Oro-maxillofacial department with the complaint of pain and swelling over lower front teeth region since few months. She noticed gradual increase in size of the chin. On extraoral examination mild facial asymmetry on right side was noted (Fig 1). Mouth opening was adequate.

On intraoral examination, a diffuse swelling of size 6 cm x 3 cm extending from 33 to 46 with labial and vestibular obliteration was noted & hard on palpation which was covered by normal oral mucosa (Fig 2). She was not syndromic and in good health condition.

FIG. 1: Extraoral Photograph

IMAGING

The orthopantomogram shows a well-defined radiolucency with radiopaque border extending from 33 to 46 region with multiple impacted teeth irt 43,44 and 45 (Fig 3).

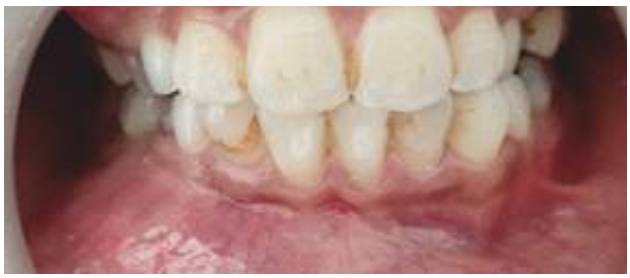


Fig. 2: Intraoral Swelling Extending from 33 to 46 Region

MANAGEMENT

Incisional biopsy was done under local anaesthesia showed a straw coloured fluid on aspiration & collected specimen sent for histopathological examination (Fig 5). A differential diagnosis of dentigerous cyst was made according to above described features.

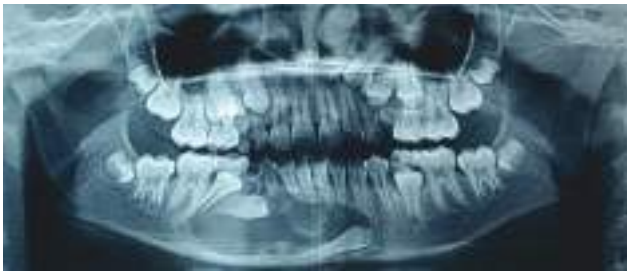


Fig. 3: Orthopantomogram

After obtaining fitness for the planned procedure the patient was aseptically prepared for cyst enucleation and surgical removal of impacted teeth under general anaesthesia. Crevicular incision made from 35 to 46 region with releasing incisions bilaterally. Full thickness mucoperiosteal flap raised buccally. There was a change in bony architecture when compared to normal bone. Bone guttering done buccally and lesion exposed. Complete lesion along with impacted 43,44,45 enucleated in toto. Irregular bony surfaces contoured using round bur. Haemostasis achieved by using cautery(FIGURE 6). After copious irrigation using Gentamicin & metronidazole, surgical cavity packed with haemostatic agent, closure was done using Vicry (l). On recall, healing was satisfactory and uneventful.

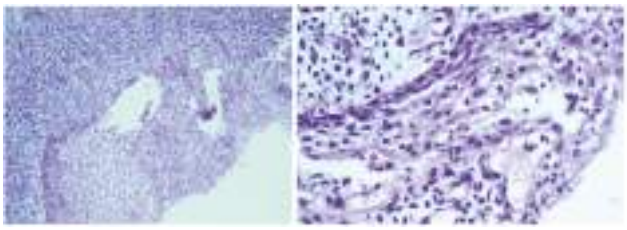


Fig. 7: Histopathological Findings

Histopathological report showed stratified squamous epithelium which is non keratinised,thick with 2-3 layers and the inflammatory cell infiltrate connective

