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A Mini-Review on Various Parameters Influencing Type 1 and Type2 Diabetes Mellitus

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ABSTRACT

There is strong evidence in the literature that oxidative stress occurs in people with type 2 diabetes mellitus and is influenced by how long they have had the disease. The current investigation discovered a favourable relationship between MDA levels and the duration of diabetes, independent of glycemic control. In conclusion, chronic diabetes mellitus enhances lipid peroxidation and MDA production without regard to glycemic control. These results suggest that supportive therapy aimed at reducing oxidative stress may help reduce problems associated with type 2 diabetes mellitus. Therefore, providing antioxidant treatment to everyone with diabetes mellitus may help to decrease problems caused by oxidative damage.

Keywords: Oxidative stress, Diabetes, Peroxidation, Antioxidant therapy

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HISTORY OF DIABETES MELLITUS

One of the first illnesses mentioned in an Egyptian papyrus that mentions "too great emptying of the urine" is diabetes. The earliest instances reported are thought to be those of type 1 diabetes [1, 2]. Around the same time, Indian doctors discovered the illness and named it madhumeha, or "honey pee," since the disease's urine attracted ants [3]. The Greek Apollonius of Memphis used the phrase "diabetes" or "to pass through" about 230 BC. The Indian doctors Sushruta and Charaka distinguished between type 1 and type 2 diabetes for the first time around 400–500 AD, with type 1 being linked to youth and type 2 being linked to obesity. John Rolle, a British physician, introduced the word "mellitus" or "from honey" in the late 1700s to distinguish the disorder from diabetes insipidus, which is similarly characterized by frequent urination [4]. The development of a successful therapy for diabetes did not occur until the early 20th century when Canadians Frederick Banting and Charles Best employed insulin for the first time in 1921 and 1922, respectively [5].

India now has 62.4 million diabetics, according to the Indian Council of Medical Research's (ICMR-INDIAB) nationwide diabetes research. By 2030, this is anticipated to reach over 100 million [6]. Type 2 diabetes accounts for more than 90% of all cases of diabetes (T2DM). T2DM, however, primarily affects those who are older. It affects the younger people in the prime of their working life in rich countries, but in developing countries like India, it poses an even bigger threat to their health. Unfortunately, the incidence of diabetes is microvascular and macrovascular consequences, which cause much of the early morbidity and death attributable to diabetes in India, increasing concurrently with the epidemic of diabetes 1 case [7, 8].

Peripheral insulin resistance and insufficient insulin production by pancreatic beta cells are two traits that define type 2 diabetes. In-islet suppression of a-cells by -cells produces an insulin-to-glucagon ratio that preserves glycaemic stability even in extremes of glucose inflow or outflow, according to a recent study [9–11]. This demonstrates that type 2 diabetes is an islet paracrinopathy, where the reciprocal link between the beta cell that secretes insulin and the alpha cell that secretes glucagon is lost, resulting in hyperglucagonemia and the ensuing hyperglycemia. Malfunctioning beta cells are a significant factor in all forms of diabetes, from prediabetes to diabetes. Beta-cell dysfunction emerges early in the pathologic process and does not always follow the stage of insulin resistance, according to research by Bacha et al. on obese teenagers [12].

Postprandial blood glucose levels rise initially as glucose tolerance transitions from normal to abnormal. Fasting hyperglycemia eventually arises due to the failure to control hepatic gluconeogenesis. Single-Nucleotide Polymorphism (SNP) genome-wide association studies have shown a variety of genetic variations linked to beta-cell activity and insulin resistance. Some SNPs make type 2 diabetes more likely [13, 14]. More than 40 distinct loci demonstrate a correlation with a higher risk of type 2 diabetes. Early in the onset of type 2 diabetes, amino acid metabolism may be important. In normoglycemic people with high fasting plasma concentrations of 3 amino acids, Wang et colleagues; found that the risk of developing diabetes was at least 4-fold greater (isoleucine, phenylalanine, and tyrosine). Before the onset of diabetes, these amino acid concentrations were increased for as long as 12 years.

