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Oxidative Stress in Diabetes mellitus and the Role of Antioxidants in Reducing Its Complications

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Abstract

An imbalance between free radicals and the antioxidant defense systems responsible for neutralizing them results in oxidative stress. Antioxidants are essential because they limit the accumulation of free radicals, thereby reducing oxidative stress within the body. Type 1 diabetes mellitus arises from the pancreas' inability to produce insulin due to autoimmune destruction of insulin-secreting β-cells. In contrast, type 2 diabetes develops through two main stages: it begins with insulin resistance in peripheral tissues, which stimulates increased insulin secretion as a compensatory response, followed by a gradual decline in β-cell function, leading to inadequate insulin production and impaired blood glucose regulation. Both types of diabetes are characterized by chronic hyperglycemia, which, if poorly controlled, can result in serious complications. Persistent high glucose levels promote the generation of free radicals through several metabolic pathways, including advanced glycation end product (AGE) formation, activation of the hexosamine and polyol pathways, and glucose auto-oxidation. These pathways collectively intensify oxidative stress and contribute to the progression of diabetes-related microvascular and macrovascular complications. Antioxidants therefore play an important supportive role by scavenging free radicals, reducing oxidative damage, and enhancing the body's antioxidant capacity. However, they are not considered a primary therapeutic treatment for diabetes; rather, they serve as adjunctive agents that help limit cellular injury associated with oxidative stress.

Introduction

Oxidative stress is a state characterized by an imbalance between the production of free radicals and the capacity of antioxidant defenses to neutralize them [1, 2]. Free radicals are chemical species that can exist independently. A free radical contains an unpaired electron, which makes it highly reactive, short-lived, and capable of initiating chain reactions. To achieve stability, these radicals react with molecules or ions, either donating or accepting electrons, acting as oxidizing and reducing agents [3]. The body naturally defends itself through antioxidants, which delay or inhibit oxidation that damages cells and tissues. Antioxidants can protect cells from free radical- induced damage even at relatively low concentrations by donating electrons to neutralize radicals, thereby interrupting chain

reactions. As a result, antioxidants are oxidized and must be regenerated or replenished. Free radical species are also degraded by antioxidant enzymes, usually within cells. Additionally, transition metal-binding proteins prevent metals like iron and copper from interacting with superoxide and hydrogen peroxide, which could otherwise generate highly reactive hydroxyl radicals [4].

Diabetes mellitus is a major global health disease that affects over half a billion people globally. Its incidence is quickly increasing, and its micro- and macrovascular consequences contribute to increased mortality [5]. Diabetes is a complex metabolic disorder characterized by chronic hyperglycemia caused by impaired insulin secretion from pancreatic β-cells or peripheral insulin resistance [6,7]. Type 1 diabetes, which makes up approximately 5–10% of cases globally but is the most common type among children, and Type 2 diabetes, which makes up more than 90% of cases globally, are the two main forms of the disease. In Type 2 diabetes, insulin resistance in peripheral tissues occurs first, followed by an inadequate compensatory insulin secretion from pancreatic; β-cells [8,9]. Type 1 diabetes is caused by absolute insulin deficiency due to the destruction of the pancreatic β-cells [10]. Persistent hyperglycemia in diabetes promotes excessive production of reactive oxygen species (ROS) through mechanisms such as glucose auto-oxidation, polyol pathway activation, and the formation of advanced glycation end products (AGEs). Moreover, common mitochondrial dysfunction in diabetes contributes to further ROS release, ultimately leading to oxidative stress [11]. Aim of the review: Assess the efficacy of antioxidants in preventing diabetes-related complications.

Oxidative Stress

Oxidative stress is a Redox imbalance condition experienced by cells or tissues when there are too many free radicals being made, either from internal or external sources, exceeding the antioxidant system's capacity to neutralize them. The increased accumulation of these unneutralized free radicals causes significant damage to essential biomolecules in the cell, like proteins, lipids, and nucleic acids. As a result, alterations in gene expression may occur changes membrane receptors, impaired cell growth or programmed cell death, as well as weakened immunity, mutations, and the deposition of proteins or lipids in tissues [12].

