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A REVIEW ON DIABETES

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ABSTRACT
Diabetes mellitus is a general term for heterogeneous disturbances of metabolism for which the main finding is chronic hyperglycaemia. The cause is either impaired insulin secretion or impaired insulin action or both. High blood glucose levels are symptomatic of diabetes mellitus as a consequence of inadequate pancreatic insulin secretion or poor insulin-directed mobilization of glucose by target cells. Diabetes mellitus is aggravated by and associated with metabolic complications that can subsequently lead to premature death. This review explores diabetes mellitus in terms of its historical perspective, biochemical basis, economic burden, management interventions along with the future perspectives.

KEYWORDS: Diabetes mellitus, Types.

INTRODUCTION
Diabetes mellitus (DM) is the most common endocrine metabolic disorder which caused by improper regulation of insulin secretion or insulin action. Deficiency of insulin leads to chronic hyperglycaemia with disturbances of fat, protein and carbohydrate metabolism.[1-4] Long term diabetes cause tissue or vascular damage and leads some dangerous complications like neuropathy,[5,6] nephropathy,[7,8] retinopathy,[9,10] cardiovascular complications[11,12] and ulceration.[13,14] First diabetic classification and diagnostic criteria was given by World Health Organization (WHO) in 1965[15] and the National Diabetes Data Group (NDDG) in 1979.[16]

Symptoms:-Blurred vision, polyurea, polyphagia, polydipsia, weight loss, constipation, cramps, thirst, hunger, weakness,[17,18] and candidiasis are common symptoms for both type-1 and type-2 DM.[1] Apart from that the patients with Type-1 DM have both microvascular problems[5-10] and macrovascular diseases such as heart, peripheral vascular and coronary artery diseases[11,12] while patients with Type 2 DM have high risk of large vessel atherosclerosis commonly associated with obesity, hypertension, hyperlipidaemia.[11,12,19,20] Most patients are die with type-2 diabetes due to cardiovascular complications and end stage renal disorder.[9-12]

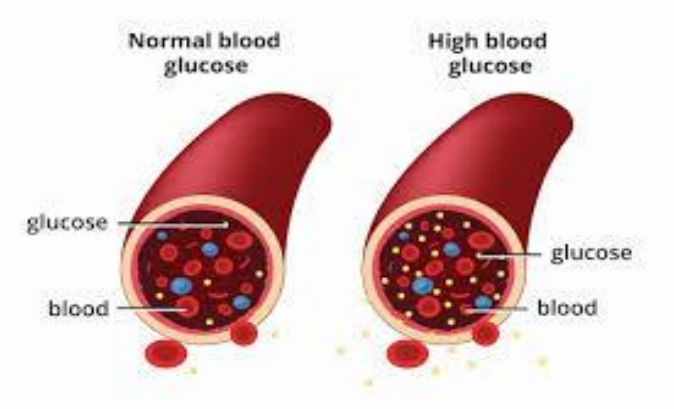

Fig. 1: Diabetes.

Types

There are several types of diabetes mellitus but two main types are type-1 and type-2.[21,22] On the basis of aetiology type-1 is describe as IDDM(juvenile-onset diabetes) and type-2 describes as NIDDM (maturity-onset).

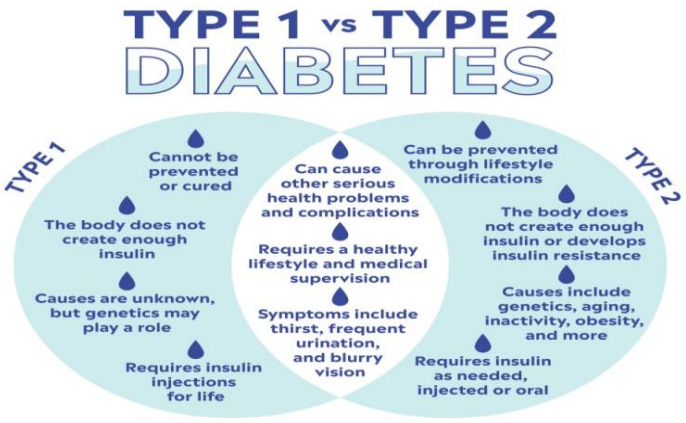

Fig. 02: Types of diabetes.