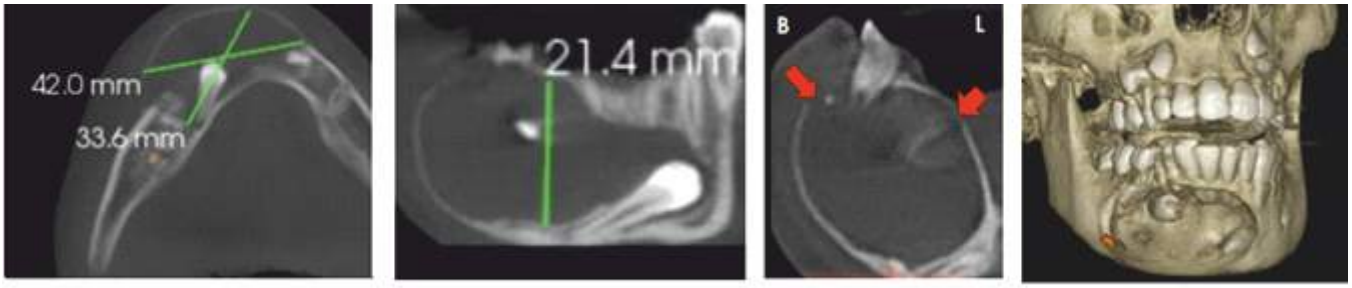
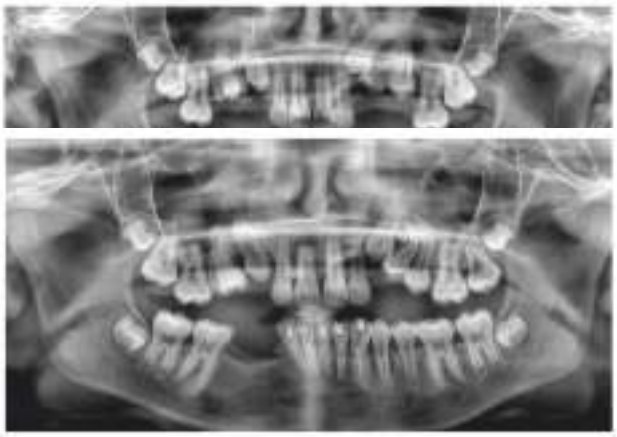
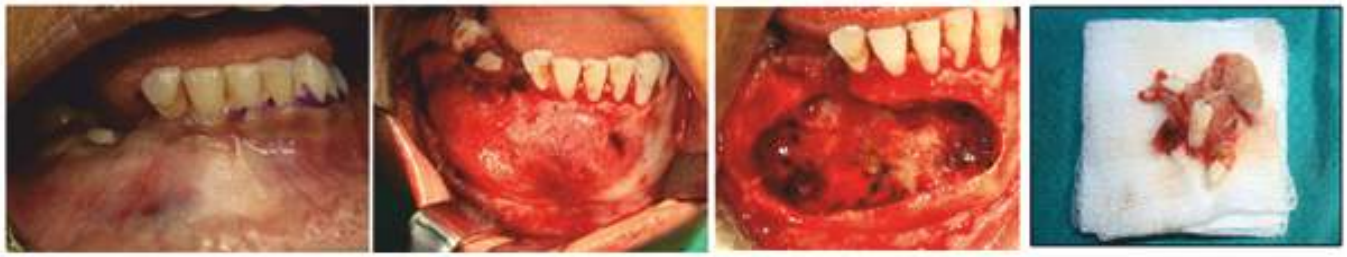


FIGURE 4 - (A) CBCT axial section showing hypodense lesion of size 42mm x 33.6mm extending from 33 to 46 region. (B)CBCT coronal section showing hypodense lesion of 21.4 mm size superoinferiorly extending from alveolar crest upto lower border of the mandible.

(C) Expansion, thinning and breach of buccal/labial and lingual co[illegible]

Fig. 5: Incisional biopsy, Aspiration revealed straw coloured fluid





A B C D

FIGURE 6 - Intraoperative photographs (A) Crevicular incision placed (B) Full thickness mucoperiosteal flap raised and lesion exposed (C) Surgical cavity after enucleation of the lesion (D) Specimen showing enucleated cyst with impacted 43,44,45

occasionally from odontomas. Dentigerous cysts are often found incidentally during radiographs, appearing as small radiolucent lesions. However, if not treated early, these cysts can grow significantly, potentially disrupting surrounding teeth, causing root resorption, or even invading and altering the surrounding bone (7,8).

Those patients with dentigerous cyst who are in the mixed dentition, caries from deciduous tooth may spread periapically and cause inflammation of the underlying developing tooth buds resulting in formation of cyst. In that cases patients are presented with both pain and swelling, then that cyst will be of inflammatory in etiology and are mostly associated with the developing lower premolar (9).