Free Radicals

Atoms with unpaired electrons that are capable of independent existence are known as free radicals [13]. Reactive oxygen species (ROS) and reactive nitrogen species (RNS) are the two primary categories of free radicals. Superoxide anions (•O2−), peroxyl radicals (•ROO), hydroxyl radicals (•OH), and hydrogen peroxide (H2O2) is a reactive oxidizing molecule capable of generating free radicals, such as hydroxyl radicals through reactions like the Fenton reaction. Nitric oxide (•NO) and peroxynitrite (•-ONOO) are examples of RNS oxidants [13,14]. Free radicals come from both internal and external sources. X-rays, ozone, industrial chemicals, ambient air pollution, pesticides, radiation, and smoking are examples of external sources [15]. Free radicals are naturally produced by internal sources due to metabolic activities such immune responses, enzymatic reactions, and electron transport in mitochondria [16].

Antioxidants

The body has strong antioxidant defenses, but these defenses can be overwhelmed when the production of reactive oxygen species (ROS) exceeds the body's capacity to neutralize them, due to factors such as environmental contaminants, poor diets, and chronic illnesses. This highlights the importance of dietary supplements or food-based exogenous antioxidants [12]. Because they neutralize free radicals and lessen oxidative damage, antioxidants are essential for controlling free radicals. They support the preservation of cellular integrity and function, which has a favorable impact on general health and the avoidance of disease [17]. Antioxidants can be acquired outside or created internally. The body produces both enzymatic and non-enzymatic endogenous antioxidants. Superoxide dismutase (SOD), catalase, and glutathione peroxidase (GPX) are important enzymatic antioxidants [18]. Glutathione (GSH) is one type of non-enzymatic antioxidant [19]. Minerals, plant components, and vitamins like E, A, and C are examples of exogenous antioxidants that can either directly scavenge free radicals or strengthen the body's defenses [20].

Diabetes Mellitus and Pathophysiology of the Disease

Diabetes mellitus is a chronic disease characterized by impaired regulation of blood glucose levels, resulting from insulin resistance in peripheral tissues and/or inadequate insulin secretion as a compensatory mechanism, or because insulin is unable to control blood glucose levels [21].

Insulin is a peptide hormone and it is produced and secreted by the β-cells of the pancreas. Insulin contributes to maintaining the level of sugar in the blood by helping glucose enter the cells, and uses it in metabolic processes [22]. Insulin resistance, a disease in which the body's cells oppose the effects of insulin, results in a decreased cellular response in diabetic patients. Reduced sensitivity to the physiological effects of insulin and reduced insulin-mediated glucose elimination are characteristics of insulin resistance [23].

Type 1 Diabetes Mellitus

Insulin insufficiency and the ensuing hyperglycemia are the hallmarks of type 1 diabetes mellitus, a chronic autoimmune illness [24]. This kind arises from the autoimmune system's destruction of pancreatic beta cells, which results in a total incapacity to produce insulin [25].

Type 2 Diabetes Mellitus

Dysfunctional insulin release from pancreatic beta cells and inadequate tissue response to insulin are the two main causes of type 2 diabetes, a widespread metabolic illness [26].

Oxidative Stress Mechanisms in Diabetes

• Glycolysis, or the Glucose Oxidation Pathway

Under normal physiological conditions, mitochondrial electron transport supported in part by intermediates derived from glucose oxidation generates superoxide anion radicals ($\bullet O_2^-$) at low concentrations that are efficiently neutralized by the cell's antioxidant defense systems [27]. In hyperglycemic states, however, the excessive influx of glucose increases mitochondrial metabolic flux, resulting in enhanced electron leakage and excessive superoxide generation. This overwhelms endogenous antioxidant mechanisms and induces

oxidative stress, ultimately leading to damage of DNA and other macromolecules [28]. Additionally, the accumulation of triose phosphates particularly glyceraldehyde-3-phosphate (GAP) and dihydroxyacetone phosphate (DHAP) can enhance their spontaneous degradation into reactive dicarbonyl compounds, most notably methylglyoxal (MG), which is considered a major precursor of advanced glycation end products (AGEs). Although GAP can undergo limited auto-oxidation, leading to minor production of hydrogen peroxide (H_2O_2), the dominant pathway associated with triose phosphate accumulation is the formation of MG. The resultant increase in MG and subsequent AGE formation substantially contributes to intracellular oxidative stress and to the progression of diabetes related cellular injury [29].

