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Insights on antioxidants therapeutic strategies in type 2 diabetes mellitus: A narrative review of randomized control trials

Shrivastav D *et al*. Antioxidants therapeutic strategies in T2DM

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Abstract

BACKGROUND

Type 2 diabetes is a metabolic disease of impaired glucose utilization. Imbalance in generation and elimination of free radicals generate oxidative stress which modulates glucose metabolism, insulin regulation, resulting in the occurrence and progression of diabetes and associated complications. Antioxidant supplements in type 2 diabetes mellitus (T2DM) can be seen as a potential preventive and effective therapeutic strategy.

AIM

To compare randomized controlled trials (RCTs) in which antioxidants have been shown to have a therapeutic effect in T2DM patients.

METHODS

We systematically search the electronic database PubMed by keywords. RCTs evaluating the effect of antioxidant therapy on glycaemic control, oxidant and antioxidant status as primary outcomes were included. The outcome considered were: a reduction in blood

glucose ; changes in oxidative stress and antioxidant markers. Full-length papers of the shortlisted articles were assessed for the eligibility criteria and 17 RCTs were included.

RESULTS

The administration of fixed-dose antioxidants significantly reduces fasting blood sugar and glycated hemoglobin and associated with decreased malondialdehyde, advanced oxidation protein products and increased total antioxidant capacity.

CONCLUSION

Antioxidant supplements can be a beneficial approach for the treatment of T2DM.

Key Words: Diabetes; Antioxidants; Oxidative stress; Malondialdehyde; Polyphenols; Antioxidant therapy

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Core Tip: Antioxidant supplementation reduce oxidative stress in diabetes. Antioxidant supplementation is a potential therapeutic approach for type 2 diabetes mellitus.

INTRODUCTION

Type 2 diabetes mellitus (T2DM), a chronic metabolic disorder characterized by hyperglycaemia which arises from resistance or deficiency of insulin secreted from pancreatic beta cells[1]. Obesity and physical inactivity are general well-known risk factors for T2DM, micro (nephropathy and retinopathy) and macrovascular (atherosclerotic cardiovascular disease) complications[2]. According to World Health Organization, the prevalence and death rate was 470 million and 1.37 million in 2017 and expected to increase continuously and estimated prevalence and death rate will be 570.9 million and 1.59 million 2025 respectively[3]. In India, the prevalence of T2DM and impaired fasting glucose was 9.3% and 24.5% respectively in 2022. 45.8% of T2DM patients are aware of their diabetes, 6.1% are taking diabetes medication, and 15.1% have diabetes under control.

Oxidative stress

Oxidative stress is the excess production or insufficient clearance of highly reactive molecules like reactive oxygen species (ROS) and reactive nitrogen species. In physiological conditions, it is generated in the non-enzymatic, enzymatic, and mitochondrial processes. Enzymes of respiratory chain, phagocytosis, prostaglandin synthesis, and mitochondrial cytochrome P450 system and purine degradation produce free radicals[4]. In diabetes, due to hyperglycaemia, the formation of free radicals is increased resulting in an increase in oxidative stress which promotes rate of protein glycation (non-enzymatic), oxidation of glucose, lipid peroxidation and ultimately impairment in cellular machinery, enzymes and insulin pathways[5].

Oxidative stress targeted molecular pathways in T2DM pathogenesis

In T2DM, the prolonged exposure of high glucose and free fatty acid level significantly contribute in dysfunction of beta cells. These beta cells are highly sensitive to free radicals (due to low quenching and antioxidant activity). Consequently, the oxidative stress can harm mitochondria and significantly decrease insulin secretion and may cause insulin

resistance (Figures 1 and 2). Under physiological conditions, cellular metabolic process like glucose oxidation, generate superoxide anion radical [$O_2(-)$] inside the mitochondria which is combat by the antioxidant defence system of the body at a certain level[6]. However, in hyperglycaemic conditions, the production of $O_2(-)$ is elevated which decrease the body's antioxidant capacity as results generate oxidative stress and damage to several biomolecules including DNA[7]. DNA damage activates poly-ADP-ribose polymerase-1 (PARP-1) (DNA damage repair enzyme). This PARP-1AP-1 enzyme is potent inhibitor of glyceraldehyde 3-phosphate dehydrogenase of glycolysis as result intracellular concentration of glycolytic intermediate including glyceraldehyde 3-phosphate, fructose-6-phosphate and glucose-6-phosphate increases[8]. So, glycolytic intermediate accumulates inside the cell and promotes some other pro-oxidant pathways like protein kinase C, advanced glycation end products hexosamine and polyol pathways[9].