Histopathology of dentigerous cyst showed that the wall of cyst is thin and is lined by stratified squamous epithelium which is non keratinised and is of 2-3 layers thickness. Abundant cholesterol clefts are present in the cystic fluid which is in accordance to the histopathology report of our case.

The treatment methods for dentigerous cysts are marsupialization(Partsch I), enucleation (Partsch II) and Waldron's method. The choice of method based on : the size and site of the cyst, whether to remove or preserve the unerupted tooth, the age of the patient , comorbidities and the feasibility of follow-up. Marsupialization is a conservative method involves suturing the walls of the cystic cavity to the adjacent mucosa after decompression. It is preferred when preserving displaced teeth is desirable, especially in young patients (9,10).

In the current case the position of impacted teeth was unfavourable for marsupialisation and the presence of an intact lingual wall and thick lower border of mandible enabled us to perform deroofing and complete enucleation followed by packing with gelatin sponge for packing the cavity. Intraoperative topical steroid over lips with steroid cream (Betamethasone) and postoperative icepack compression yielded minimal post operative oedema and pain. Paresthesia was not present over right side of lips and chin & patient was discharged on third postoperative day.

CONCLUSION

Dentigerous cyst commonly associated with an unerupted tooth & sometimes it is an accidental finding in the radiographs. Orthopantomogram is always an initial basic radiographic investigation for ruling out of the same. Proper planning according to the patient history, clinical, radiological ,histological findings is mandatory. Larger cystic lesions liked the ones described in this case report requires management under general anesthesia and prior planning to optimize post surgical outcomes and to reduce complication rates.

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Case Report

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CASE REPORT: COLORECTAL CARCINOMA IN A YOUNG ADULT MALE

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ABSTRACT

This case highlights the significance of early detection and immediate operative management in managing colorectal carcinoma, especially in young patients who may present atypically. The diagnosis of colorectal adenocarcinoma in a young adult male underscores the need for increased awareness and consideration of malignancy even in younger patients presenting with obstructive symptoms.

KEYWORDS: Colorectal cancer, Adenocarcinoma, Rectosigmoid junction.

INTRODUCTION

Colorectal cancer (CRC) being a substantial worldwide healthcare challenge stands as the 3rd most commonly diagnosed cancer worldwide, following lung and breast cancer (1). Each year, an estimated 1.2 million emerging cases of CRC adenocarcinoma are reported, with about 600,000 associated deaths (2). The incidence rates for colon cancer are relatively similar across genders; however, rectal cancers are more frequently observed in men (3).

Several factors contribute to likelihood of developing CRC. Increasing age being a prominent risk factor, with the bulk of cases observed in individuals aged 50 and above (4). Other important risk factors include a history of colorectal polyps, family background of CRC, and lifestyle habits like low dietary fiber intake, high consumption of animal protein and fat, cigarette smoking, excessive alcohol consumption, and physical inactivity (5). Genetic predispositions also play a critical role, with hereditary conditions like Familial Adenomatous Polyposis (FAP) and Hereditary Nonpolyposis Colorectal Cancer (HNPCC) significantly increasing the risk of CRC (6).

Recent studies have also highlighted the potential protective effects of certain medications and lifestyle modifications. Nonsteroidal anti-inflammatory medications (NSAIDs) and hormone therapy have been found to substantially reduce the incidence of CRC (7).

CASE REPORT

A 27-year male patient presented to the department of surgery with a 5-day history of lower abdominal pain, vomiting, and abdominal distension. He also reported an inability to pass stools and flatus for 4 days. The pain was sudden in onset, colicky, progressive, and non-radiating, initially located in the periumbilical region before generalizing. The pain was aggravated by lying down and changes in posture but was somewhat relieved by medications. Vomiting began a few hours after the onset of pain, initially containing food particles and later becoming bilious and foul-smelling. Generalized abdominal distension with bloating was noted, and there was a significant loss of appetite over the past 8-10 months. There was no history of fever, dysuria, diet changes, swelling, chronic cough, trauma, jaundice, weight loss, irregular bowel habits, back pain, or rectal bleeding/mucus discharge.