• Glycation Reaction

Glycation reaction, are present inside and outside the cellular environment [30]. Proteins inside and outside the cell undergo detrimental modifications, converting into AGEs as soon as their amino groups react with AGE precursors such as glyoxal, methylglyoxal, and deoxyglucosone [31].

Once formed, AGEs can bind to various AGE receptors, including AGE-R1, AGE-R2, AGE-R3, and RAGE, or interact abnormally with components of the extracellular matrix, which promotes the production of reactive oxygen species and exacerbates oxidative stress [32].

• Protein Kinase C Pathway

Protein kinase C (PKC) represents a family of serine/threonine kinases that regulate a wide range of cellular processes through the phosphorylation of target proteins in a tightly coordinated cascade. The activation of conventional PKC isoforms requires the presence of calcium ions (Ca^{2+}), phosphatidylserine, and diacylglycerol (DAG), which collectively stabilize the enzyme in its active conformation and facilitate its downstream signaling functions [33].

Under hyperglycemic conditions, inhibition of glyceraldehyde-3-phosphate dehydrogenase (GAPDH) leads to intracellular accumulation of glyceraldehyde-3-phosphate (G3P). The elevated G3P is subsequently interconverted to dihydroxyacetone phosphate (DHAP) through the action of triose phosphate isomerase. DHAP serves as a metabolic precursor for the de novo synthesis of diacylglycerol via its reduction to glycerol-3-phosphate and entry into the glycerolipid biosynthetic pathway. The resulting increase in DAG levels promotes sustained activation of PKC isoforms. Persistent PKC activation enhances oxidative stress, alters vascular permeability, disrupts endothelial and neuronal signaling, and contributes to the molecular mechanisms underlying chronic diabetic complications. This sequence—hyperglycemia-induced GAPDH inhibition, elevation of G3P and DHAP, increased DAG production, and PKC hyperactivation represents a central metabolic–signaling axis implicated in diabetes-related cellular dysfunction [32].

• Hexosamine Pathway

Fructose-6-phosphate (F6P), generated during glycolysis, is partially metabolized through the hexosamine biosynthetic pathway [34]. Under normal blood glucose conditions, only a small fraction of F6P is diverted into this pathway. The activity of the rate-limiting enzyme, glutamine: fructose-6-phosphate amidotransferase (GFAT), remains low due to tight regulatory control, including feedback inhibition by the end-product UDP-N-acetylglucosamine (UDP-GlcNAc). This ensures physiologically low flux through the

hexosamine pathway. In hyperglycemic states, elevated intracellular levels of F6P increase substrate availability for GFAT, leading to enhanced enzyme activity and higher flux through the hexosamine pathway, which has been implicated in the development of glucose-mediated cellular dysfunction [35].

As a consequence of increased flux through the hexosamine biosynthetic pathway, intracellular levels of UDP-N-acetylglucosamine (UDP-GlcNAc) rise, leading to enhanced activity of O-GlcNAc transferase (OGT). This modification affects the O-GlcNAcylation of various nuclear and cytoplasmic proteins, which can indirectly influence gene expression. Upregulation of specific growth factors, including transforming growth factor-beta (TGF-β), has been more consistently associated with hexosamine pathway overactivity, whereas effects on transforming growth factor-alpha (TGF-α) appear less direct and may involve secondary regulatory mechanisms. Increased O-GlcNAcylation contributes to alterations in extracellular matrix remodeling, including thickening of the basement membrane, modulation of mesangial cell growth, and enhanced deposition of collagen [36]. Collectively, these changes illustrate the hexosamine pathway's role in promoting oxidative stress and tissue remodeling in diabetes, particularly in the pathogenesis of diabetic nephropathy [37].

•The Polyol Pathway

More than 30% of glucose can be diverted by elevated glucose levels in diabetes into this pathway, where it's first glucose undergoes a reduction process to become sorbitol and is then oxidized to form fructose. NADPH, a substance necessary for the re-formation of glutathione in its reduction revolution, is depleted when aldose reductase uses it as a cofactor. Cellular oxidative stress occurs as a result of decreased glutathione levels. Furthermore, an increase in NADH coincides with a decrease in NADPH, which intensifies the generation of reactive oxygen species [38]. Figure 1 illustrates hyperglycemia-induced metabolic pathways and their role in oxidative stress in diabetes."