Type-1 diabetes:- It occurs in those patients who have no or little endogenous insulin secretory capacity and require insulin therapy for survival. Type-1 diabetes is further divided into two categories; Type-1a:- which is characterized by presence of islet cell antibody (ICA), anti-glutamic acid decarboxylate (anti-GAD) and insulin antibodies (IA-2) that identify the autoimmune process with ß-cell destruction.[22,23] and is caused by immunological destruction of pancreatic ß cells and leads to insulin deficiency and other is type-1b; which is idiopathic and have no autoimmunity.[23,24]

Type-2 diabetes:-Globally 5-7% of the world's population[25,26,27] and in Western countries up to 7% of the population is affected by type-2 diabetes.[27,28] Urban areas have high incidence of type-2 diabetes than in rural areas.[26,29,30] Type-2 diabetes is associated with obesity, decreased physical activity, heredity and characterized by the disorders of insulin secretion and insulin resistance.[31] It is common in individuals over the age of 40[19,20] and is usually controlled through dietary therapy, exercise and hypoglycaemic agents.[32,33]

Gestational Diabetes (GD) mellitus:-Gestational diabetes is occurs during second or third trimester of pregnancy.[34] It occurs in about 4% of all pregnancies. GD Patients have 30% to 50% chance of developing DM, usually type 2 DM.

Other types of diabetes mellitus include genetic defects of the pancreatic ß cell or in insulin action pathways (insulin receptor mutations or post-receptor defects).[35] Endocrinopathies producing insulin counter regulatory hormones (e.g., Cushing's syndrome, acromegaly), disease of the exocrine pancreas (e.g., Pancreatitis, pancreatic reaction, or cystic fibrosis) may produce DM.[36] several medicines such as niacin, glucocorticoids, pentamidine, and a-interferon may also lead to DM.[37]

Epidemiology:-In 2011, 4.6 million deaths occurs by DM and estimated that 366 million people are suffering from diabetes mellitus in 2011 which may risen to 552 million in 2030.[38] In 2030, 439 million people would have type 2 DM and the causes of type 2 DM varies by environmental and lifestyle risk factors.[39] The incidence of DM is common in adults of which type 2 DM is becoming prominent and will increase in the next two decades in developing countries where most of the patient are aged between 45 and 64years.[40]

Diabetes in India:-In 2010 approx 285 million people worldwide (6.6%) have diabetes and most of the diabetic patients are belonging to the age between 20-79years which will increase up to 438 million people (7.8%) in 2030. According to Diabetes Atlas 2006 which was published by International Diabetes Federation, around 40.9 million people have diabetes in India which is expected to be rise up to 69.9 million.[41] In 2000, India (31.7 million) topped the world with the highest number of people with diabetes mellitus followed by China (20.8 million) with the United States (17.7 million) in second and third place respectively.[10,14] Diabetes is potentially epidemic in India with more than 62 million diabetic persons currently diagnosed with this disorder.[42,43]

Free radicals:-In human body, during manufacture of plastics, ageing of paints and the combustion of fuels produce Free radicals in a wide range of chemical and biological systems. In living organisms, free radicals and other 'reactive species are controlled by a group of antioxidant defences, which reduces oxidative damage to bio molecules. In human disease, the balance of 'oxidant–antioxidant' is tilted in the favour of reactive species, so that oxidative damage levels increase. In some diseases, this may contribute to tissue injury, provide growth for therapeutic intervention with rationally designed antioxidant drugs.[44,45] Free radical can be defined as an atom or molecule containing one or more unpaired electrons, an unpaired electron being one

that is alone in an orbital and is capable of independent existence.[46] Free radicals are involved in many pathological conditions such as many types of diabetes, neurodegenerative diseases, cardiovascular diseases (CVDs), cancer, cataracts, asthma, rheumatoid arthritis, inflammation, burns, intestinal tract diseases, progerias and ischemic and post-ischemic pathologies.[47]

Sources of free radicals

The ROS can be produced from either endogenous sources such as mitochondria, peroxisomes and endoplasmic reticulum, where the oxygen consumption is high or exogenous sources.

Mitochondria:- Mitochondria is capable of producing intracellular ROS. The superoxide radicals are produced from two major sites in the electron transport chain, namely NADH dehydrogenase (complex I) and ubiquinone cytochrome "c" reductase (complex III). The generation of superoxide is non-enzymatic and therefore higher the metabolic rate, the greater is the production of the ROS.[48] Monoamino oxidase, aketoglutarae dehydrogenase, glycerol phosphate dehydrogenase and p66shc are the other mitochondrial components which contribute in formation of ROS.[49]