There was no history of hypertension, diabetes mellitus, Tb, bronchial asthma, COPD, jaundice, thyroid disorders, heart diseases, or COVID-19. He had experienced similar abdominal complaints 8-10 months prior, which were managed conservatively. No prior surgeries or blood transfusions were done. No significant family history of any similar complaints or chronic disorder. A per rectal examination revealed an anal tag and decreased anal tone.

Parameters including liver and kidney function tests, electrolytes, and coagulation profile were within normal limits. Imaging studies included an ultrasound of the abdomen showing dilated bowel loops with fecal matter and sluggish peristalsis, indicating likely intestinal obstruction, along with bilateral pleural effusion and minimal fluid in the hepatorenal pouch. An X-ray of the abdomen revealed multiple air-fluid levels and distended bowel loops. CT abdomen showed thickened and edematous rectosigmoid junction and sigmoid colon causing luminal narrowing with loco-regional lymphadenopathy, suggesting a likely neoplastic

process. There were also signs of small bowel obstruction, hepatomegaly, and right renal concretions.

An emergency exploratory laparotomy was performed ,which unveiled a hard annular mass in the colon near the junction of rectum and sigmoid colon, causing obstruction.Histological sample from the mass was obtained and sent to the department of pathology.Histopathological analysis unveiled an infiltrating tumor composed of glands lined by atypical cells with a high nuclear-cytoplasmic ratio, nuclear pleomorphism, hyperchromasia, and prominent nucleoli, consistent with adenocarcinoma of the rectum.

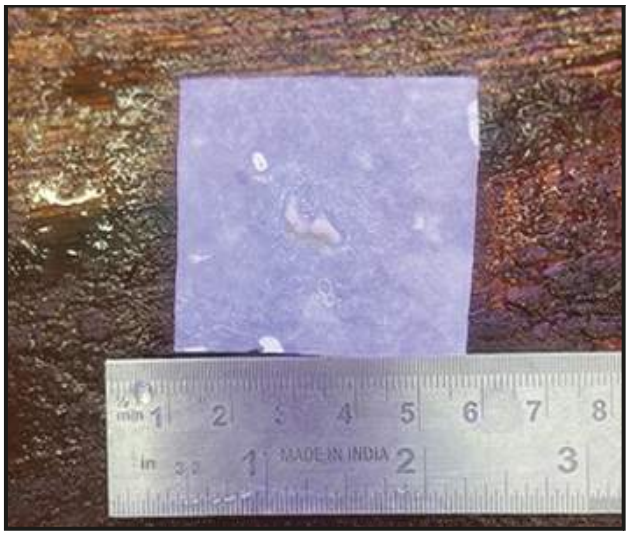

Fig. 1: Gross picture of Colonoscopic guided Biopsy

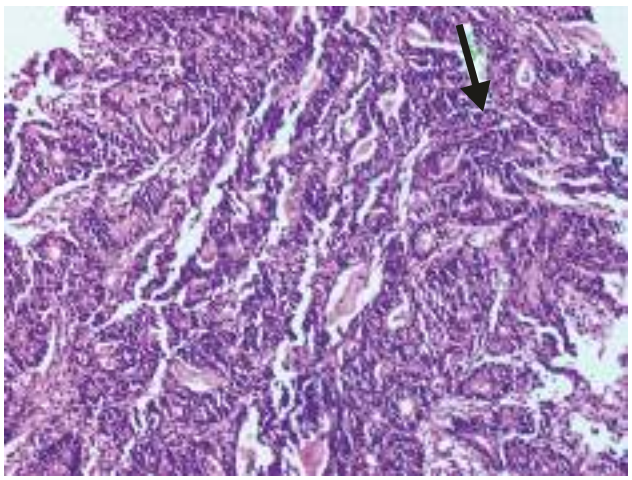

Fig. 2: Histopathological section of Adenocarcinoma of the rectum (H&E stain, ×10). The arrow highlights malignant glandular structures infiltrating the stroma with irregular architecture and desmoplastic response, indicative of invasive adenocarcinoma

