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A REVIEW ON ETIOPATHOGENESIS OF TYPE 2 DIABETES MELLITUS

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ABSTRACT

Type 2 Diabetes Mellitus (T2DM) is a hyperglycemic syndrome with several characteristic features. It continues to rise unabatedly in all pockets of the world, parallels with affluence and can be controlled but not cured. It has a definite involvement of genetic component but environmental factors play overwhelmingly dominant role in etiopathogenesis. Insulin resistance (IR) and obesity are singular instigators of T2DM. Hyperglycemia induces OS through multiple routes : a)stimulated polyol pathway where in ≤ 30% glucose can be diverted to sorbitol and fructose, b)increased transcription of genes for proinflammatory cytokines and plasminogen activator inhibitor-1 (PAI-1) c) activation of protein kinase-C (PKC) leading to several molecular changes d)increased synthesis of Advanced Glycation End Products (AGEs) e)changes in a receptor far AGEs and f) autooxidation of glucose with formation of ketoimines and AGEs. All these processes are accompanied with alteration in redox status, Reactive Oxygen Species (ROS), Reactive Nitrogen Species (RNS) and Oxidative Stress (OS) which trigger T2DM and its complications. Initial hurriedly planned and executed experimental and clinical studies showed promising results of antioxidant therapies, but recent studies indicate that excess intake/ supplement may have adverse outcomes including increased mortality. It is advocated that antioxidants should be given only if preexisting deficiency is present. Selection of antioxidant is another important aspect. Lastly but most importantly the impact of OS is not obligatory but facultative. As such only those diabetic patients will be benefited by antioxidant therapies that have impelling punch of prooxidants.

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INTRODUCTION

"All the diseases are the result of collection of waste materials, the latter being initiated by many causes to produce symptoms; wastes collect due to in correct dieting and living" –*Atharva-Veda*

Selsus 30 BC- 38 AD is credited for the first clinical description of the diabetes mellitus (DM) "as a disease of polyuria without pain but with emaciation and hunger". Tchang-Tchang, (200 AD), a Chinese physician described it as a "disease of thirst". Avicenna, (1000 AD), an Arab physician, described the clinical manifestation vividly including its complications like gangrene, retinopathy and nephropathy. In the late 17th century the name mellitus, meaning sweet, was added. Occurrence of proteinuria in DM is known since 18th century. (1) Cullen (1776) outlined the difference between diabetes mellitus and diabetes insipidus. (2) The later is a much rarer disease resulting from deficiency of antidiuretic hormone (ADH) where there is polyuria but urine is not sweet. It was only in 1776 that Dobson proved the presence of sugar in diabetic urine which was later on indentified as glucose (Chevreul, 1815). Subsequently attributed the foul breath (Rotten apple) of to the presence of acetone in diabetic patients. Gregor,(1850) recognized hyperglycemia in cases of T-2DM. In the same year Fehling devised the test for detecting the presence of sugar in the urine. Petters, (1857) detected acetone like substances; identified acetocetic acid and Kutz, (1945-95) documented β-hydroxy butyric acid in the urine of diabetics (Quoted from N.E.J., 1976). (3)

In 1860, Paul Langerhan demonstrated histologically the presence of islet cells in pancreas. Minkowski, (1889) reported that the internal secretion of these islet cells has got important role in carbohydrate metabolism and anti-diabetic properties (Quoted from Harpers Biochemistry, Ed. 1997). Benedict in 1910 gave the idea of Benedict reaction to detect sugar in urine. In 20th century, when diabetes was well recognized as an abnormality of carbohydrate metabolism, several scientists reported that experimental removal of islet of langerhans from the pancreas produced diabetes in dogs. This finding led to the discovery of insulin by two Canadian doctors, Fredrick Banting and Charles Best in 1921, which was any yardstick was a revolutionary discovery and fetched them noble prize. The importance and of this impact discovery can be further realized by the fact that Sanger received noble prize for sequencing the structure on insulin. In the intervening period in 1922 on January 11th for the first time a patient of diabetes was treated with insulin (Quoted from Medical and Health Encyclopedia Vol. 4, 1984). (4, 5)

Tobson *et al*., (1942) and Loubatieres, (1944-1946)

introduced sulphonylurea derivatives as oral hypoglycemic agents. In 1953, glomerulosis was detected as one of the manifestation of widespread microangiopathy. Presently is recognized as a syndrome characterized by insulin resistance, abnormal insulin secretion, derangement in carbohydrate and lipid metabolism, and is diagnosed by presence of hyperglycemia. The changes in carbohydrate and lipid metabolism are usually consequence of the disease. The altered lipid profile can lead to cardiovascular complications in DM is abundantly documented in literature. DM is a global problem and alarmingly its incidence is on rise in almost all pockets of the world. The estimated number of people in different region is given in table 1 (WHO 1980). Due to increasing obesity, sedentariness and dietary habits in both western and developing countries, the prevalence of T-2DM is growing at an exponential rate. Type-I DM is less common.

