

ANTIOXIDANTS AND OXIDATIVE STRESS IN DIABETES MELLITUS

Abstract

The frequency of diabetes mellitus, a common metabolic condition, has significantly increased among adults worldwide. Based on projections, there might be a significant increase to 30 million cases by 2025, which is a concerning rise from 135 million cases in 1995. This long-term illness, which is the fourth largest cause of death worldwide, mostly affects people between the ages of 45 and 65. One important etiological component of diabetes is revealed to be oxidative stress. Diabetes complications include vascular diseases that result in amputations of limbs, an increased risk of heart disease, and poor blood vessel development that causes ulcers on the feet that do not heal. Oxidative stress is a major factor in insulin resistance and diabetic comorbidities because it is associated with the generation of free radicals. Cellular damage is a result of an imbalance between the production of free radicals and antioxidant defense systems. Through a variety of processes, antioxidants become viable therapeutic agents to combat oxidative stress in diabetes. Research demonstrates the effectiveness of plant polyphenols and antioxidant vitamins like C and E in reducing problems associated with diabetes.

Keywords: Oxidative stress, Reactive oxygen species, Antioxidants, Diabetic mellitus, Free radicals, Cardiovascular diseases, Diabetic complications, Lipid peroxidation

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I. INTRODUCTION

Diabetes mellitus is a long-lasting metabolic disorder. Adult diabetes prevalence has considerably grown all over the world. According to predictions, there can be 30 million individuals suffering from diabetes by 2025, up from 135 million in 1995. Mostly diabetes patients range in age from 45 to 64 years old in poor nations to 63 to 65 years old in industrialized nations. Six people die from the consequences of diabetes every minute, making it the fourth greatest cause of mortality in the world (King et al., 1998).

A significant factor in the etiology of diabetes is oxidative stress. Antioxidant supplements and medicinal plants with antioxidant properties have been documented to produce hypoglycaemic effects. Antioxidants are utilized to cure and lessen diabetes mellitus complications. Vitamin and antioxidant supplements in one's diet are helpful in the management of diabetes. The formation of free radicals is facilitated by hyperglycemia. Whenever the production of free radicals exceeds the controlling capacity of the defense system provided by endogenous antioxidants, macro and microvascular problems occur. Vitamin C, N-acetylcysteine, and lipoic acid are antioxidants that are efficient in lowering diabetes problems. This is suggestive of the benefits associated with the consumption of natural antioxidants or dietary supplements

II. COMPLICATIONS ASSOCIATED WITH DIABETES MELLITUS

Over sixty percent of all non-traumatic limb amputations in the United States are caused by diabetic vascular disorders and neuropathy. Heart disease risk is up to eight times higher in people with diabetes mellitus and poor glucose tolerance (Norhammar et al., 2002). Furthermore, diabetic individuals' ability to produce new blood vessels in response to ischemia is hindered. This inhibits the production of collateral vessels in ischemic hearts and can result in the development of non-healing foot ulcers (Abacl et al., 1999). In the United States, diabetes and its associated difficulties are a noteworthy cause of mortality and morbidity. The occurrence of diabetes has now reached epidemic stages here, in the last 20 years. As per certain studies, a greater number of individuals are prone to diabetes and will have to manage it for the majority of their lives because of elevated childhood obesity cases and an increase in type 2 diabetes mellitus (T2DM) diagnoses among children and young adults (Deshpande et al, 2008).

III. OXIDATIVE STRESS IN DIABETES MELLITUS

Numerous cellular mechanisms that lead to insulin resistance and diabetes comorbidities have connections to oxidative stress and free radical generation. Extended exposure to excessive glucose might result in the creation of Reactive oxygen species (ROS) and can be harmful even after glucose management. Early impacts of elevated glucose may increase the presence of potentially beneficial pathways. Free radicals attack lipid membranes, proteins, and nucleic acids in cells in high quantities, which may eventually result in cell death (Sarrafchi et al., 2016). Additionally, an increase in ceruloplasmin during hyperglycemia suggests an increase in ROS. Oxidative stress can cause the pancreatic beta cells to become damaged and less sensitive to insulin, which can lead to the development of diabetes mellitus. ROS have the capacity to cross through cell membranes and kill those cells (Maritim et al., 2003). ROS and reactive nitrogen species (RNS) are two examples of highly