Antioxidants

To counteract the oxidative stress, the human body produce antioxidants in low concentration which significantly delay or inhibit cellular damage[4]. Humans have extremely complex antioxidant systems that protect the body's cells and organ systems from free radical. Antioxidant can be categorized as antioxidant enzymes and substrates[19], natural substance[20] combination medications[21], synthetic antioxidants[22], and pharmaceuticals[23]. In antioxidant enzyme and substrate system, superoxide dismutase, glutathione peroxidase, glutathione reductase, and catalase can combat the oxidative stress either directly or sequentially and abolish its excessive development of deleterious effects[24]. Antioxidant system (non-enzymatic) are endogenously produced and scavenge free radicals. It includes vitamin C, vitamin D, vitamin E, carotenoids, lipoic acid, selenium, and other dietary derivatives such as glutathione, ubiquinol[25].

Antioxidants therapy in diabetes

Exogenous antioxidant supplementation may reduce oxidative stress in T2DM by increasing antioxidant levels and decreasing free radical formation[26]. This supplementation potentially improves the metabolic pathways including nitric oxide (NO) production, endothelial dysfunction, mitochondrial function and vascular NAD(P)H oxidase activity[28,29]. According to recent clinical data in diabetic patients, supplementation of antioxidants improves glycaemic status [glycated hemoglobin (HbA1c) and random blood sugar], reduces oxidative stress biomarkers [malondialdehyde (MDA)], and increases serum level of antioxidant enzymes; superoxide dismutase (SOD), catalase and glutathione peroxidase[27]. Golbidi *et al*[62] investigated the therapeutic use of antioxidants as an adjuvant to standard diabetes treatment. Authors search the last ten years clinical trial study using terms vitamin E, vitamin C, coenzyme Q10 (CoQ10), alpha lipoic acid, L-carnitine, ruboxistaurin or LY 333531 and diabetes and conclude that vitamin supplementation are not beneficial for managing diabetes complications. In this review, we tried to compare randomised control trial interventional studies in which antioxidants have been shown to have a therapeutic effect in the treatment of T2DM.

MATERIALS AND METHODS

Search methodology

The literature search was carried out in the PubMed NCBI database. The search strategy was carried out by combination of ("Diabetes Mellitus, Type 2"[MeSH]) AND "Antioxidants"[MeSH]) AND "Oxidative Stress"[MeSH]) combining with each other using Boolean operators. The fixed dose of antioxidant was inclusion criteria for eligibility.

At starting of literature search the NCBI PubMed data base showed 726 articles. After applying filters, limiting the search with “full text”, “five years” (2017 to 2022) “human randomized controlled trials” which gives 23 randomized control trials studies. Full-length papers of the shortlisted articles were assessed for the eligibility criteria and 17

randomized controlled trials that fulfilled the inclusion criteria were included in the study (Figure 3 as PRISMA flow diagram and Table 1).