CLASSIFICATION

The latest criteria of classification are given as below. (6) The spectrum from normal glucose tolerance to diabetes in type 1 DM, type 2DM and other specific types of diabetes, and gestational DM in shown from left to right. Mostly in types of DM, the individual traverses from normal glucose tolerance to overt diabetes. Arrows indicate that changes in glucose tolerance may be bi-directional in some types of diabetes for example, individuals with type 2 DM may turn to the impaired glucose tolerance category with weight loss; the gestational diabetes may revert to impaired glucose tolerance or even normal glucose

Table 1: Criteria for classification (Powers, 2005)

Type of diabetes	Normal glucose tolerance	Hyperglycemia			
		Impaired fasting glucose or impaired glucose tolerance	Not insulin requiring	Insulin required for control	Insulin required
Type 1					
Type 2					
Other specific types					
Gestational diabetes					
Time (yrs)					
Fasting plasma glucose (mg/dl)	<100	100 -125	>123		
2-hr plasma glucose (mg/dl)	<140	140 -199	>200		

tolerance after delivery. (7, 8)

1. IGT defined as 2-h plasma glucose between 7.8 and 11.1 mmol/L (140-200 mg/dl)
2. Impaired fasting glucuse (IFG), fasting plasma glucose between 6.1 and 7.0 mmol/L (110-126 mg/dl).

Table 2: Definition of glucose tolerance states (WHO criteria 1999 & ADA 1997)

		2-h Plasma glucose, mmol/L (mg/dl)		
		<7.8 (140)	7.8 11.0 (140-199)	e11.11 (200)
Fasting Plasma Glucose mmol/L (mg/dl)	<6.1 (110)	Normal	IGT	Diabetes on an isolated 2 hr hyperglycemia IPH (isolated post challenge hyperglycemia)
	6.1-6.9 (110-125)	IFG	IFG and IGT	
	≥7.0(126)	Diabetes on an isolated fasting hyperglycemia		Diabetes on both fasting and 2-hr hyperglycemia

Table 3: Classification of diabetes

Type 1(-cell dysfunction, usually leading to absolute insulin deficiency)

- Autoimmune
- Idiopathic

Type 2 Ranges from pre-dominantly insulin resistant with relative insulin deficiency, to a predominantly insulin secretory defect, with or without insulin resistance.

- Other specific types
- Genetic defects of -cell function
- Genetic defects of insulin action
- Disease of endocrine pancreas
- Endocrinopathies
- Drug induced or chemical induced
- Infections
- Uncommon forms of immune-mediated diabetes
- Other genetic syndromes sometimes associated with diabetes
- Gestational diabetes.

The Global Surveys distinctly reveal that type-2 DM is a threat to human health and requires comprehensive attention. DM type 2 is highly correlated with BMI. A study from this region also confirmed it and concluded the subjects with BMI≥23 kg/m^2 are more prone to DM type-2 (Shah, 2005). The various risk factors are summarized as under (Powers, 2005). The various risk factors are summarized as under:

- Family history of diabetes (i.e., parent or sibling with type 2 DM).
- Obesity (BM≥25 Kg/m^2)
- Habitual physical activity
- Race/ethnicity (e.g., African-American, Hispanic-American, Native-American, Asian-American, Pacific Islanders).
- Previously identified IGF or IGT.
- History of GDM or delivery of baby >4 Kg (>9lbs) i.e., microsomia.
- Hypertension (BP≥140/90 mmHg)

- HDL-Cholesterol level ≤ 35 mg/dl (0.90 mmol/L) and/or a triglyceride level ≥ 250 mg/dl (2.82 mmol/L).
- Polycystic ovary syndrome or acanthosis nigricans
- History of vascular disease
- Free radical injury
- Weak antioxidant status
- Low antioxidant non-antioxidant level
- Poor dietary antioxidant status

In the recent years growing evidence strongly suggests that free radicals either independently or with many other risk factors can initiate or exacerbate diabetes mellitus. Their role has been implicated both in type 1 and type 2 DM, but with stronger evidence in the latter. Increased production of relative oxygen species (ROS) has been abundantly reported, but in majority of the reports poor antioxidant status has been involved. Diminished receptor sensitivity to insulin and diminished number of insulin receptors particularly in obese diabetics has also been proposed to be the etiological factor. (9) Dyslipipoproteinemia is an independent risk factor for the development of coronary artery diseases, myocardial infarction, and hypertension in hyperlipidemic patients. (10) Clinically diabetic patients are characterized by marked increase in blood glucose level followed by normal or mild hyperlipidemia.