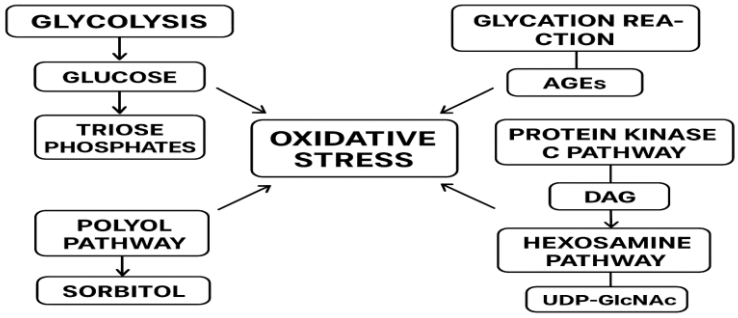

Fig. 1: *Hyperglycemia-induced metabolic pathways and their role in oxidative stress in diabetes.*

Impact of oxidative stress on the development of diabetes complications

Microvascular Complications

1. Diabetic Retinopathy [39].
2. Diabetic Nephropathy [40].
3. Diabetic Neuropathy [41].

Macrovascular Complications

Atherosclerosis is the primary pathogenic mechanism underlying macrovascular problems. Chronic inflammation and damage to the arterial wall in the peripheral or coronary vascular system lead to atherosclerosis. This injury makes it easier for oxidized low-density lipoprotein (LDL) particles to build up inside the artery endothelium. Acute vascular occlusion may result from these atherosclerotic plaques rupturing [39]. Figure2 illustrates impact of oxidative stress on the development of diabetes complications

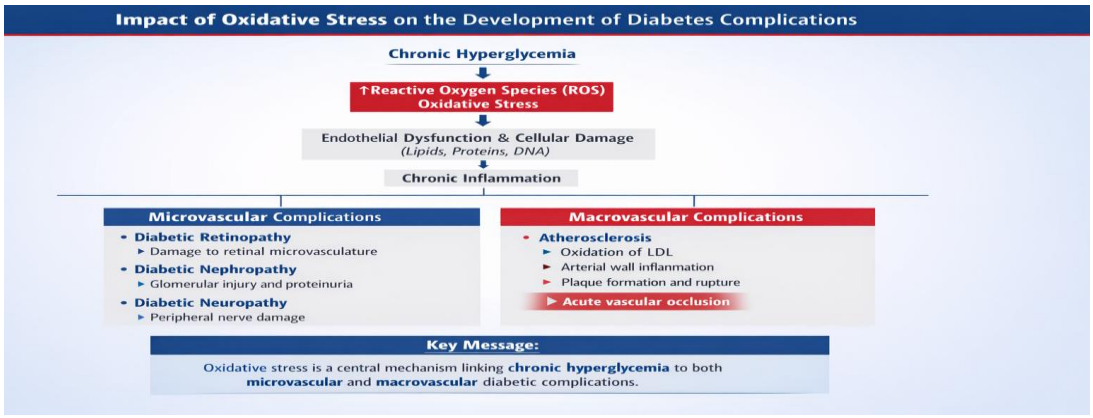

Fig. 2: *Impact of oxidative stress on the development of diabetes complications*

Clinical evidence on the role of antioxidants in reducing diabetes complications

Several studies have suggested to improving the oxidative state mainly by boosting non-enzymatic antioxidant defenses since oxidative stress is present throughout the development of diabetes and its consequences. The association between oxidative and inflammatory indicators, plasma or dietary vitamin E levels, type 2 diabetes, and its consequences has been the subject of numerous clinical investigations. While some studies [42, 43] found an inverse association between vitamin E levels and these indicators, other studies [42, 44] found no positive benefits.

Studies examining the connection between vitamin A, C intake and improvements in this disease and its adverse effects have also shown contradictory results [45]. Alpha-lipoic acid (ALA) may help reduce diabetes complications such as retinopathy, nephropathy, and neuropathy, according to studies. It has been demonstrated that ALA strengthens the body's antioxidant defenses, lowers oxidative stress, and improves inflammatory indicators [46,47].