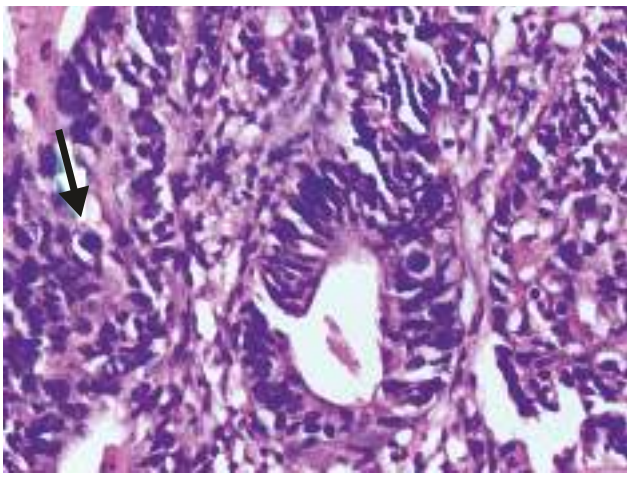

***Fig. 3:* High-power view of Adenocarcinoma of the rectum (H&E stain, ×40). The arrow points to malignant glandular epithelium with Hyperchromatic nuclei, loss of polarity, and prominent atypical features within the Tumor Glands**

CONCLUSION

Early detection and timely surgical intervention were pivotal in management of this condition. Despite the absence of a significant family history and typical risk factors, the presentation with obstructive symptoms necessitated thorough investigation and prompt action. The findings from the imaging and histopathological examination confirmed the presence of an aggressive malignancy, underscoring the potential for rapid progression even in younger patients.This case reinforces the need for increased vigilance and early screening strategies, particularly for individuals presenting with gastrointestinal symptoms that could indicate malignancy, regardless of age. It also calls for a broader awareness and consideration of colorectal cancer as a differential diagnosis in younger patients with gastrointestinal complaints, to ensure timely and effective treatment.

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Case Report

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TUMOUR RECURRENCE OF METAPLASTIC SPINDLE CELL CARCINOMA BREAST

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ABSTRACT

Metaplastic carcinomas are malignant tumours of breast in which there is differentiation of epithelial components into non-glandular elements such as spindle cell, squamous, osseous and chondroid features. A 50-year-old woman presented with a complaint of a lump in her left breast, measuring 12 × 6 × 5 cm. She is a follow up case of left mastectomy which was done 1.5 years back followed by 6 cycles of adjuvant chemotherapy in view of carcinoma breast. Ultrasonography showed well defined lobulated heteroechoic space occupying lesion with significant internal vascularity in left chest wall likely BIRADS IV/V. Fine needle aspiration cytology showed Recurrence of malignant mesenchymal neoplasm with following differentials- Malignant phylloides tumour and metaplastic carcinoma.Excision and removal was done under general anaesthesia.The specimen was sent to the pathology department for histopathological analysis, which confirmed a diagnosis of recurrent metaplastic spindle cell carcinoma of the breast.

KEYWORDS: Tumour recurrence, Metaplastic, Breast, Spindle cell, Mastectomy.

INTRODUCTION

Metaplastic breast carcinoma is a rare and highly aggressive form of breast cancer, accounting for just 0.2–0.5% of all cases. It is associated with the poorest prognosis among breast cancer subtypes and plays a significant role in breast cancer-related mortality worldwide (1).Histologically, this subtype is characterized by the coexistence of multiple cellular components, typically involving epithelial and mesenchymal elements (2). Due to its rarity and aggressive behaviour, fully elucidating the molecular and genetic characteristics of this disease has been challenging. Metaplastic carcinomas are characterized by the presence of cell populations undergoing metaplastic differentiation in which glandular cells transform into non-glandular forms (3).These changes often involve carcinomatous features, such as squamous differentiation, as well as sarcomatous elements like spindle cell, chondroid, and osseous components (1).Additionally, these tumors show a higher propensity for both local and distant recurrence and display greater aggressiveness compared to invasive ductal carcinoma, even when adjusted for factors such as age, grade, and tumor stage (4).

Spindle cell carcinoma, an aggressive subtype of metaplastic carcinoma, is characterized by spindle-shaped cells exhibiting moderate to severe atypia.It is often associated with regions of necrosis and elevated mitotic activity. This variant can exhibit diverse architectural arrangements, with cells often forming wavy, interwoven, overlapping fascicular, or irregular "patternless" structures. While focal squamous differentiation may occur, it is not consistently observed (5)(6).