RESULTS

This study was performed to find role of antioxidants on oxidative stress in T2DM patients by comparing randomized controlled trials studies. After a literature search on database, it was found that the antioxidants including (vitamins, free fatty acid, natural products *etc.*) plays a diverse role to combat oxidative stress in T2DM patients[33]. It is well known that non-enzymatic antioxidants like vitamins A, C, and E, glutathione, lipoic acid, mixed carotenoids, CoQ10, a number of bioflavonoids, antioxidant minerals like copper, zinc, manganese, and selenium, as well as cofactors like albumin, folic acid, uric acid, and vitamins B1, B2, B6, and B12 are involved in diverse biological functions. Antioxidants have shown promise as a potential therapy for the prevention and treatment of cancer, diabetic complications, and cardiovascular disease (CVD) even though ROS have been linked to these diseases. In a study by Cojic *et al*[35], vitamin D supplements were given to proven T2DM patients with an average history of 4-6 years during a 6-mo follow-up period, and it was found that vitamin D supplementation (14000 IU weekly or 4 drops daily for 6 mo) can improve blood HbA1c and reduced advanced oxidation protein products (AOPP). The triglyceride/thiobarbituric acid-reactive substances (TG/TBARS) index, homeostasis model assessment of insulin resistance (HOMA-IR) index, and MDA level are likewise affected by this vitamin D treatment[35] Boonthongkaew *et al*[36] studied the effect of vitamin C supplementation (1000 mg daily for 6 wk) on blood pressure (BP), oxidative stress and NO release in T2DM patients and revealed that vitamin C supplementation improves blood pressure regulation, increase NO release, and significantly lowers serum MDA and F2-isoprostanes (IsoPs) levels. In another study, supplementation of vitamin E (alpha-tocopherol-400 IU) on T2DM patients with (duration of diabetes 9-11 years) for 6-wk daily arms and analyse the reactive hyperaemia index (RHI) and augmentation index in primary data and Pulse-Wave velocity (PWV), carotid intima media thickness (CIMT), inflammation (hsCRP),

derivatives of reactive-oxygen metabolites (dROMs), biological antioxidant potential (BAPs), HbA1c, low-density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C) and oxidised LDL-C (ox-LDL) was measured in secondary data. Dalan *et al*[37] concluded that vitamin E supplementation does not significantly improves RHI, PWV, CIMT, hsCRP, dROMS, BAPs, HDL-C and HbA1c however a significant fall in ox-LDL levels were observed. Further in subgroup analysis, vitamin E supplementation can increase reactive hyperaemia index, LDL and ox-LDL concentrations in non-Hp-2-2 group. Similarly, El-Aal *et al*[38] revealed that supplementation of vitamin C and/or vitamins E for 90 consecutive days to T2DM patients regulate fasting blood sugar (FBS), HbA1c, HOMA-IR and quantitative insulin sensitivity check index (QUICKI). Further it also improves serum level of glutathione-S-transferase, MDA, glucose-6-phosphate dehydrogenase, glutathione (GSH)-peroxidase, reduced glutathione in erythrocyte lysate, reduced glutathione in whole blood. Polyunsaturated fatty acids (n-3 PUFAs) are long-chain polyunsaturated fatty acids that have antioxidant properties. Indeed, n-3 PUFA supplementation has been demonstrated to reduce oxidative stress-related mitochondrial dysfunction and endothelial cell mortality, with the benefit mediated by increased endogenous antioxidant enzyme activity[39]. In another study conducted by Fayh *et al*[40], supplementation of n-3 PUFA (capsules containing 180 mg of eicosapentaenoic acid and 120 mg of docosahexaenoic acid) to T2DM patients (diabetes history of 6-8 years) non-significantly reduce serum level of TBARS, F2-IsoPs and serum triglycerides. CoQ10 is a powerful antioxidant found naturally in mitochondria that is endogenously synthesised and fat soluble. Because of its antioxidant properties, it can effectively inhibit the oxidation of fat, protein, and DNA in the body. Deficiency in CoQ10, particularly ubiquinol (the reduced form of CoQ10), is common in T2DM patients[63]. Yen *et al*[41] revealed that supplementing T2DM patients with ubiquinol (100 mg/day for 12 wk) resulted in significant reductions in blood HbA1c, fasting glucose, anti-glycaemic agent (thiazolidinediones by 25% to 83%), and increased SOD activity. However, there were no significant changes in the levels of serum MDA and ox-LDL. After 12 wk of supplementation, there was a further substantial association

between the plasma CoQ10 level and the insulin level, HOMA-IR, and anti-hyperglycaemic medication effect scores.

