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Biochemical Balances Between Oxidant/Antioxidant Biomolecules In Diabetic Patients

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Abstract

Diabetes mellitus is regarded as the leading cause of disability and increased mortality rate among people. It is characterised by elevated glucose concentration because of a defect in resistance to insulin and insulin secretion action. However, Diabetes may contribute to other diabetic complications. Therefore, DM management is essential, requiring strict control of the blood glucose level by utilising pharmacological and non-pharmacological measures. Aside from other complications, the imbalance between oxidants and antioxidants is primarily observed among patients with Diabetes. Although Oxidants such as ROS reactive oxygen species contribute to intracellular signalling, cell survival and proliferation, apoptosis, gene expression, and ion transportation, their overproduction could damage several biomolecules such as lipids, carbohydrates, DNA, and proteins. In addition, oxidants may also cause cell damage and homeostatic disruption. The production of free radicals or Oxidants is strictly regulated by antioxidant defence systems (ADS), which aim to eliminate or minimise the negative impact of these reactive products. Studies have noticed increased production of oxidants and free radicals among diabetic patients compared to healthy people. While on the other hand, the potential activity of the antioxidants defence system is also reduced among patients with Diabetes which is responsible for the detoxification of these reactive products. The study's primary aim is toevaluate several pathways through which the oxidant/antioxidant imbalance may lead to hypoglycemia among diabetes patients. While on the other hand, Modern drugs that are more disease-specific have emerged to retain the balance between oxidants/antioxidants such as nebivolol, celiprolol and carvedilol.

Keywords: Diabetes; Hyperglycemia; Oxidant; Antioxidant; Free Radical.

Diabetes Mellitus(DM)

DMis a metabolic disorders group characterised by raised glucose concentration due to a defect in resistance to insulin and insulin secretion action[1]. DM is the most common health issues[2].According to the international diabetes federation report in 2019, Diabetes mellitus affecteda population of around 463 million around the globe[3]. By 2030, the number is expected to

reach 578 million, and by 2045, up to 700 million people worldwide [3]. Furthermore, Diabetes is regarded asthe foremost cause of disability and an increased rate of mortality among people[3].In 2019, DM and its complications were responsible for more than4 million deaths among adults aged 20–79 years, this account for 11.3% of deaths from all other causes [4].

DM isbroadlydivided into twokey categories;type 1 and 2 diabetes, also referred to as (T1D) and (T2D) [1]. In T1D, also called insulin-dependent diabetes mellitus (IDDM), cellular-mediated auto-immune the pancreatic β-cells destruction, resulting in an absolute deficiency of insulin secretion[5]. On the other side, the specific aetiology of T2D (or the non-insulin-dependent diabetes mellitus (NIDDM)) is unknown[1]. In T2D, there is resistance to insulin action, and the secretion of insulin is insufficientto compensate for the insulin resistance[1]. T2D is responsible for 90 to 95% of all diabetes cases (6). It is most frequent in obese people and is often linked to dyslipidemia and hypertension [6,7]. In addition, Diabetes may contribute to other diabetic complications if not sufficiently managed. Such as including atherosclerosis, neuropathy, nephropathy, heart disease, retinopathy and cataract formation [8]. These problemsare the key causes of high morbidity and mortalityamong diabetic patients[9].

DM management requires strict control of blood glucose levels [10] by utilising non-pharmacological measures such as regular physical exercise and diet regime andpharmacological agents such as oral hypoglycaemic or antidiabetic agents [11]. Insulin is the primary therapy for patients with T1D; however, patients with T2D may also require insulin when the other treatment measures fail to achieve or maintain the desired glycaemic control [12]. In addition, it is essential for the patients suffering from Diabetes mellitus to manage possible risk factors that could further worsen the condition. Such as hypertension anddyslipidaemia.Taking these factors into consideration and managing them properly help delay or prevent the diabetic complicationsonset [10].

Studies have noticed increased production of oxidants and free radicals among diabetic patients compared to healthy people. While on the other hand, the potential activity of the antioxidants defence system is also reduced among patients with Diabetes which is responsible for the detoxification of these reactive products[13]. The imbalance generated between thepre-existing defence system and the consistent free radical oxidative stress production is also called oxidative stress. This phenomenon is responsible for most of the complications seen in diabetic patients.