CASE REPORT

A 50-year-old woman visited Surgery OPD at Era's Lucknow Medical College and Hospital with a lump in the left breast, measuring 12 x 6 x 5 cm.The lump was hard and she complained of pain in the lump occationally.There was no history of nipple discharge or any change in the colour of breast.On general examination,CNS- Patient was conscious,oriented to time place person.GCS was 15/15 and all higher functions were normal, CVS- S1S2 present, RS- Bilateral air entry present, Per abdomen- Abdomen was distended,umbilicus in midline,inverted,no scars,sinuses,fistulas,no dilated veins,all quadrants move equally on respiration,She is a follow up case of left mastectomy which was done 1.5 years back followed by 6 cycles of adjuvant chemotherapy in

view of carcinoma breast. Ultrasonography showed well defined lobulated heteroechoic space occupying lesion with significant internal vascularity in left chest wall likely BIRADS IV/V. Fine needle aspiration cytology showed Recurrence of malignant mesenchymal neoplasm with following differentials- Malignant phylloides tumour and Metaplastic carcinoma.Excision and removal was done under general anesthesia and sample was forwarded to the pathology department for histopathological examination.

Fig. 1: Ultrasonography showed well defined lobulated heteroechoic space occupying lesion with significant internal vascularity in left chest wall likely BIRADS IV/V.

PATHOLOGICAL FINDINGS

Gross- Received a yellowish white tissue piece partially covered with skin measuring 15x10x5 cm. Overlying skin ellipse separately measures 14.5x2.5 cm. Outer surface is gray white to gray brown and smooth with attached fat. Cut surface shows gray-brown to gray-black solid and hemorrhagic areas.(Representative Sections Taken)

Fig. 2: Outer surface of the Breast with skin Ellipse

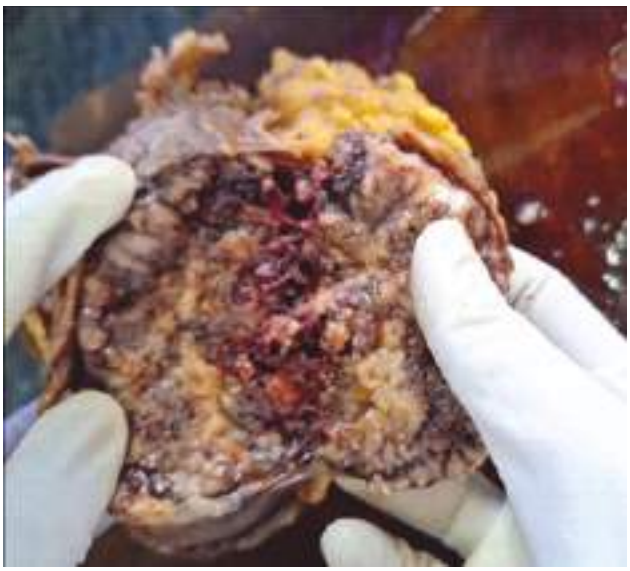

Fig. 3: Cut surface of the Breast Showing Solid and Hemorrhagic Areas.

MICROSCOPY

The tissue section reveals an invasive tumor consisting of atypical spindle cells arranged in a storiform pattern.These atypical cells have high nuclear cytoplasmic ratio, prominent nuclear pleomorphism, open chromatin, plump, elongated and amphophilic cytoplasm. Areas of necrosis and hemorrhage are also seen. The section includes skin with both epidermal and dermal layers; the epidermis is covered by stratified squamous epithelium, while the dermis contains mild chronic inflammatory infiltrates composed of lymphocytes and plasma cells. All surgical margins are involved. Immunohistochemical evaluation shows that the tumor is ER and PR negative but Her2/neu positive.

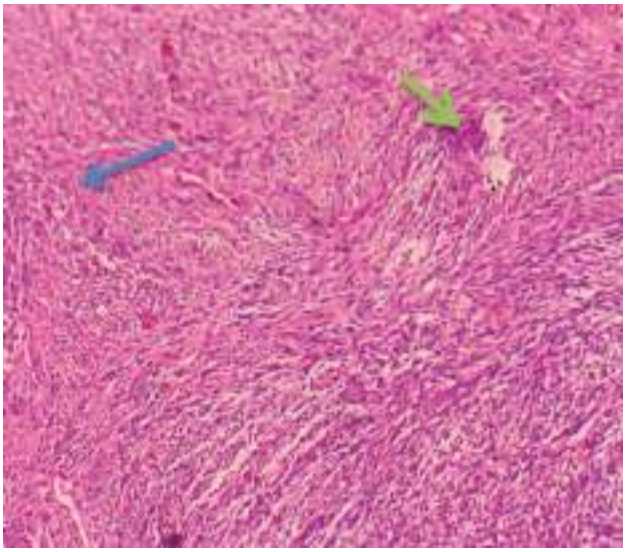

Fig. 4: Malignant Neoplasm with Pleomorphic oval to spindle shaped Nuclei (black arrow)(100x)