Plant-based natural antioxidants are mostly composed of polyphenols (phenolic acids, flavonoids, anthocyanins, lignans, and stilbenes), carotenoids (xanthophylls and carotenes), and phenolic acids. These naturally occurring antioxidants, particularly polyphenols and carotenoids, have a variety of biological effects, including anti-inflammatory, antibacterial, antiviral, anti-aging, and anticancer properties[42]. A traditional ayurvedic herb *Terminalia chebula* is well-known for its antioxidant and antihyperlipidemic properties. Pingali *et al*[43] suggested that the supplementation of aqueous extract of *Terminalia chebula* (250 mg and 500 mg twice daily for 12 wk) to T2DM patients significantly improved endothelial function, serum NO level, lipid profile, hsCRP levels and oxidative stress markers (GSH and MDA)[43]. Dill, also known as *Anethum graveolens L* (*A. graveolens*), is an herb that is frequently used as a spice and a remedy. The oils of *A. graveolens* are also a source of antioxidants, have antibacterial and antispasmodic qualities, and are also a source of minerals, proteins, and fibres. According to research, A. graveolens exhibits anticancer, antibacterial, anti-gastric-irritation, anti-inflammatory, and antioxidant effects[65]. The interventional study of Haidari *et al*[44] suggested that, the supplementation of *A. graveolens* (dill) powder (3 capsules per day, 1 g each daily) to T2DM patients (duration of diabetes 8-9 years) significantly decrease serum insulin, HOMA-IR, LDL-C and serum total cholesterol (TC), MDA and increase the serum level of HDL and total antioxidant concentration level. However, non-significant difference observed in inflammatory marker serum hsCRP level. Curcumin ($C_{21}H_2OO_6$) is a lipophilic substance and polyphenol in nature. Due to its chemical structure and presence of hydroxyl and methoxy groups, it is attributed to many properties, in particular antioxidant, antimicrobial, anti-inflammatory, anti-angiogenic, and antimutagenic ones. This curcumin regulates cyclooxygenase-2, lipoxygenase, xanthine oxidase, Inducible nitric oxide synthase (NOS) enzymes, and reduce serum level of MDA[66]. In another trial, Asadi *et al*[45] suggested that, the supplementation of nano-curcumin (80 mg per day for 8 wk) to T2DM patients (diabetes history 10-11 years)

significantly improves serum HbA1c, random blood sugar, total neuropathy score and total reflex score. Similarly, the administration of curcuminoids (daily dose of 500 mg/day co-administered with piperine (5 mg/day for 3 mo) can control insulin, HbA1c, and HOMA-IR index. Further it also reduces serum hsCRP and creatinine level in T2DM patients[46]. A bioflavonoid, Hesperidin (30,5,7-trihydroxy-40 -methoxy-flavanone7-rhamnglucoside) well known antioxidant which reduce risk of cardiovascular function and T2DM[47]. The oral administration of 500 mg/day hesperidin for 6 wk in T2DM patients (disease history of 3-11 years) increase total antioxidant concentration (mean percent change 13.35% ± 19.21%) and reduces the serum concentration of fructosamine (mean percent change 10.10% ± 16.84%), 8-hydroxy-2′-deoxyguanosine (mean percent change 25.11% ± 28.23%) and MDA (mean percent change 16.46% ± 18.04%)[48]. Various studies evidently prove that Propolis (a resin like material synthesized by honey bee) have antioxidant properties and sufficiently capable of scavenging free radicals[49]. The oral supplementation of Propolis (500 mg, three times a day for 8 wk) to T2DM patients (disease history 3-11 years) decrease FBS, 2-hp (2-hour postprandial glucose), insulin and HbA1c by 14% HOMA-IR by 25%, and upregulate total antioxidant capacity (TAC) by 19% SOD by 3% and GSH by 17%[50]. Anthocyanin is one of the major secondary metabolites which have antioxidant property. Bilberry (*Vaccinium myrtillus L.*) is natural and big source of anthocyanins[51]. Although bilberry is most typically used to improve vision, it has also been shown to lower blood sugar, have anti-inflammatory and lipid-lowering properties, as well as increase antioxidant defense and reduce oxidative stress. As a result, bilberry may be useful in the treatment or prevention of inflammation, dyslipidaemia, hyperglycaemia, or elevated oxidative stress, as well as CVD, cancer, Diabetes, dementia, and other age-related disorders[52]. The oral supplementation of bilberry (1.4 g/day of extract) daily for 4 wk reduce serum HbA1c level by 4.6% and ascorbic acid by 14%. Further decrease serum level of vitamin E lipid standardized, allantoin, glutathione peroxidase, and superoxide dismutase non-significantly[53]. The non-essential α-amino acid, L-citrulline plays major role in liver and kidney regulations. L-citrulline is also beneficial for NO production and endothelial cells regulation[54]. The