Free Radicals and the Antioxidant Defence System

Free radicals are also called molecular species that tend to comprise one or more than one unpaired electron left in the outermost orbit[14]. Many free radicals are unbalanced and highly reactive species, attacking other molecules through an oxidative-reduction reactions series. This highlights

that free radicals have the potential to reason damage to other molecules[15].It is produced as a by-product of various cellular metabolismreactions carried out in the body, such as cellular respiration, ATP generation via mitochondrial electron transport and activation of phagocytes. In addition, they can be obtained from external sources such as pollution, cigarette smoke, or radiation [16].Free radicals may behave like oxidants by donating electrons or reductants if they accept electrons from other molecules [14]. The ROS and the RNS are two of the most important reactive species produced in the human body (18). The hydroxyl radical (•OH), oxygen singlet (1O2), superoxide anion radical (•O2–), per hydroxyl radical (•HO2), nitric oxide radical (•NO) and hydrogen peroxide (H2O2), are all examples of reactive oxygen species [17]. Contrarily,one significant example of the RNS is theperoxynitrite ONOO− and its reaction products, whereas the product is derived from the reaction between superoxide radicals and nitric oxide[18]. ROS/ RNS include both oxidants of radical and non-radical [19]. Free radicals are more reactive and less stable than non-radical oxidants. Non-radical oxidants or derivatives, on the other hand, maybe easily transformed into free radicals in living organisms through a variety of processes [15]. For example, hydrogen peroxide can accept one electron in the metal ions presencesuch as Fe, Cu, or Mg and eventually splitinto hydroxyl radical and hydroxyl anion [20].

Bothare the notable speciesthat tend to play a crucialrole inseveral cellular activitiesincluding intracellular signalling, cell survival and proliferation, apoptosis, gene expression and ion transportation[18,19], however, the overproduction of these reactive product harm health as a result of their ability to damage several biologically relevant molecules such as proteins, lipids, DNA,and carbohydrates, and may cause cell damage and homeostatic disruption[14].

Under normal physiologic conditions, free radical production is strictly regulated by antioxidant defence systems (ADS), which aim to eliminate or minimise the negative impact of these reactive products[19]. An antioxidant is any substance produced by the body (endogenous) or taken by the food (exogenous)), with the ability to prevent or slow down the oxidation of macromolecules[21]. The endogenous antioxidant could be categorised into several types of enzymatic antioxidants that may includeglutathione (GSH) dependent antioxidant system, non-enzymatic antioxidants,superoxide dismutase (SOD), thioredoxin (TRX), peroxiredoxins (PRX),and catalases (CAT), etc.[22,23].

Antioxidants perform their action by various mechanisms, including scavenging the free radicals by donating an electron or hydrogen to the reactive free radical or non-radical oxidant[9]. For example, SOD, CAT, GPx and vitamin C donate an electron to the reactive radicaltoneutralise it and inhibit its ability to cause damage[9]. In addition, phenolic compounds such as Vitamin E reacts with radicals by donating a hydrogen atom from its phenolic subunit[9]. On the other hand, the oxidised phenolic

molecule is generally stable and does not participate in subsequent oxidative chain reactions. Another mechanism of antioxidants is inhibiting the free radical'sgeneration by chelating the pro-oxidative metals (Fe, Cu, and Mg). Furthermore, some antioxidants, including coenzyme Q10, lipoicacid, N-acetylcysteine, vitamin B9, and Vitamin D, indirectly affect the free radicals.

To facilitate ROS diminution, the reduction of O_2•– is catalysed, which eventually results in the breakdown of lipid hydroperoxidesinto lipid alcohol andH2O. Another potential scavenger of ROS is the vitamin C that acts by giving an electron to a substratum such as O2•– [6]. Therefore, the production of ROS is promoted by these trace elements, such as the •OH production through the catalyses ofFenton reaction by the Fe^{2+} molecule(Fe^{2+} +H2O2• OH+ OH^-+ Fe^{3+}).