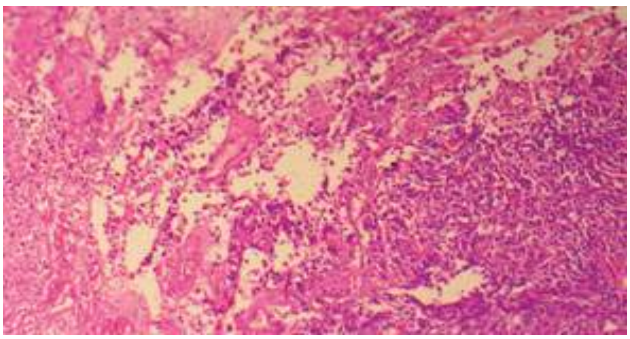

Fig. 5: Atypical spindle cells with hemorrhage (green arrow) and necrosis (blue arrow) (100x)

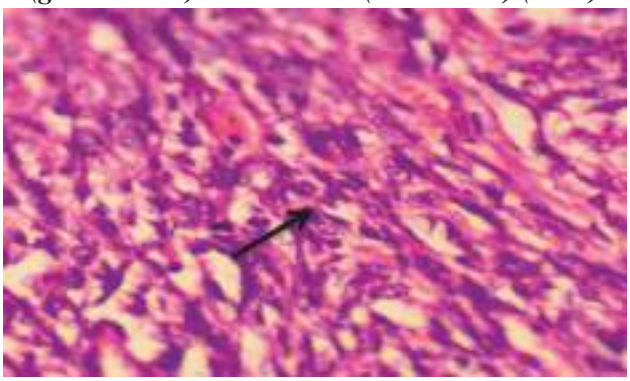

Fig. 6: Malignant Neoplasm with Pleomorphic oval to spindle shaped Nuclei (black arrow) (400x)