Carotene compounds and diabetes have been strongly linked in a number of research [48,49,50]. Carotene compounds have been shown to improve immunity and reduce oxidative stress in diabetic patients [51], improve vision [52,53], lower biomarkers of inflammation [54], and improve kidney disorders related to diabetes [55]. According to a study by (Jayasree et al., (2011)), flavonoids compound function as compound that stimulate insulin receptor, reducing negative consequences of diabetes. Flavonoid consumption has been shown to ameliorate diabetic complications [56] and be inversely correlated with the

incidence of diabetes [57,58,59,60]. Supplementing with glutathione (GSH) has been demonstrated to improve cellular response insulin [61], enhance production of insulin [62], lower glycosylated hemoglobin levels [62], lower oxidative stress levels across all constituents of blood [63], and restore body GSH stores [62].

Conclusions

Elevated blood glucose levels increase the production of free radicals through multiple metabolic pathways, leading to oxidative stress, which plays a central role in the development of diabetic complications. Both endogenous and exogenous antioxidants are crucial in scavenging free radicals and protecting cells from oxidative damage. Clinical studies have shown that antioxidant interventions can reduce oxidative stress, improve insulin sensitivity, and mitigate the progression of diabetes-related complications, highlighting their therapeutic potential in diabetes management. However, evidence from clinical studies remains inconsistent, largely due to variations in study design and outcome measures. While some investigations report improvements in biochemical markers of oxidative stress and inflammation, others focus on clinical endpoints such as glycemic control, insulin sensitivity, or organ-specific complications.

Consequently, molecular-level improvements observed in certain studies do not always translate into immediate or measurable clinical benefits. In conclusion, although substantial clinical evidence supports the protective role of antioxidants in diabetes, variability in reported outcomes underscores the need for well-designed, long-term randomized controlled trials. The use of standardized dosages, clearly defined clinical and biochemical endpoints, and stratification of participants according to disease stage and oxidative status is essential to accurately identify the patient populations most likely to benefit from antioxidant-based therapeutic strategies.

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الإجهاد التأكسدي في داء السكري ودور مضادات الأكسدة في الحد من مضاعفاته

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الخلاصة:

ينتج الإجهاد التأكسدي عن اختلال التوازن بين الجذور الحرة وأنظمة الدفاع المضادة للأكسدة المسؤولة عن معادلتها. وتُعد مضادات الأكسدة ضرورية لأنها تحدّ من تراكم الجذور الحرة، مما يسهم في تقليل الإجهاد التأكسدي داخل الجسم. ينشأ داء السكري من النوع الأول نتيجة عجز البنكرياس عن إنتاج الإنسولين بسبب التدمير المناعي الذاتي لخلايا بيتا (β) المفرزة للإنسولين. أما داء السكري من النوع الثاني فيتطور عبر مرحلتين رئيسيتين؛ إذ يبدأ بمقاومة الإنسولين في الأنسجة الطرفية، مما يحفّز زيادة إفراز الإنسولين كاستجابة تعويضية، تليها مرحلة تدهور تدريجي في وظيفة خلايا بيتا، يؤدي إلى عدم كفاية إنتاج الإنسولين واضطراب تنظيم سكر الدم. يتميّز كلا النوعين من داء السكري بفرط سكر الدم المزمن، والذي قد يؤدي في حال عدم السيطرة عليه إلى مضاعفات خطيرة. إن الارتفاع المستمر في مستويات الغلوكوز يعزّز توليد الجذور الحرة عبر عدة مسارات أيضية، من بينها تكوّن نواتج الغلَيكَة المتقدمة (AGEs)، وتنشيط مساري الهيكسوزأمين والبوليول، إضافة إلى الأكسدة الذاتية للغلوكوز. وتؤدي هذه المسارات مجتمعةً إلى زيادة شدة الإجهاد التأكسدي وتسهم في تطور المضاعفات الوعائية الدقيقة والكبيرة المرتبطة بداء السكري. وبناءً على ذلك، تؤدي مضادات الأكسدة دورًا داعمًا مهمًا من خلال اقتناص الجذور الحرة، وتقليل الضرر التأكسدي، وتعزيز القدرة المضادة للأكسدة في الجسم. ومع ذلك، لا تُعد مضادات الأكسدة علاجًا أساسيًا لداء السكري، وإنما تُستخدم كعوامل مساندة تساعد على الحد من الأذى الخلوي المرتبط بالإجهاد التأكسدي.