Diabetic retinopathy

The most frequent microvascular consequence of diabetes may be diabetic retinopathy. In the U.K. Prospective Diabetes Study, it was discovered that hypertension and the degree of hyperglycemia were both associated with diabetic retinopathy in individuals with type 2 diabetes (UKPDS). In those with type 2 diabetes, retinopathy may develop as early as seven years before the diagnosis of diabetes. Various hypothesized pathological pathways explain how diabetes could cause the development of retinopathy. Sugar alcohol buildup has been associated in animal models with developing micro aneurysms, thickening basement membranes, and pericyte loss. Oxidative stress may also significantly influence cellular damage by hyperglycemia [15, 16].

Diabetic nephropathy

Renal failure has diabetes as a primary cause. It is defined as proteinuria > 500 mg in 24 hours when diabetes is present, while smaller levels of proteinuria, or "microal buminuria," come before this [17]. Microalbuminuria is an albumin excretion of 30 to 300 mg per 24 hours. When they are initially diagnosed with type 2 diabetes, up to 7% of individuals may already have microalbuminuria. A spot measurement of microalbumin or a 24-hour collection can be used to screen for diabetic nephropathy or microalbuminuria [18].

Diabetic neuropathy

Although the specific nature of the damage caused by hyperglycemia to peripheral nerves is unknown, it is most likely connected to processes including polyol accumulation, damage from AGEs, and oxidative stress [18].

Macrovascular complications of diabetes

Atherosclerosis is the primary pathogenic mechanism behind the macrovascular disease. Oxidized lipids from LDL particles build up in the endothelial lining of arteries due to endothelial damage and inflammation [19]. The process ultimately leads to developing a fibrous-capped, lipid-rich atherosclerotic lesion. The primary cause of mortality in patients with type 2 diabetes is cardiovascular disease. The risk of myocardial infarction (MI) in persons with diabetes is equal to the risk in non-diabetic patients with a history of prior MI, according to more recent research.

Lipid Peroxidation and Its Byproducts

Ordinarily, the air we breathe contains around 21% oxygen, and life would be impossible without it. However, "oxidative metabolism" has a drawback since it causes harmful oxidative damage when intracellular oxygen is used. To defend themselves against this toxicity, the organisms created a variety of "antioxidants" that enabled them to maintain a balance between oxidative damage and the effective utilization of oxygen for energy production. Uncontrolled oxidation of cell targets results in forming Reactive Oxygen Species (ROS) and a condition of "oxidative stress," frequently harmful to the cells. Decreased antioxidant defenses or enhanced oxidative processes cause this. The pathophysiology of many human illnesses, particularly the development of metabolic disorders like diabetes mellitus, is affected by this stress. Human obesity and diabetes, as well as animal models of both disorders, show a substantial rise in oxidative stress indicators [20]. Accumulation of ROS can be harmful on its own or cause proteins, nucleic acids, and lipids to oxidize, producing subsequent byproducts. The special way that PolyUnsaturated Fatty Acids (PUFAs) are reactive with ROS when they are present in cell membranes causes lipid peroxidation, a process that results in hazardous aldehydes [21].

Malon-Di-Aldehyde (MDA) and 4-Hydroxy-2-NonEnal (HNE) are two of them that have been substantial research. These aldehydes, once just lipid peroxidation indicators, have now been linked to cellular dysfunction through the activation of signalling pathways, induction of apoptosis, and changes in enzyme activity. Lipid aldehydes might be mediators of oxidative insults, spreading tissue injury and activating cellular stress signalling pathways, in addition to being markers of oxidative damage [22]. Aldehydes have recently been linked to impaired insulin action and signalling, and several studies have linked obesity and diabetes with lipid peroxidation byproducts. Reactive oxygen species are produced in excess under oxidative stress, which encourages the peroxidation of PolyUnsaturated Fatty Acids (PUFA).

Thio Barbituric Acid (TBA) testing has been widely used to quantify lipid peroxidation in biological materials. Malon-Di-Aldehyde (MDA), a byproduct of non-enzymatic PUFA oxidative breakdown, is detectable

Table 1: Comparison of RI values based on site and degree of obstruction.