supplementation of L citrulline (3 g daily for 2 mo) to T2DM patients (history 3.5 years) significantly reduce serum fasting blood glucose and MDA level by 16% and 25% respectively. However, it significantly increases serum level of NOx, SOD and GPx level by 27%, 2% 2.2% respectively[55]. Wheat germ (WGEs) is a by-product of the wheat milling process that contains a variety of bioactive chemicals. WGEs show potential as antioxidants since they include a variety of bioactive components. According to the findings, bioactive compounds present in WGEs lower plasma lipid and oxidation levels[56]. Supplementation of WGEs (20-g per day for 8 wk) to T2DM patients decrease significant change in serum TC level but it neither affects serum level of FBS, HbA1C, TG, LDL-C, HDL-C, VLDL, MDA, and TAC nor HOMA-IR, HOMA-B, QUICKI, TG/HDL, LDL/HDL, systolic blood pressure, diastolic blood pressure[57].

A polyphenolic compound, resveratrol (3,5,4′-trihydroxy-trans-stilbene); type of plant secondary metabolite is a potent antioxidant which potentially scavenge the free radicals[58]. Oral supplementation of 800 mg/day resveratrol for 2 mo by T2DM patients decrease MDA by 8%, and Carbonyl protein by 18.54%. However, increase total thiol by 12%, NOS by 3% and catalase 12%. Further it also upregulates expression of nuclear factor erythroid 2-related factor 2 (oxidative stress responsive gene)[59]. Similarly, 100mg resveratrol tablet (total resveratrol: oligo-stilbene 27.97 mg/100 mg/day) daily for 12 wk effectively regulate arterial stiffness and downregulate Resveratrol supplementation decreased systolic BP and reactive oxygen metabolite significantly and also reduce risk of atherosclerosis in T2DM[60]. In this study, we tried to analyze that how imbalance between the production and inactivation of ROS leads to the development of Insulin resistance and metabolic syndrome. Therefore, preventing the damage caused by oxidation can prove to be effective therapeutic strategy in diabetes. We conducted randomized control trials comparison and reviewed available literature to summarizes the evidence covering the pathophysiological impact of oxidative stress on type 2 diabetes. Despite these, this study has several limitations including the heterogeneity and lower sample size in RCTs lowering its generalizability. Further, the large size

randomized controlled trials on population of different ethnicity and gender are needed to assess its therapeutic implications in type 2 diabetes.

DISCUSSION

The literature search revealed that non-enzymatic antioxidants such as vitamins A, C, and E, glutathione, lipoic acid, mixed carotenoids, CoQ10, and antioxidant minerals have diverse biological functions that can potentially prevent and treat cancer, diabetic complications, and cardiovascular diseases. The studies reviewed demonstrated that supplementation of vitamins D, C, and E, n-3 PUFAs, and CoQ10 can regulate fasting blood sugar, HbA1c, and oxidative stress biomarkers such as AOPP, TBARS, and MDA. In particular, vitamin D supplementation significantly improved blood HbA1c and reduced AOPP, while vitamin C supplementation improved blood pressure regulation and significantly lowered serum MDA and F2-IsoPs levels. On the other hand, vitamin E supplementation did not significantly improve RHI, PWV, CIMT, hsCRP, dROMS, BAPs, HDL-C, and HbA1c, but it caused a significant decrease in ox-LDL levels. Furthermore, supplementation of n-3 PUFAs non-significantly reduced serum levels of TBARS, F2-IsoPs, and serum triglycerides, while ubiquinol supplementation resulted in significant reductions in blood HbA1c, fasting glucose, anti-glycaemic agent, and increased SOD activity. However, there were no significant changes in the levels of serum MDA and ox-LDL. The study highlights the potential benefits of antioxidant supplementation in managing T2DM and the importance of further research to establish optimal dosages, treatment durations, and patient populations.