reactive molecules that are often formed in excess within the body or not eliminated sufficiently and cause oxidative stress (Maritim et al., 2003). Along with hydrogen peroxide (H_2O_2) and hydrochloric acid (HCl) which are nonradical species, the ROS also comprises free radicals like superoxide (O_2^-), hydroxyl (OH), peroxy (RO_2), and hydroperoxyl (HRO_2). RNS comprises nonradicals like peroxynitrite ($ONOO^-$), nitrous oxide (HNO_2), and alkyl peroxynitrates ($RONOO$), and free radicals such as nitric oxide (NO) and nitrogen dioxide (NO_2) (Turko et al., 2001).

An imbalance between the systems responsible for producing and eliminating free radicals can result in oxidative stress. Increased free radical generation or decreased antioxidant defense activity are certain examples. Enhanced endothelial cell apoptosis has also been linked to hyperglycemia-induced oxidative stress both in vitro and in vivo (Kangralkar et al., 2010). Numerous studies have demonstrated that free radical production is raised and antioxidant capacity is diminished in diabetes mellitus (types 1 and 2), which results in oxidative degradation of cell components (Bashan et al., 2009). In diabetes, oxidative stress can come from nonenzymatic, enzymatic, or mitochondrial mechanisms. The oxidative metabolism of glucose is the cause of nonenzymatic oxidative stress. Increased ROS production can be directly caused by hyperglycemia. The autoxidation of glucose can result in the production of OH radicals (Bashan et al., 2009). Additionally, advanced glycation end-product (AGEs) are created as a result of a nonenzymatic reaction between glucose and proteins. At several stages of this process, ROS is produced. Increased glucose metabolism via the polyol (sorbitol) route occurs in hyperglycemia, which also leads to increased generation of O_2^- .

IV. REDUCED ANTIOXIDANT DEFENSE MECHANISM

Cells have developed very sophisticated enzymatic and non-enzymatic antioxidant mechanisms that cooperate and complement one another to shield the body from the harm caused by free radicals.

Antioxidant barriers may be weaker in diabetics, according to a number of lines of research. These include studies of decreased ascorbic acid and vitamin E levels as well as the decreased total antioxidant status of the plasma or serum. Also reduced scavenging activity of the free radicals, and plasma oxidative dysfunction in type 2 diabetics form a part of the research. Additionally, diabetics have been shown to have decreased activity of the antioxidant enzymes catalase, glutathione peroxidase, and superoxide dismutase. It has also been hypothesized that type 2 diabetics have decreased endothelial NO production, which, in addition to weakening vascular antioxidant defense, would inevitably exacerbate any deficiencies in NO's anti-atherogenic signaling function (Laight et al., 2000). The amount of oxidized fatty acids is higher in T2DM patients, and HDLs' anti-inflammatory and antioxidant functions are less active (Morgantini et al., 2011).

V. ROLE OF ANTIOXIDANT IN DIABETES MELLITUS

Inhibiting the production of intracellular free radicals may serve as a therapeutic method to stop oxidative stress and the connected vascular problems linked to diabetes. Antioxidants can work in a variety of ways, such as by scavenging free radicals, preventing ROS production, or enhancing the antioxidants' defense enzyme capacities. Re-coupling

endothelial nitric oxide synthase (eNOS) and reducing vascular NAD(P)H oxidase activity can help in reducing the harmful effects of diabetes mellitus. Antioxidant, and NO-producing factor administration may be able to alleviate endothelial dysfunction in diabetes mellitus (Hamilton et al., 2007).