Obstruction	Number	RI In The Obstructed Kidney	RI In Control Kidney	Δ RI
Proximal	25	0.72	0.61	0.11
Distal	25	0.66	0.6	0.06
Complete	16	0.71	0.62	0.09
Partial	34	0.67	0.6	0.07

by TBA. This has been utilized as a lipid peroxidation marker for many years. MDA is an unsaturated aldehyde that belongs to a group of substances with the general chemical formula C=C-C=O. A conjugated double bond (C=C) between carbons 2 and 3 and an aldehyde group (C=O) on carbon 1 define it. The carbonyl group's oxygen boosts the polarity of the double bond in this structure, making unsaturated aldehydes powerful electrophiles. MDA is a dicarbonyl molecule, and the additional oxygen atom increases the reactivity of the double bond. These aldehydes are among the "reactive electrophile species" that may combine with phospholipids' nucleophilic groups to produce covalent adducts [23]. The thiol group of glutathione reacts spontaneously with DNA, proteins, and physiological circumstances to generate the Michael adduct by attacking the double bond of aldehydes with the glutathione's nucleophilic group.

Additionally, they can react with thiol groups found on cysteine residues of certain proteins, impairing their biological function. Schiff bases and Michael adducts are produced when a primary amine group reacts with the aldehyde's carbonyl group (especially alkaline pH). Advanced Lipoxidation End Products are precursors to the aldehydes formed during lipid peroxidation (ALEs). They build up in cells and tissues with Advanced Glycation End Products (AGEs) produced during glycoxidation. These adducts build up and cause "carbonyl stress," which encourages protein malfunction and, as a result, pathological processes, including inflammation and apoptosis.

Cellular effects

Cytotoxicity

Strong electrophilic unsaturated chemicals have a significant potential for cytotoxicity and mutagenesis. They have been well investigated for how they affect cell viability. Depending on the aldehyde, length of exposure, and cell type, the lethal concentration 50 (LC5 0-concentration that results in the death of 50% of the cells) varies. MDA has an LC50 range of around 1 mM in cortical, endothelial, and fibroblast cells, although the cell killing caused by MDA has not been adequately studied. Additionally, it was shown that MDA causes cell cycle arrest, which explains why MDA causes cytotoxic damage to cells and causes cell death. Interestingly, aldehydes' propensity to form covalent adducts on proteins is strongly connected with their toxicity. According to studies, LCSO are closely related to how well each can help in vitro form covalent adducts on albumin. This describes how aldehydes primarily cause cytotoxicity and other biological consequences by chemically adducting other biomolecules [20].

Oxidative stress and ROS production

Lipid peroxidation is sparked by oxidative stress, resulting in the production of aldehyde byproducts. The ability of lipid aldehydes to produce ROS, however, is regarded to be crucial to understanding their harmful consequences. In cells treated with MDA, an accumulation of intracellular ROS has been observed. HHE is known to cause ROS in neurons and tubular epithelial cells. In contrast, HNE may cause oxidative stress within the mitochondria in the cells of the liver, skeletal muscle, vascular muscle, and neurons. It has been shown that several aldehydes significantly reduce the potential of the mitochondrial membrane, which raises the possibility that mitochondria may be the source of ROS. By activating the nuclear factor kappa B (NF-KB) family, MDA can also drive cellular proliferation, apoptosis, and inflammatory responses and control the expression of antioxidant enzymes [24].

Concentration in plasma and tissues

Except for MDA and HNE, which have been frequently employed as lipid peroxidation indicators; little information is known on the amounts of aldehydes in biological fluids. MDA levels in plasma range from 1-3 M in healthy individuals and can be 2-fold higher in type 2 diabetics. According to studies, among obese people, MDA has a favorable correlation with BMI and waist size.

MDA adducts

Low-Density Lipoprotein (LDL) modification and their metabolic shift toward macrophages are greatly influenced by MDA's reaction with Lys residues, which results in the formation of Schiff bases. Bifunctional aldehydes' ability to modify proteins can also result in the intra- or intermolecular cross-linking of proteins.

LDL modification

According to the oxidative hypothesis of atherosclerosis, one of the most well-known impacts of ALEs precursors is their part in the alteration of LDLs, which is implicated in the creation of early atherosclerotic lesions. For the particular apoB/E receptor, expressed in all cell types except macrophages, to recognize LDL, MDA must interact with the Lys residues of apoB. LDL modification changes their apoB/E receptor affinity and diverts their metabolism to cells with scavenger receptors (macrophages and smooth muscle cells), eventually forming foam cells. Foam cell buildup results in the development of fatty streaks, which are typical of early atherosclerosis lesions.