Peroxisomes

In peroxisomes the respiratory pathway involves in transfer of electrons from various metabolites to the oxygen leads to H2O2 formation,[50] but is not coupled to oxidative phosphorylation to produce ATP, only free energy is released in the form of heat. beta-oxidation of fatty acids is the major metabolic process of producing H2O2 in the peroxisomes. H2O2, O 2 •- OH• and NO• are other free radicals which are produced in peroxisomes. There are different peroxisomal enzymes such as acyl CoA oxidases, D-amino acid oxidase, L-alpha-hydroxy oxidase, urate oxidase, xanthine oxidase, D-aspartate oxidase are capable to produce different ROS.[51]

Endoplasmic reticulum:- Diamine oxidase and enzymes of endoplasmic reticulum such as Cytochrome p-450 and b5 contribute to the formation of ROS. The other endogenous sources of ROS include prostaglandin synthesis, auto-oxidation of adrenalin, phagocytic cells, reduced riboflavin, FMNH2, FADH2, cytochrome P 450, immune cell activation, inflammation, mental stress, excessive exercise, infection, cancer, aging, ischemia etc.[52]

Oxidative stress

Oxidative stress is the situation of a severe imbalance between production of reactive species and antioxidant defence. In 1968, Irvin Fridovich discovered superoxide dismutase (SOD) which is a very unique enzyme that catalyzing the transition of O2• into H2O2.[53,54] Then few years later, Chance and coauthors reported that mitochondria are the key producer of O2*in cells[55] and has been found that free radicals are produce in biological system and their concentrations are regulated by enzymatic mechanism. Later it has been proved that non-radical products such as H2O2 or hypochlorous acid, which are also powerful oxidizing agents, participated in free radical reactions same as free radicals.[56] Radicals and the non-radicals species are collectively known as "reactive oxygen species" (ROS) where as Nitric oxide (NO•) and peroxynitrite were also interact with ROS, and all of these species were known as RONS which is produced by immune system[57] but excessive production of RONS would damaged almost all classes of biomolecules, such as lipids[58] proteins[59] and DNA.[60,61] The term "oxidative stress" was introduced in 1970s and 1980s to describe these deleterious processes. Helmut Sies defined oxidative stress as; it is an imbalance between oxidants and antioxidants in favor of the oxidants, potentially leading to damage.[62] Induction of oxidative stress is very important for immune system as it play significant defense mechanism against bacteria.[63]

After observation of oxidative damage reactions of biomolecules shows that primary RONS such as O2•, H2O2 or NO•, in most cases reversibly react with the target molecules and oxidative damage is primarily associated with secondary RONS, such as •OH, ONOOand HOCl.[64-66] There are two major reactions leading to the formation of toxic RONS are: (i) the Fenton reaction between ferrous ions and H2O2 yielding •OH; and (ii) the reaction of O2• with NO• yielding ONOO. Iron ions can directly react with organic peroxides, inducing lipid peroxidation and presence of iron and copper ions involve in double-strand breaks of DNA.[67] Oxidative damage to proteins is regularly associated with the reaction between amino acids and ONOO which forms nitrated amino acids like nitrotyrosine.[68]

Rons

ROS (Reactive oxygen species):- oxygen derived radicals are most important radical species which are generated in living system. Molecular oxygen is a radical and has a special electronic configuration. Addition of one molecule to dioxygen forms superoxide anion radical[69] and it is generate mainly in a cell of mitochondria.[70]

Superoxide anion are generated through metabolic processes or by physical irradiation which called as primary ROS and these ROS further interact with other molecule to generate secondary ROS.[71] Both complex 1 and complex III electron transport chain are involved in producing superoxide and when they are in anionic form, it is more charged and easily crosses the inner mitochondrial membrane. Recently, it has been confirmed that complex1 dependent superoxide is completely released into matrix.[72] The superoxide radicals participated in the Haber- weiss reaction which combines a fenton reaction and the reduction of Fe3+ by superoxide yielding Fe2+ and oxygen[73] Hydroxyl

radical is very dangerous because of its high reactivity and half life of approximately 10ˉ 9s in vivo. Hydroxyl radical is the neutral form of hydroxide ion.[74] According to fenton reaction the most flexible hydroxyl radical is produce when Mn+ is iron, chromium, cobalt and copper[75] Organism which have higher amount of iron (hemochromatosis, b-thallasemia, hemodialysis) contain large quantity of "free available iron" and are transported into an intermediate, labile iron pool which represents a steady state exchangeable and readily chelatable iron compartment.[76] Other reactive radicals which are produced by oxygen in living system is peroxyl radicals and HOO* is the most simple form of peroxyl radical, called hydroperoxyl radical[77] Hydroperoxyl radical begin the fatty acid peroxydation by two pathways:- fatty acid hydroperoxide independent and LOOH dependent ways.[78]