Hyperglycaemia and Increased Free Radical Production

The intracellular glucose is metabolised by glycolysis in the cytoplasm. Through this pathway, the C_6 glucose molecule is broken down into two glyceraldehyde 3-phosphate molecules[24]. The latter is oxidised with the help of glyceraldehyde-3-phosphate dehydrogenase (GAPD) to 1,3-bisphosphoglycerate. This reaction is fixed with the NAD^+ to NADH reduction. Several steps afterwards, pyruvate will be formed, which may cause inter the mitochondria and further oxidised by the citric acid cycle (CAC) to produce more NADH molecules. Finally, the malate-aspartate shuttle transports NADH into mitochondria or converts pyruvate to lactate, which exits the cell and serves as a substrate for hepatic gluconeogenesis.

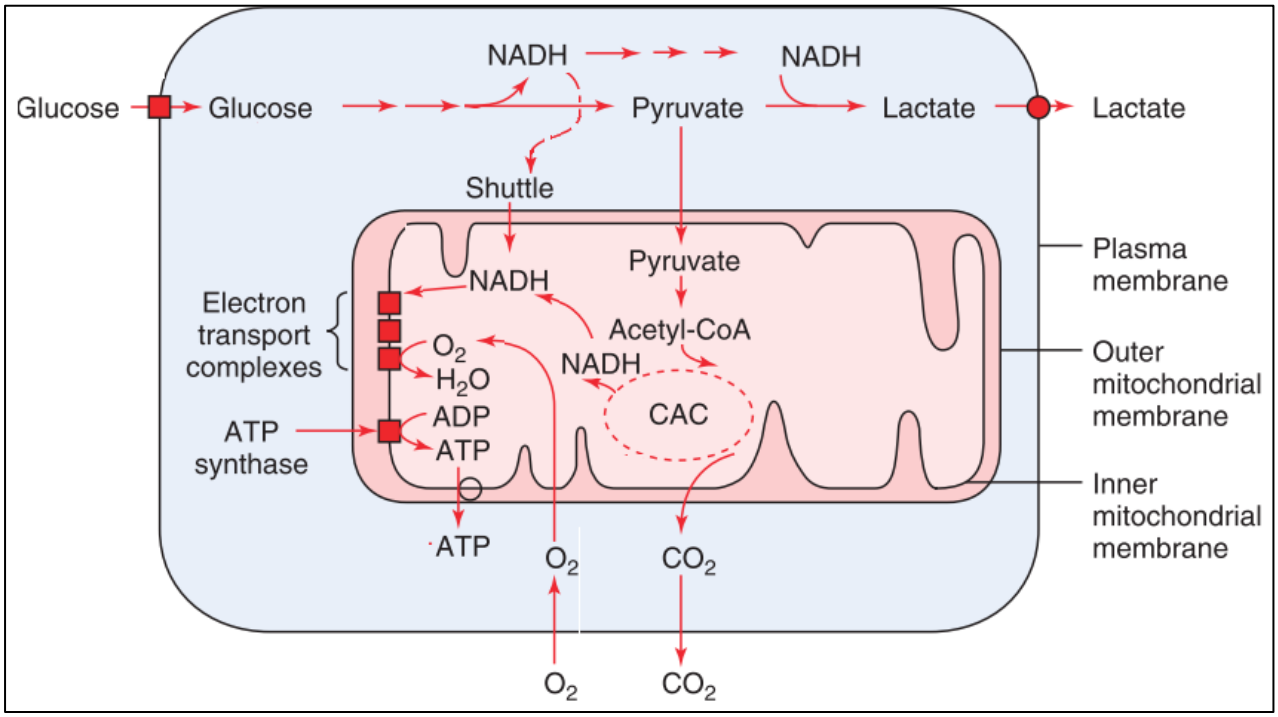

Figure 1. Shows that NADH derived from both cytosolic glycolysis process and mitochondrial CAC activity donates electrons to the electron transport chain (ETC).