In general, the administration of antioxidant enzymes and substrates, biogenic substances, combination pharmaceuticals, synthetic antioxidants, and medications with antioxidant activity may be grouped into categories for antioxidant pharmacotherapy. In addition, there are several naturally occurring antioxidant components in cells that counteract free radical damage. These components make up the majority of cellular defence systems. The ROS can be removed immediately or in a sequential manner by enzymatic antioxidants found within the copper, zinc, manganese superoxide dismutase, glutathione reductase, glutathione peroxidase, and catalase, limiting their excessive buildup and resulting negative consequences. Inorganic scavengers like glutathione, ubiquinol, and uric acid, as well as dietary components like vitamins C and E, lipoic acid, carotenoids, selenium, etc., make up non-enzymatic antioxidant systems (Silva et al., 2010). The vitamins C, E, A, and carotenoids, an integral part of many research, are well-known antioxidants that are obtained through food. If the diabetes is predominantly hereditary in origin or brought on by obesity along with a sedentary routine, exogenous antioxidants may generally make up for the reduced plasma antioxidant levels frequently reported (Ruhe and McDonald, 2001). Both vitamin E and vitamin C have well-known antioxidant effects. In addition to these antioxidant vitamins, vegetables and fruits also include additional chemicals that ensure health advantages from eating them. Plant polyphenols are a significant class of antioxidants that play a protective role, according to research gathered over the previous ten years. These include phenols, phenolic acids, and flavonoids, which are present in practically all plant diets and are frequently present in high concentrations (Pietta, 2000).

Vitamin C consumption was shown to be considerably effective in lowering the occurrence of T2DM cases in a prospective cohort investigation (Feskens et al., 1995). Serum-tocopherol levels were linked to a reduced incidence of T1DM or T2DM across three prospective study designs. Vitamin E consumption was substantially related to a lower incidence of T2DM in another prospective trial population of more than 4000 non-diabetic patients during a 23-year period (Montonen et al., 2004). Certain researchers showed that 8 weeks of vitamin C, E, and beta-carotene supplementation resulted in a substantial decrease in GHS, TBARS levels, and GHS-Px, a rise in Cu-SOD, and no alteration in catalase action in the kidneys in streptozotocin (STZ) diabetic rats (Mekiňová et al., 1995). In addition, vitamin C and E supplementation were demonstrated to reduce kidney weight, glomerular basement membrane width, and urine albumin excretion in STZ diabetic rats (Kędziora-Kornatowska et al., 2003).

VI. TECHNIQUES USEFUL IN THE TREATMENT OF DIABETES MELLITUS

Insulin pumps and islet cell transplants are the two main treatment options for Type 1 diabetes. An effective substitute for injecting with an insulin pen is the use of an insulin pump. It may allow for greater freedom of choice in the treatment of diabetes. The biggest benefit of this treatment approach, however, is the decrease in hypoglycemia crises and the increased flexibility it affords in terms of dietary and lifestyle patterns (Jr., Raphael et al., 2006). Additionally, an islet cell transplant may be an option for someone with Type 1

diabetes (Agarwal et al., 2012). Both professionally and therapeutically, the area of islet cell transplantation has developed and seen great advancement. This could prevent encountering extreme instances of blood sugar drops.

The majority of Type 2 diabetes treatments begin with pills and medicine. There are several various types of tablets, with metformin being the most popular (Papanas et al., 2009). Sulphonylureas are one type of medicine that triggers the pancreas to generate insulin. Additionally, there are several bariatric operations for obesity that may be performed on the stomach or intestine to aid with weight loss. Numerous studies have shown that this can aid in the resolution of Type 2 diabetes (Affinati et al., 2019). Also, many patients with Type 2 diabetes choose to manage their condition through healthy nutrition and regular exercise rather than taking any medications. Some recent studies have demonstrated that losing weight may subside the symptoms of Type 2 diabetes. In the short term, insulin can be administered to assist in swiftly lowering blood sugar levels. Some people might require insulin for a specific reason, such as during pregnancy, a serious sickness, or following surgery. However, it may also be required as a therapy if other drugs have failed to control blood sugar levels or are ineffective (Swinnen et al., 2009). A person with diabetes might experience both physical and emotional turmoil. A person may require assistance for whatever feelings they're experiencing, regardless of whether they have had diabetes for many years or recently received their diagnosis. This could involve feeling stressed out, down and sad, or burned out. They should have plenty of emotional support from those around them while going through the various stages of treatment (Kalra et al., 2018).