Elevated level in low density lipoprotein (LDL) along with triglyceride especially in very low density lipoprotein(VLDL) and cholesterol in low density lipoprotein with free radicals mediated formation of modified LDL is recognized as a leading cause of development of Atherosclerosis in CAD with T2DM patients.(11) Furthermore hyperlipidemia may also induce abnormalities like resistance to insulin in muscle and liver cells in CAD with T2DM patients. (12)

Coronary artery diseases (CAD) and CAD with T2DM are the most frightening of the health prediction for the new millennium worldwide. According to world health report 2002, CVD will be the largest death causing disease in India. In India by 2020AD, 2.6 million Indian are predicted to die due to CAD, which constitutes 54.1 % of all CVD death. (13) CAD, the most common form of heart disease is characterized by atherosclerosis and the development of fibro-fatty plaques, which is followed by the formation of occlusive thrombi and the precipitation of acute events that interrupts the blood flow. (14) This condition leads to a disparity between oxygen supply and demand. If this imbalance is exceeds, it results in myocardial infarction (MI). (15) Type 2 Diabetes Mellitus (T2DM) is a group of abnormal metabolic paradigms with the essential feature of hyperglycemia and is dubbed as the disease of "premature ageing". Incidence of CAD with T2DM is rising all over the world at worrying rate, despite, comprehensive and coordinated effects of World Health Organization (WHO), International Diabetes Federation and Several Social Science Agencies. (16)

All efforts have failed till date to arrest this rising incidence. 6.6 % of the world population was affected by this disease in 2010 with an estimated 285 million carriers and the number may become almost double (552 million) by 2030. India is facing an even grimmer scenario. In 2000, the number of diabetic carriers was 31.7 million which rose to 58.7 million in 2010 and 12 million more patients are expected to get added in another 20 years.

On the basis of affected population, both in terms of percentage and numbers India has significantly more patients than China and other neighboring countries and is often referred to as the diabetic capital of the world. The reasons for this lopsided proclivity are still poorly understood. (17) Metabolically, CAD with T2DM is a hetrogenous multifactorial syndrome with environmental and pleotropic involvement in which the former are overwhelmingly significant factors. Indeed, hyperglycemia is an essential expression due to relative or absolute lack of insulin action or secretion. Pathway selective insulin resistance is a cardinal, if not essential feature.

It is almost inevitably accompanied with hyperglycemic complexities such as altered lipid metabolism and raised oxidative status due to unfavorable "Cellular Redox Homeostatic Box". Several researchers have corroborated this condition by animal cell culture and *in vitro* studies and our recent animal studies also support those findings. (18-20) Therefore, present study was design to assess the level of altered lipid profile, lipoprotein sub fractions, oxidative stress and antioxidants in CAD with T2DM patients.

CONCLUSION

In summary, the glucose homeostasis is a cusply coordinated process and is operated by several parallel, serial and cross switches. Indeed, the hormone insulin is the most powerful molecule to act as a central director through an army and arsenal of intracellular and extracellular molecules known as "Insulin Signaling Cascade". Ironically our knowledge in this regard is still incomplete. Influence of ROS, RNS and antioxidants has been under scanner on this cascade in triggering diabetes. Evidence is mounting to suggest : I) ROS and RNS are important regulators of glucose homeostasis in blood and tissues and this deregulation may trigger T-2DM and may set additional complications in due course of time. II) The

FR could be causative factors is the genesis of IR. III) Redox perturbations in mitochondria consequent to altered ATP generation in electron transport chain results in enhanced leakage of electrons to form more superoxide anion. IV) metabolic changes in cytosol consequent to changes in enzyme activities of NADPH oxidase, xanthine oxidase uncoupled nitric oxide synthase and many others increase the generation of reactive species. Both of these activities may participate in the pathogenesis of T-2DM. V) many environmental factors overwhelmingly tilt the redox homeostasis toward proxidizing conditions which affect the insulin signaling cascade and genetic disposition to diabetes and lastly. VI) the reactive species may promote diabetes risk by provoking genetic factors. Antioxidants are undoubtedly essential spokes of human life but their excess intake is undesirable. Further our studies on several series of diabetic patients and those of others indicate that raised OS is not an inevitable phenomenon in diabetes. Thus, despite all the loaded evidence for the involvement of reactive species in the diabetes, the debate continues on three points: a) is it selective in patients or present in all patients but not detectable by available methods, b) is it facultative, that is, it is capable of causing disease but does not necessarily do so in all patients and c) is it obligatory, that is, it universally participates in the genesis of diabetes. As the evidence stands today, the participation of ROS and RNS is selective and facultative. Antioxidants have so for not received putative pat in the medicine though FR involvement has lately been given recognition. The crux of the lesson is that controversies should not deter and discourage us rather infuse determination in us to carry the work to final destination by scrupulously veracious precision work. We would only like to post a caution "Those who fail to read the history are destined to suffer from repetition of the mistakes". We must therefore tread carefully with exactitude in future.