Hyperglycemia causes an overabundance of ETC, resulting in the generation of superoxide species. Following that, mitochondrial and cytosolic OS is produced.Thus, hyperglycemia, increase mitochondrial production of superoxide ion.Furthermore, the hyperglycemia-induced mitochondrial superoxide overproduction will result in a reduction in the activity of GAPDH, which in turn cause upregulation of the proximal glycolytic intermediatesuch as (glucose, glucose-6-phosphate, and fructose-6-phosphate) [25,26]. Thus, hyperglycemia and three key pathways responsible for damage of hyperglycemic is linked by increased superoxide generation by the mitochondrial ETC [26,27].

High glucose levels can stimulate overproduction of reactive species, including ROS, through several mechanisms, including the following; i)activation of polyol (sorbitol) pathway; Hexosamine pathway; Diacylglycerol pathway; autooxidation of glucose [28] and non-enzymatic protein glycation[29].

The Polyol (Sorbitol) Pathway: It is a well-known hyperglycemiaconsequence and has been thought to contribute significantly to the diabetic complications pathogenesis[28–30]. This pathway is of minor importance at normal glucose levels as glucose is metabolised by the normal glycolytic pathway[31].At high glucose levels, hexokinase (the first enzyme in the glycolysis pathway) becomessaturated. In contrast, the amount of glucose in surplus amount will be metabolisedbyother pathways, including the polyol pathway[31,32]. In this pathway, the glucose is reduced by aldose reductase to form sorbitol, coupled with oxidation of NADPH to $NADP^+$. Afterwards, sorbitol dehydrogenase, an enzyme, converts sorbitol into fructose while reducing NAD^+ to NADH [33].Enhancement of the polyol pathway as a result of hyperglycemia will result in increased consumption of NADPH coenzyme.NADPH is essential for glutathione reductase to regenerate reduced glutathione (GSH) fromits oxidised form[9]. As a result of decreased regeneration of GSH regeneration, ROS are overproduced, leading to theenhancement of oxidative stress [9].

Moreover, nitric oxide synthase also utilises NADPH; therefore, the reduced concentration of NADPH will reduce nitric oxide production, thereby facilitating platelet aggregationand vasoconstriction [34].At the other end, the increased NADH production as a result of oxidation of sorbitol to fructose can be transported into the mitochondria to be oxidised by the electron transport chain, causing the generation of superoxide radicals and other ROS derived from it [35,36]. Thus, the overall load of NADH is increased in the mitochondria, which eventually contributes to the overproduction of ROS that could attack macromolecules and induce oxidative damage. In addition, Even sorbitol can increase ROS generation indirectly by generating AGEs through protein glycation[33].

Hexosamine Pathway: Another pathway that may increase the number of prevailing free radicals and ROS production is the increased fructose-6-phosphate flux into the hexosamine pathway due to hyperglycemia[26,37]. This pathway, under normoglycemic conditions, is a minor branch of glycolysis and accounts for less than 5% of the total glucose metabolism [31]. However, under the condition of hyperglycaemia, the overload of fructose-6-phosphate provides fructose-6-phosphate aminotransferase (GFAT), in the hexosamine pathway, the first and rate-limiting enzyme, as a glutamine substrate [38]. GFAT mediates Fructose-6-phosphate conversion into glucosamine-6-phosphate that is further converted into the molecule of uridinediphosphate N-acetylglucosamine, also referred to as (UDP-GlcNAc) [38]. The UDP-GlcNAc is the primary substrate for o-GlcNActransferases which catalyses the O-glycosylation reactions of proteins [38].

UDP-GlcNAc post-translationally modifies several transcription factors, nuclear and cytoplasmic proteins[31] may result in pathological changes in gene, protein, expression function, or their downstream mechanisms [26,37,39]. One example is the specificity protein 1 (SP1), which UDP-GlcNAc modifies due to hyperglycemiamediated overexpression of GFAT [26,37]. The over-modification of SP1 increases the gene expression that contributes to diabetic complications pathogenesis [26,37]. Another example is the endothelial nitric8 oxide synthase (eNOS) inhibition, thus reducing nitric oxide production, which plays a critical part in vascular diabetic complications [9,40]. The enhanced hexosamineactivity pathway in Diabetes leads to redox imbalance and provoke oxidative stress [41–43]. It induces insulin resistance and deterioration of beta-cell function [44] and provokes oxidative stress by enhancing hydrogen peroxide production, reducing antioxidant enzyme expression, and in beta cells lowering insulin secretion [45]. In addition, the overexpression of GFAT lower insulin gene expression, glucokinase, and glucose transporter 2,which eventually boosts the production of the free radicals. [37,44,46].