VII. CONCLUSION

The majority of the negative consequences often linked to T2DM are caused by hyperglycemia, an unavoidable side effect of the condition. High blood glucose levels encourage the production of free radicals through auto-oxidation of glucose. The production of free radicals causes macro- and microvascular dysfunction as well as polyneuropathy when it exceeds the capacity of endogenous antioxidant defences to scavenge them.

It is possible to benefit from ingesting natural antioxidants or dietary supplements since antioxidants like vitamin C, N-acetylcysteine, and lipoic acid are good in lowering diabetes complications. Antioxidants are proven to be crucial tools in the study of diabetes and diseases linked to oxidative stress. They have a high potential to be used as a substitute treatment. Even though there isn't enough clinical proof to support the positive effects of vitamin antioxidants in managing diabetes, this fact shouldn't stop us from conducting further studies on clinical grounds. Instead, various guidelines originating from the findings of multiple studies should serve as the standard for evidence-based medicine to alleviate the complications associated with diabetics.

REFERENCES

- [1] Abacı, A., Oguzhan, A., Kahraman, S., Eryol, N. K., Ünal, S., Arınç, H., & Ergin, A. (1999). Effect of diabetes mellitus on formation of coronary collateral vessels. *Circulation*, 99(17), 2239-2242.
- [2] Affinati, A. H., Esfandiari, N. H., Oral, E. A., & Kraftson, A. T. (2019). Bariatric Surgery in the Treatment of Type 2 Diabetes. *Current diabetes reports*, 19(12), 156. <https://doi.org/10.1007/s11892-019-1269-4>.
- [3] Agarwal, A., & Brayman, K. L. (2012). Update on islet cell transplantation for type 1 diabetes. *Seminars in interventional radiology*, 29(2), 90–98. <https://doi.org/10.1055/s-0032-1312569>