REFERENCES

1. Selsus cited by Allen FM, Stilman E and Fitz R. Total dietary regulation in the treatment of diabetes. New York Rock feller Institute of Medical Research (30 BC – 38 AD).1919: 2.
2. Cotunnius Nepropathy in diabetes. Disch. Med. Wochenschr.1770; 107 :732-735.
3. Cullen. Complication in diabetes, Diabetes. 31. 1776: 846-848.
4. Chevreul. Cited by Allen FM, Stillman E and Fitz R. Total dietary regulation in the treatment of diabetes, New York Rockefeller Institute for Medical Research.1815: 18.
5. Tobson et al. (1942). Quoted from encyclopedia.1970;23: 268.
6. Powers AC Diabetes mellitus, Text Book of Internal Medicine Harrison 16th edition Eds. Kasper et al.2005: 2152-2181.
7. Loubatieres. Quoted from encylopedia.1970; 23: 268.
8. WHO expert committee on diabetes mellitus. Second report WHO. Tech Rep. Ser.1980; 646: 1-80.
9. Singh pp, Mahdi F, Roy A and Sharma P, Reactive oxygen species, reactive nitrogen species and antioxidants in etiopathogenesis of diabetes mellitus type-2. Indian Journal of Clinical Biochemistry. 2009; 24(4): 324-342.
10. Kumar V, Mahdi F, Singh R, Mehdi AA, and Singh RK. A clinical trial to assess the antidiabetic, antidyslipidemic and antioxidant activities of Tinospora cordifolia in management of type – 2 diabetes mellitus. Int J Pharm Res. 2016; 7(2): 757-764.
11. Kumar V, Karoli R, Singh M, Mishra A, Mehdi F. Evaluation of oxidative stress, antioxidant enzymes, lipid and lipoprotein profile in type-2 diabetic patients. Int J BioAssay. 2015; 4 (10): 4365-4368.
12. Kumar V, Mishra D, Khanna P, Karoli R, Singh M and Mehdi F. A review of antioxidant enzymes, oxidative stress, lipid profile and lipoprotein constituent in the patients of coronary artery disease (cad) with type 2 diabetes mellitus (T2DM). Int J BioAssay. 2015; 4 (10): 4443-4447.
13. Verma P, Kumar V, Rathore B, Singh RK and Mahdi AA. anti-diabetic and anti-oxidant properties of aloe vera in alloxan induced diabetic rats. Int J Pharmacogonsy. 2016; 3 (7): 319-324.
14. 5. Verma P, Kumar V, Rathore B, Singh RK and Mahdi AA: Hypolipidemic Activity of Aloe Vera in Hyperlipidemic Rats. Int J Pharmacognosy 2016; 3(4): 196-00.
15. Neerja J, Verma P, Kumar V, Mahdi F, Mahdi AA, Khanna AK, Saxena JK and Singh RK: Antidyslipidemic and Antioxidant Activity of Medicinal Plants In Rat Model of Hyperlipidemia. Int J Pharm Sci Res 2016; 7(11): 4579-4587.
16. Tamboli SB, Sontakee SP, Parsode RB. 2013. Study of hypoglycemic activity of Tinospora cordifolia in alloxan induced diabetic rats. Int J Basic Clin Pharmacol., 2(5): 559–561.
17. Whiting DR, Guariguata L, Weil C, Shaw J. IDF,

2011. Diabetes Atlas. Global estimates of the prevalence of diabetes for 2011 and 2030. Diabetes Res Clin Pract., 94: 311-21.

18. Kumar V, Mahdi F, Chander R, Khanna AK, Husain I, Singh R, Saxena JK, Mehdi AA, and Singh RK, 2013. Tinospora cordifolia regulates lipid metabolism in alloxan induced diabetic rats, Int. J. Pharm. & Lif. Scie., 4(10): 3010-3017.

19. Singh M, Anwer E and Kumar V: Assessment of biochemical parameters in the patients of coronary artery disease with type 2 diabetes mellitus. Int J Pharm Sci Res 2017; 8(3): 1420-1426.

20. Kumar V, Singh R and Singh RK. Review on role of herbal remedies on cardiovascular system. Biomedical Sciences and Herbal Medicines; Edited by Professor Mahdi AA. 2017: 329-340.

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