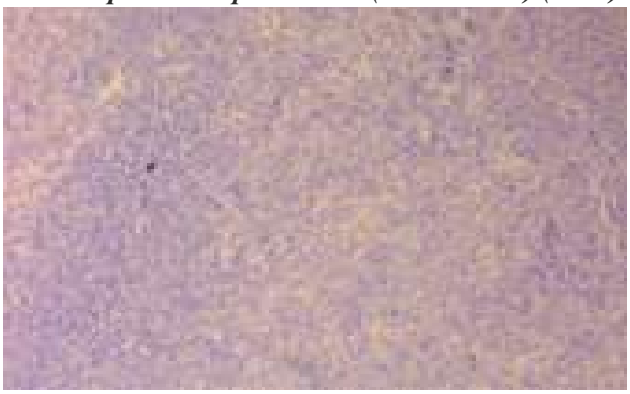

Fig. 7: **ER Negative(100x)**

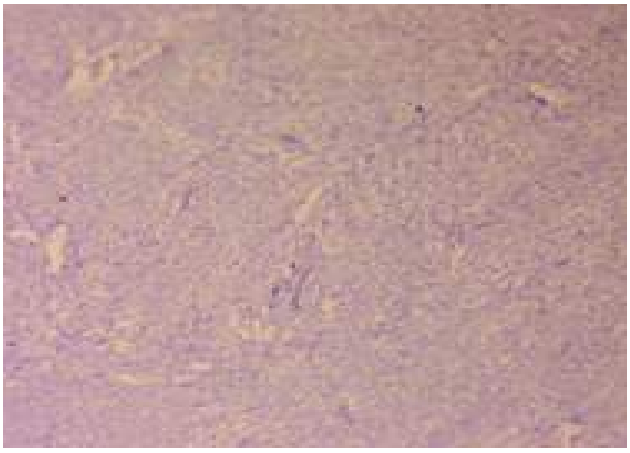

Fig. 8: **PR Negative (100x)**

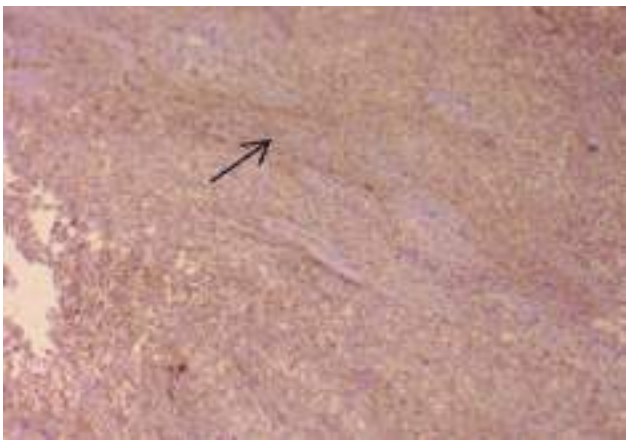

Fig. 9: **Her 2/neu Positive (Black Arrow (100X)**

FINDING

Histomorphology is suggestive of tumour recurrence (metaplastic spindle cell carcinoma- left breast).

DISCUSSION

Metaplastic breast cancer is a rare and aggressive tumor with the worst prognosis among breast cancer subtypes. Spindle cell carcinoma is considered an exceptionally aggressive variant of metaplastic carcinoma. The differential diagnosis includes phyllodes tumor, fibromatosis-like metaplastic carcinoma as well as primary and metastatic sarcomas (7).

Immunohistochemical staining is pivotal in confirming the diagnosis (5,8). Spindle cell carcinoma has highly aggressive behaviour and poorer prognosis. Its distinctive histopathological features, particularly the spindle cell morphology, are associated with higher recurrence rates. A study by Rakha et al. (2017) underscores that the diverse cellular composition and elevated mitotic activity in spindle cell carcinoma correlate with increased tumor aggressiveness and recurrence risk (9). The molecular landscape of spindle cell carcinoma often includes mutations in genes related to cell proliferation and survival, such as TP53, PIK3CA, and PTEN. These genetic abnormalities drive tumor development and contribute to treatment resistance. Research by Weigelt et al. (2014) highlighted that these mutations in spindle cell carcinoma are linked to its poor therapeutic response and higher recurrence rates (10).

MSCC often displays a biphasic pattern comprising both epithelial and mesenchymal elements, which can make diagnosis challenging. Immunohistochemical staining is crucial, with markers such as cytokeratin, vimentin, and p63 aiding in distinguishing MSCC from other spindle cell lesions. (Jung et al. (2020)) emphasized the importance of comprehensive histological evaluation and immunohistochemistry in accurate diagnosis(11). Achieving clear surgical margins during tumor resection is

critical in preventing local recurrence. However, the infiltrative growth pattern of MSC makes it challenging to obtain clean margins. Chen et al. (2016) observed that incomplete removal of the tumor is a major contributor to local recurrence in patients with MSC. This emphasizes the necessity of employing meticulous surgical methods and potentially integrating adjuvant therapies to address any remaining microscopic disease (12). Factors influencing the likelihood of recurrence in metaplastic spindle cell carcinoma (MSC) include lymph node involvement, tumour size and histological grade. Rayson et al. (2020) noted that larger tumours and higher histological grades are linked to an elevated risk of recurrence. Moreover, lymph node involvement serves as a key indicator of distant metastasis and overall patient survival (13).

CONCLUSION

Metaplastic breast cancer is an uncommon and highly invasive malignancy characterized by a significant risk of recurrence. Even with comprehensive treatment, such as mastectomy and adjuvant chemotherapy, recurrence poses a significant challenge in managing this disease. Accurate diagnosis relies on detailed histopathological evaluation supported by immunohistochemical analysis to differentiate it from other spindle cell lesions. Ensuring negative surgical margins and establishing rigorous follow-up strategies are crucial in reducing recurrence rates. Advancing our knowledge of the molecular and genetic features of metaplastic breast cancer, along with the creation of targeted therapies, is essential for enhancing patient outcomes and reducing mortality rates.

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