CONCLUSION

The modern lifestyle, which includes an unhealthy diet, a lack of physical activity, and exposure to a variety of chemicals from various sources such as pesticides, heavy metals, food additives, and environmental pollution, can all influence the appearance of oxidative stress. Oxidative stress plays an important role in the pathogenesis of various metabolic disorder including pre-obese, obese and T2DM. The production of ROS by

endogenous and/or exogenous mode are the significant contributors in the development of T2DM and its complications. The constant efforts have been made by researchers at global level to develop the therapeutic model to treat type 2 diabetes which can ameliorate oxidative stress. In general, oxidative stress can be reduced by adopting a balanced lifestyle and healthy diet. Although nutrition plays a critical role but the supplementation of diet with antioxidants like vitamins and natural products have the sufficient capacity to downregulate oxidative stress by quenching free radicals, enzymatic and non-enzymatic reactions. It is also suggested that these antioxidants may mitigate T2DM *via* various mechanisms like synchronize or control insulin related cell signalling which can regulate gene replication, transcription and translation and increase insulin secretion, improve function of hepatic β cells and glucose reabsorption. Ideally antioxidant rich food can be taken as part of life in early age. Further, it is also clear that antioxidants are sufficiently capable to reduce low grade inflammation with associated diseases. However, the antioxidants therapy might prove to be beneficial while supplementation at the late stage of diabetic patients.

ARTICLE HIGHLIGHTS

Research background

Type 2 diabetes is a condition that affects how the body uses glucose for energy. When there is an imbalance between the creation and removal of free radicals, oxidative stress can occur, which affects how the body regulates glucose and insulin, leading to the development and worsening of diabetes and related complications. Taking antioxidant supplements may be a promising way to prevent and treat type 2 diabetes.

Research motivation

To investigate the role of oxidative stress in the pathogenesis of type 2 diabetes mellitus (T2DM) and to explore the potential of antioxidant therapy as a treatment option. T2DM is a chronic metabolic disorder with increasing prevalence worldwide, and oxidative

stress is implicated in its complications. Antioxidants may counteract this process and improve metabolic pathways.

Research objectives

To review the current evidence on the role of oxidative stress in the pathogenesis of Type 2 diabetes mellitus and to evaluate the effectiveness of antioxidants as a potential therapy for managing diabetes and its complications.

Research methods

We systematically search the electronic database PubMed by keywords. RCTs evaluating the effect of antioxidant therapy on glycaemic control, oxidant and antioxidant status as primary outcomes were included. The outcome considered were: a reduction in blood glucose; changes in oxidative stress and antioxidant markers. Full-length papers of the shortlisted articles were assessed for the eligibility criteria and 17 RCTs were included.

Research results

The administration of fixed-dose antioxidants significantly reduces fasting blood sugar and glycated hemoglobin and associated with decreased malondialdehyde, advanced oxidation protein products and increased total antioxidant capacity.

Research conclusions

In conclusion, the modern lifestyle and environmental factors can contribute to oxidative stress, which plays a significant role in the development of metabolic disorders such as pre-obesity, obesity, and type 2 diabetes. The use of antioxidants through a balanced diet and/or supplementation can reduce oxidative stress, which may mitigate the development and complications of type 2 diabetes. Antioxidants can also reduce low-grade inflammation associated with various diseases. Further research is needed to determine the optimal timing and dosage of antioxidant therapy for diabetic patients.

Research perspectives

Future research should focus on identifying new antioxidants and their mechanisms of action in reducing oxidative stress and preventing or managing type 2 diabetes. Additionally, studies on the effectiveness of antioxidant supplementation in combination with other therapies, such as exercise and medication, should be conducted. Further investigation is also needed to determine the optimal timing and dosage of antioxidant supplementation for diabetes prevention and treatment.

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