Lipid aldehydes and insulin secretion

Studies on diabetic rats revealed that the pancreas had elevated lipid peroxidation levels, and isolated rat islets exposed to lipid peroxidation byproducts were inhibited in secreting insulin in response to glucose. Treatment with aldehydes reduces glucose uptake and oxidation, indicating that they may hinder glucose-induced insulin release by interfering with the citric acid cycle and the glycolytic pathway. Evidence shows that beta cells exposed to NO donors and interleukin-I beta produce oxidative stress and lipid peroxidation byproducts, which activate the apoptotic pathway and reduce beta cell mass.

Direct adduction of the insulin polypeptide

Studies have demonstrated that MDA produced during lipid peroxidation modifies human insulin's B-chain in vitro, primarily at the His B5 and His B10 residues, by the development of Michael adduction.

Lipid Peroxidation By products association With Type-2 Diabetes

According to studies, fasting glycemia negatively correlates with plasma glutathione and positively correlates with oxidative stress indicators, including 8-epi-PGF2a and TBARs. According to studies, both normal and Type 2 diabetic people have weak antioxidant defences during an oral glucose tolerance test. Both conditions are linked to low levels of glutathione and vitamin C. The results of exercise and food restriction enhance insulin sensitivity, according to studies, which is connected to lower lipid peroxidation products. The strong relationship between oxidative stress, oxidation byproducts, and insulin resistance is revealed by the fact that insulin sensitivity may also be increased with antioxidant or carbonyl scavenging therapy. To a lesser extent, MDA and HNE are two unsaturated aldehydes that have been investigated as oxidative stress indicators in diabetes and are up to 2-fold elevated in both human and animal models of type-2 diabetes. Additionally, research by Nakhjavani et al. suggests that the duration of Type-2 diabetes is independently linked to higher levels of lipid peroxidation [25].

Preventing the deleterious effects of aldehydes

Glutathione and enzymatic detoxification

An essential coenzyme in many enzymatic reactions, glutathione (GSH), a tripeptide (L-y-glutamyl-L-cysteinyl-glycine) found in high concentration in the cytoplasm of living cells, exerts its antioxidant activity primarily through the regeneration of vitamin E as well as through direct interaction with free radicals and aldehydes. Reduced glutathione (GSH) is essential for these enzymes' functioning to function properly in the detoxification of electrophile byproducts, such as lipid peroxidation. Studies indicate that GSH plays a significant role in metabolic syndrome because it prevents obesity and insulin resistance in mice lacking in GSTs and increases the risk of type 2 diabetes in humans with GST null polymorphisms [26].

Scavengers of lipid peroxides

A molecule that may eliminate or inactivate undesired reaction products is known as a scavenger. Strong nucleophile molecules known as scavengers for aldehydes are those on which lipid peroxide aldehydes would form a covalent adduct.

Alpha-lipoic acid

The fatty acid is a naturally occurring substance that may be found in small amounts in various foods, including beef, potatoes, and broccoli. Treatment with lipoic acid reduces oxidative stress in adipocytes and muscle cells, according to research by Maddux et al. from 2001. Additionally, studies demonstrate that administering lipoic acid to insulin-resistant mice reduces the levels of lipid peroxidation indicators. Alpha lipoic acid, which had already been licensed in Germany for the treatment of diabetic neuropathy, became the first antioxidant supplement utilized for the treatment of diabetes complications as a result of the existing literature's support for its use in this regard [27].

N-Acetyl Cysteine (NAC)

Cysteine derivative N-acetyl cysteine is well known for being a strong antioxidant. This characteristic is brought about by the thiol group, which can decrease free radicals and serve as a precursor to glutathione synthesis. NAC has established its protective scavenging effect against aldehydes and protection against MDA rise and GSH reduction in animal models of insulin resistance. NAC has been shown in clinical studies to reduce oxidative stress markers and raise GSH in type 2 diabetes individuals [28].

CONCLUSION

In conclusion, there is a lot of evidence indicating the beginning of diabetes complications is mostly influenced by the activation of oxidative stress. Very little understood are the particular processes through which oxidative stress may hasten the onset of problems in diabetes. Experimental, clinical, and epidemiological research showing that antioxidants may be useful in treating diabetes and its consequences have provided evidence for the protective impact of antioxidants. However, neither primary patients without clinical evidence of CVD nor secondary patients with clinical evidence of CVD have shown a significant benefit from antioxidant supplementation (vitamins C, E, and -carotene) in the prevention of cardiovascular events, according to the majority of prospective randomized controlled antioxidant clinical trials.

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