DiacylglycerolPathway: As a result of the hyperglycemia, Diacylglycerol (DAG), a physiological activator of Protein Kinase C, is produced when the glycolytic intermediate dihydroxyacetone phosphate (DHAP) is converted to glycerol-3-phosphate (PKC) [45,47]. Hyperglycemia can also indirectly induce PKC activation through the increased polyol pathway activity and ligation of AGE receptors [40]. Moreover, PKC activation is also held accountable as a sign of free radical production source amongdiabetes patients[45]; PKC is involved in the phosphorylation of subunits of the NADPH oxidase enzyme, whereas this phosphorylation is a process required to create an active form of NADPH oxidase [47]. In addition, The NADPH oxidase enzyme catalyses the transfer of an electron to molecular oxygen by using NADPH as an electron source. As a result of this process, hydrogen peroxide or superoxide is formed [49]. As a result, activation of PKC might lead to an increase in ROS

generation and oxidative stress. Furthermore, treatment with a PKC inhibitor reduces ROS generation [38], and reducing DAG formation is one way to control PKC activity [37].

PKC also activate NF-κB, which proves that the oxidative stress induced by hyperglycemia may lead to inflammation. In addition, it is also known that PKC activation impacts numerous additional activities, including transforming growth factor (TGF), endothelin-1 (ET-1), vascular endothelial growth factor (VEGF), and plasminogen activator inhibitor-1 (PAI-1). In comparison, all these molecules tend to play a critical part in vascular disorders commonly seen in Diabetes [31].

Advanced Glycation End Products (AGEs) Pathway: The formation of AGEs is another key route through which hyperglycemia can trigger oxidative damage [38]. Hyperglycemia, oxidative stress, and the production of AGEs have all been linked in several animals and human investigations [50–52]. The non-enzymatic interface between the carbonyl group of falling sugar, such as glucose, and the free amino group of proteins results in AGEs, which can be generated endogenously or exogenously[48].This interaction will first produce a reversible Schiff basethat rapidly undergoessignificant rearrangements to form the Amadori product, a more stable early glycation product [48,49]. In the later stages, To produce irreversible AGEs, the Amadori products undergo more complicated processes, including rearrangement, dehydration, and condensation [49,50].

Methylglyoxal (MG), a highly reactive dicarbonyl compound produced from glyceraldehyde-3-P during glycolysis, is a more potent glycating agent than glucose [51]. The MG formation and other dicarbonyl compounds increases due to the persistent hyperglycemiain Diabetes [51]. Therefore, in the case of Diabetes, the active production of AGEs is triggered, which starts to circulate in the plasma and accumulate in various tissues. The actively produced AGEs tend toplay a significant part in developing diabetes-associated complications [52]. Furthermore, the oxidative condition found in Diabetes enhances the AGEs production, increasing ROS production and impairing antioxidant systems [53]. In addition, AGEs have an increased affinity for metals, increasing the probability of ROS production through the Fenton reaction [8].

RAGEs, the AGEs receptor found on many cells, including macrophages, neurons, endothelial cells, and smooth muscle cells, is where AGEs trigger their biological effects [59,60]. Even in the presence of functional antioxidant systems, AGEs–RAGE interactions activate numerous transcription factors and molecular pathways that activate NADPH oxidase and enhance free radical production [9,46]. When antioxidant defence systems are weakened, however, this process is likely to be accelerated and exacerbated. For instance, Yan et al. (1994) demonstrated in their study that infusion of AGEs of albumin from diabetic plasma into normal animals induced free radicals production and oxidative stress worsening[54]. Wautier et al. (1994) also showed that the interaction of AGE with their receptors in erythrocytes of diabetic patients causes ROS generation foremost to oxidative stress in

the vasculature [53].AGEs also cause chronic inflammation–RAGE interactions, which activate inflammatory cytokines and adhesion molecules via regulating the transcriptional regulator NF-B and the PKC pathway [9].