RNS (reactive nitrogen species):-Nitric oxide is an important reactive radical that act as oxidative biological signalling molecule in different physiological processes such as defence mechanism, blood pressure regulation, immune regulation, neurotransmission and smooth muscle relaxation.[79] NO* is soluble in both liquid and lipid medium and readily diffuse through cytoplasm and plasma membranes Half-life of NO* is only few seconds in an aqueous environment and has greater stability in an environment with low oxygen concentration.[80] NO reacts with oxygen and water to form nitrate and nitrite ions. Excess production of reactive nitrogen species called nitrosative stress[81,82] which may lead to nitrosylation reaction and alter the protein structure and inhibit their normal function. During inflammation process, cells of immune system produce both super oxide anion and nitrogen oxide during oxidative burst and readily react together to produce oxidatively active molecule such as peroxynitrite anion which is a very potent oxidising agent that can cause DNA fragmentation and lipid oxidation.[83]

Table 1: Different types of ROS and RNS produced in the cell.

Reactive Oxygen Species (ROS)

Radicals:	
$O_2^{\cdot -}$	Superoxide
$OH^{\cdot}$	Hydroxyl
$RO_2^{\cdot}$	Peroxyl
$RO^{\cdot}$	Alkoxyl
$HO_2^{\cdot}$	Hydroperoxyl

Non-Radicals:	
H_2O_2	Hydrogen peroxide
$HOCl^-$	Hypochlorous acid
O_3	Ozone
$^1O_2$	Singlet oxygen
$ONOO^-$	Peroxynitrite

Reactive Nitrogen Species (RNS)

Radicals:	
$NO^{\cdot}$	Nitric Oxide
$NO_2^{\cdot}$	Nitrogen dioxide

Non-Radicals:	
$ONOO^-$	Peroxynitrite
ROONO	Alkyl peroxynitrites
N_2O_3	Dinitrogen trioxide
N_2O_4	Dinitrogen tetroxide
HNO_2	Nitrous acid
NO_2^+	Nitronium anion
NO^-	Nitroxyl anion
NO^+	Nitrosyl cation
NO_2Cl	Nitryl chloride

Relation between oxidative Stress and Diabetes

Immune response of the body such as response against self-cells and self-biomolecules is directly linked with all 3 types of diabetes so any disturbance in immune response can cause any type of diabetes. In many other studies it is proved that the auto-reactive CD8+ T cells are able to cause type-1 diabetes where as immune cells destroyed the beta islets of Langerhans and cause type-1 diabetes.[84,85] Same as Type 2 and Type 3 diabetes are connected with immune response. It was hypothesized that the non-specific response of the immune system may produce diabetes and found that the patient with diabetes have association of interleukin-6 (IL-6) and C-reactive proteins (CRP).[86] A review showed that increase fat content in food leads to an increase in CRP and IL-6 and ultimately increasing the risk of diabetes. Free radical peroxidation of lipids causes destruction of enzymes and receptors activity which are bound to the membrane and local damage to cell membranes, lastly injured the organs. False immune system cause diabetes and

therefore lipid peroxidation is takes place. Stress can arouse hypoglycemia, hyperglycemia or have no affect on glycemic condition in diabetes.[87] In obese person, the adipose tissue becomes saturated with fat, adipocytes starts secreting low level of tumor necrosis factor-α, and stimulates preadipocytes for production of monocyte chemoattractant protein-1. High lipid content of adipose tissue also triggers oxidative damage.[88] In a study it has been clearly shown that the immune reactions involve ROS, causes lipid peroxidation.[89] and observed excessive production of free radicals in both Type-1 and Type-2 diabetes.[90] In hyperglycemic condition oxidative stress is increased which cause peroxidation of cellular membrane lipids and enhance oxidative modification of DNA and amino acids[91] In type-2 diabetic patients oxidative modification of Phospholipids is takes place which leads to increase peroxide lipids.[91]

CONCLUSION

The global burden of diabetes is increasing worldwide as it is a costly disease for developing economies of the world. To reduce the pandemic of type 1 and type 2 diabetes and its effects on lives and economies worldwide, it is necessary to have an improved understanding of its etiology, pathogenesis and pathophysiology to focus therapeutic and research efforts appropriately. A coordinated multidisciplinary approach is needed that involves scientists, public health practitioners, educators, clinicians and diabetics, with support from government authorities and nongovernmental organizations to reduce the incidence of diabetes significantly.

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