- [4] Bashan, N., Kovsan, J., Kachko, I., Ovadia, H., & Rudich, A. (2009). Positive and negative regulation of insulin signaling by reactive oxygen and nitrogen species. *Physiological reviews*.
- [5] Deshpande, A. D., Harris-Hayes, M., & Schootman, M. (2008). Epidemiology of diabetes and diabetes-related complications. *Physical therapy*, 88(11), 1254–1264. <https://doi.org/10.2522/ptj.20080020>.
- [6] Feskens, E. J., Virtanen, S. M., Räsänen, L., Tuomilehto, J., Stengård, J., Pekkanen, J., ... & Kromhout, D. (1995). Dietary factors determining diabetes and impaired glucose tolerance: a 20-year follow-up of the Finnish and Dutch cohorts of the Seven Countries Study. *Diabetes care*, 18(8), 1104–1112.
- [7] Hamilton, S. J., Chew, G. T., & Watts, G. F. (2007). Therapeutic regulation of endothelial dysfunction in type 2 diabetes mellitus. *Diabetes and Vascular Disease Research*, 4(2), 89–102.
- [8] Jr., Raphael, & Durval, D. (2006) Insulin pump therapy in type 1 diabetes mellitus.[fecha de Consulta 24 de Julio de 2023]. ISSN: 0021-7557. <https://www.redalyc.org/articulo.oa?id=399738113004>. *Jornal de Pediatria*, 82(4), 249–254. <https://doi.org/10.2223/JPED.1507>
- [9] Kangralkar, V. A., Patil, S. D., & Bandivadekar, R. M. (2010). Oxidative stress and diabetes: a review. *Int J Pharm Appl*, 1(1), 38–45.
- [10] Kędziora-Kornatowska, K., Szram, S., Kornatowski, T., Szadujkis-Szadurski, L., Kędziora, J., & Bartosz, G. (2003). Effect of vitamin E and vitamin C supplementation on antioxidative state and renal glomerular basement membrane thickness in diabetic kidney. *Nephron Experimental Nephrology*, 95(4), e134–e143.
- [11] Kalra, S., Jena, B. N., & Yeravdekar, R. (2018). Emotional and Psychological Needs of People with Diabetes. *Indian journal of endocrinology and metabolism*, 22(5), 696–704. https://doi.org/10.4103/ijem.IJEM_579_17
- [12] King, H., Aubert, R. E., & Herman, W. H. (September 1, 1998). Global Burden of Diabetes, 1995–2025: Prevalence, numerical estimates, and projections. *Diabetes Care*, 21(9), 1414–1431. <https://doi.org/10.2337/diacare.21.9.1414>.
- [13] Laight, D. W., Carrier, M. J., & Ånggård, E. E. (2000). Antioxidants, diabetes and endothelial dysfunction. *Cardiovascular research*, 47(3), 457–464.
- [14] Maritim, A. C., Sanders, A., & Watkins Iii, J. B. (2003). Diabetes, oxidative stress, and antioxidants: a review. *Journal of biochemical and molecular toxicology*, 17(1), 24–38.
- [15] Mekiňová, D., Chorvathova, V., Volkovova, K., Staruchova, M., Graňičová, E., Klvanova, J., & Ondreič, R. (1995). Effect of intake of exogenous vitamins C, E and β -carotene on the antioxidative status in kidneys of rats with streptozotocin-induced diabetes. *Food/Nahrung*, 39(4), 257–261.
- [16] Montonen, J., Knekt, P., Jarvinen, R. I. T. V. A., & Reunanen, A. (2004). Dietary antioxidant intake and risk of type 2 diabetes. *Diabetes care*, 27(2), 362–366.
- [17] Morgantini, C., Natali, A., Boldrini, B., Imaizumi, S., Navab, M., Fogelman, A. M., ... & Reddy, S. T. (2011). Anti-inflammatory and antioxidant properties of HDLs are impaired in type 2 diabetes. *Diabetes*, 60(10), 2617–2623.
- [18] Norhammar, A., Tenerz, Å., Nilsson, G., Hamsten, A., Efendic, S., Rydén, L., & Malmberg, K. (2002). Glucose metabolism in patients with acute myocardial infarction and no previous diagnosis of diabetes mellitus: a prospective study. *The Lancet*, 359(9324), 2140–2144.
- [19] Papanas, N., & Maltezos, E. (2009). Metformin: A review of its use in the treatment type 2 diabetes. *Clinical Medicine. Therapeutics*, 1, 1367–1381. <https://doi.org/10.4137/CMT.S1085>.
- [20] Pietta, P. G. (2000). Flavonoids as antioxidants. *Journal of natural products*, 63(7), 1035–1042.
- [21] Ruhe, R. C., & McDonald, R. B. (2001). Use of antioxidant nutrients in the prevention and treatment of type 2 diabetes. *Journal of the American College of Nutrition*, 20(sup5), 363S–369S.
- [22] Sarrafchi, A., Bahmani, M., Shirzad, H., & Rafieian-Kopaei, M. (2016). Oxidative stress and Parkinson's disease: new hopes in treatment with herbal antioxidants. *Current pharmaceutical design*, 22(2), 238–246.
- [23] Silva, S. B. D., Costa, J. P., Pintado, M. E., Ferreira, D. D. C., & Sarmiento, B. (2010). Antioxidants in the prevention and treatment of diabetic retinopathy—a review. *Journal of Diabetes & Metabolism*, 1(3).
- [24] Swinnen, S. G., Hoekstra, J. B., & DeVries, J. H. (2009). Insulin therapy for type 2 diabetes. *Diabetes care*, 32 Suppl 2(Suppl 2), S253–S259. <https://doi.org/10.2337/dc09-S318>
- [25] Turko, I. V., Marcondes, S., & Murad, F. (2001). Diabetes-associated nitration of tyrosine and inactivation of succinyl-CoA: 3-oxoacid CoA-transferase. *American Journal of Physiology-Heart and Circulatory Physiology*, 281(6), H2289–H2294.