Glucose Autoxidation: Several studies reported that the glucose autoxidation process could also be responsible for increasing ROS in diabetic patients[8,55,56]. In the presence of transition metals like Fe^{2+} and Cu^{2+}, glucose may generate an enediol radical anion. The enediol radical decreases molecular oxygen to generate superoxide anions (O2•–), which undergo a dismutation process to form H_2O_2, which produces very reactive hydroxyl radicals (•OH) in the transition metals presence[57,58]. Thus, elevated glucose in Diabetesincreases glucose autoxidation, increasing ROS and oxidative stress[59].

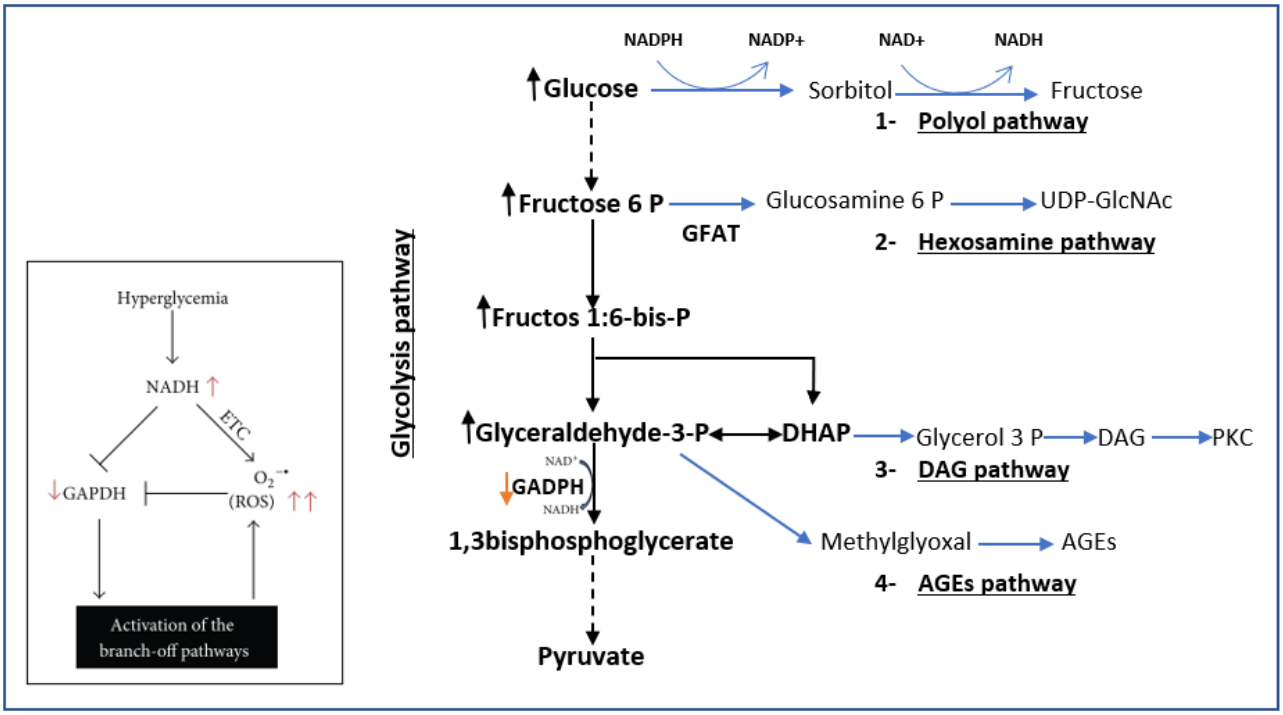

Figure 2. Shows the other Sources of Free Radicals in DM: Hyperinsulinemiaand Hypo-Insulinemia

Decreased Antioxidant Activities due to Diabetes

Evidence from several studies suggests that the ADS capacity may be lower in both types of Diabetes. First, a reduction in the total amount of antioxidants was observed in the plasma of T1D patients [60] and T2D patients [61]. Second, the antioxidant enzymes activity such as SOD, CATand finally, the scavenger vitamins E and C were significantly lowered in T2D patients, negatively correlating the development of complications or the duration of the disease [62]. Gupta and Chari (2006) observed that the SOD level and vitamin C was significantly lowered in T2D patients with ischemic heart disease (IHD) as compared with diabetic patients without IHD and non-diabetics with IHD [63]. Furthermore, the SOD activity and CAT was significantly reduced in T2D with or without

diabetic nephropathy compared with the healthy control. However, the CAT activity of diabetic individuals with diabetic nephropathy was considerably lower than that of diabetic patients without diabetic nephropathy [64].

In the same study, the erythrocyte glutathione content (GSH) was only significantly lower in DM patients with diabetic nephropathy [64]. However, in another similar study, an importantdecline in GSH was observed in DM patients with or without diabetic nephropathy [65]. Similar results were obtained; several studies on streptozocin (STZ)-induced diabetic rats reported reduced SOD, CAT and GSH antioxidant enzymes [66–73]. Thus, the most common antioxidant deficiencies noted in DM patients are GSH, SOD, CAT, and the scavenger vitamins E and C, especially in poorly controlled patients with diabetic complications, which reflect the increased free radical level.

Oxidative Stress in Diabetes (Role of Oxidative Stress in Diabetic Complications)

Oxidative stress (OS) is an "imbalance between oxidants and antioxidants favouring the oxidants, potentially leading to damage".It is pointed to as an essential phenomenon associated with many disease states. Such as Neurodegenerative disorders, cancer, apoptosis, obesity, hypertension, ageing and cardiovascular diseases[74]

Antioxidant as a Therapy to Retain the Oxidant/Antioxidant Balance

Oxidative stress is a rather complex process generated from the negative imbalance of oxidant/antioxidants and therefore tends to impact the organism negatively. However, the intensity of its impact depends on its production site, the antioxidants composition produced, and the activity of the repair system. Although the body reacts to oxidative stress through the pre-existing pool of endogenous antioxidant defences, the action could not be sufficient under certain circumstances. Increased levels of oxidants and reactive species may eventually counter the endogenous defence system of antioxidants. Based on this assumption, studies have suggested that an exogenous source of antioxidants must be administered to counter oxidative stress through amelioration. Therefore, the exogenous antioxidant sources tend to compensate for the inefficiency of the endogenous defence system while also enhancing the overall antioxidant response, whereas the oxidant/antioxidant balance is retained [75]. These could be administered through diets such as vitamin E, vitamin C, phenolic phytochemical-rich food, and flavonoids. The various modes of administration of exogenous antioxidant sources to enhance the internal defence system are termed Antioxidant Therapy. Although antioxidant therapy has faced huge success in the recent decade, the drug suitability of these antioxidant sources is still controversial. However, to attain effective therapeutic antioxidant agents, developing appropriate delivery antioxidant systems [76]. Rather

than targeting the dietary source of antioxidants, generating disease-specific drugs could be a more successful approach to retain a balance between oxidants/antioxidants.Modern, more disease-specific medicines have emerged to balance oxidants/antioxidants such as nebivolol, celiprolol, and carvedilol. These drugs proved effective in the management of hypertension while interfering with the generation of ROS/RNS.

Conclusion

Antioxidants are molecules that tend to prevent reactive species and transition metals from causing potential damage to the body cells. Reactive oxygen species, also called ROS, are the most significant example of such damage-causing reactive species. ROS may worsen human diseases such as cancer, stroke, and other neurological disorders when levels are consistently high. On the other hand, antioxidants greatly delay or prevent the oxidation of biomolecules, even when their concentration is lower than that of the oxidised substrates. Furthermore, antioxidants work by scavenging free radicals, blocking enzymes involved in overproducing reactive species, regulating gene expression, and sequestering transition metal ions, among other methods (chelation activity). Based on this knowledge, it is evident that antioxidants therapies could be a crucial factor in balancing the oxidants and antioxidants within the body.

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