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Antioxidant therapy for hemodialysis patients

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Abstract

Kidneys are the potential organs that play the important roles in controlling concentrations of body fluid, acid-base balance as well as blood and urine volume. Chronic renal failure especially hemodialysis causes the high mortality risk in patients. One of the causes of hemodialysis and mortality is the generation of reactive oxygen species (ROS). Thus, to control and to mitigate the adverse effects of dialysis in these patients, dietary antioxidants including vitamin C and flavonoids are necessary. Therefore, the aim of this review article is to clarify the effects of antioxidant therapy on hemodialysis patients.

Introduction

Kidneys are the dynamic organs filtering and secreting the final products of metabolism and the excess of electrolytes (1). They also produced the important hormones including erythropoietin, vitamin D as well as rennin (1). Kidneys are located in the back of the abdomen at the level of the lower ribs (1). Notably, approximately 20% of the blood comes to the kidneys from the hearts. The concentrations of the body fluids are controlled as the kidneys function normally (2). Besides its fluid concentrations, kidneys play vital roles in regulation of acid-base balance, and also urine and blood volume (3). Chronic renal failure happens, when kidneys stop working properly. It might occur suddenly or slowly during a long period (3). Thus, nephropathy is known as a decrease in the glomerular filtration rate, as evidenced by persistent albuminuria (2). Chronic kidney disease is known that the kidneys fail to remove the metabolic end-products from the blood, to regulate the fluid and electrolyte and also pH balance in the extracellular fluids (3). The common sign of renal failure is an accumulation of nitrogenous wastes in the blood followed by the decline in the glomerular filtration rate (4). Urea is the first nitrogenous wastes that accumulate in the blood and is referred as blood urea nitrogen (BUN). It increased up to as high as 80 m/dL in the chronic renal failure (5). The incidence of chronic renal failure is one of the main health problems leading to worse consequences and also high costs (6). The probable risk factors involved in hemodialysis include physical inactivity, hypertension, diabetes mellitus, hyperlipidemia, reactive oxygen species (ROS), and inflammation-related factors (7-9). Approximately 40% of patients have diabetes especially type 2 diabetes (8). Hypertension causes the high stress on blood vessels and consequently, increases the kidney filters (7). Glomerulonephritis is one of the inflammatory diseases damaging the kidneys; as the result, it induces the chronic kidney disease (9).

Core tip

Chronic renal failure especially hemodialysis causes the high mortality risk in patients. One of the causes of hemodialysis and mortality is the generation of reactive oxygen species (ROS). Thus, to control and to mitigate the adverse effects of dialysis in these patients, dietary antioxidants including vitamin C and flavonoids are necessary.

Materials and Methods

While, oxidative stress is one of the main causes of induction of chronic renal failure in people, it seems administration of antioxidants can help to mitigate the high mortality risk. Hence, the aim of this review article is to determine the effects of antioxidant therapy as a new treatment strategy on the alleviation of hemodialysis patients.

For this review, we used a diversity of sources by searching through PubMed/Medline, Scopus, EMBASE, EBSCO and directory of open access journals (DOAJ). The search was conducted, using combination of the following key words and or their equivalents; antioxidants, medicinal plants, herbal antioxidants, free radicals, free radical scav-

engers, antioxidants, reactive oxygen species and phytonutrients, chronic renal failure, hemodialysis, flavonoids, reactive oxygen species, mortality, end-stage renal disease

Hemodialysis

Hemodialysis is considered to use for removal of high toxins and metabolic products from patients with chronic renal failure (10). It removed BUN and creatinine from the blood. Patients with end-stage renal disease undergoing hemodialysis manifest an increased atherosclerosis and cardiovascular disease responsible for the most mortality (11,12). In spite of advances in medical care during dialysis, there is high risk of mortality and morbidity in these patients especially in people aged more than 64 years (13). Hemodialysis patients have the high risk of cardiovascular disease and mortality rate (14). Hemodialysis causes the mortality rate ranging from 42% to 88% (15). Approximately 34% of death in hemodialysis patients is obtained as the result of cardiovascular disease (16). Endothelial dysfunction as the consequence of generation of ROS and free radicals is involved in the high cardiovascular risk and mortality (17,18). The probability of patients with chronic renal disease to expose the cardiovascular disease is three to five folds higher than health people (19). Notably, its probability in hemodialysis patients is 3.5 to 50 times (20). Abnormalities in lipid accompanying with the increased oxidative stress in patients on hemodialysis maintenance progress atherosclerosis and cardiovascular disease (21). Patel et al (21) studied the alterations in 60 patients with chronic renal failure or hemodialysis. They found that the serum very-low-density lipoprotein (VLDL), low-density lipoprotein (LDL) and triglyceride values were increased in patients on hemodialysis, but the serum high-density lipoprotein (HDL) value was decreased in patients with chronic renal failure. Hypertriglyceridemia is a common disorder in hemodialysis patients; because patients with chronic renal failure mainly manifest insulin resistance activating hormone sensitive lipase; consequently, it leads to the raised free fatty acid and the production of VLDL (22). On the other hands, oxidants obtained during dialysis procedure are resulted from oxidative burst of activated neutrophils and superoxide anion production (23). Furthermore, the augmented ROS interact with inactivate nitric oxide during dialysis procedure resulting in generation of highly reactive compounds including peroxynitrite and peroxynitrous acid. As the result, they react with several important biological molecules such as lipid, protein and DNA (23).

With respect to the high mortality rate in hemodialysis patients, therapeutic strategies are recommended to alleviate its adverse effects. Therapeutic strategies administrated in hemodialysis patients include dietary supplement of antioxidant vitamins, administration of vitamin E-coated dialysis membrane and also electrolyte-reduced water (24).

Oxidative stress and hemodialysis

Oxidative stress is known as imbalance between the generation of ROS and the antioxidant status. The generation of high ROS contributes to chronic kidney disease (25). Excessive oxidative stress has been known in the pathogenesis of hemodialysis patients (25). The decreased antioxidant capacity and the increased generation of oxidative compounds are responsible for excessive oxidative stress status especially in hemodialysis patients (26). The two main ROS derived from activated neutrophils by myeloperoxidase are hydrogen peroxide and hypochlorite (26). On the other words, the four different pathways of oxidative stress are as follow: 1) Classical oxidative stress, 2) chlorinated stress; 3) nitrosative stress, and 4) carbonyl stress (27).

ROS have been shown to elevate in uremic patients involving in the pathogenesis of atherosclerosis in hemodialysis (28). Several mechanisms are proposed for increasing ROS including: first, the suppressed antioxidant system might be responsible for high oxidative damage during dialysis (27). Second, it might be caused by the interaction between blood and dialysis membrane (27). Third, bacterial products during dialysis cross its membrane via stimulating neutrophils. Fourth, malnutrition induces the excessive oxidative stress via a decline in the uptake of dietary antioxidants (27).

The total oxidant level is raised in restless legs syndrome of hemodialysis patients (29). Given oxidative stress and inflammation are two causes of end-stage renal disease (29). ROS are mainly generated by inflammation (29), the presence of endogenous oxidants in plasma (30). The inflammatory status induced by dialysis procedure acts the role in activating NADPH oxidase, hence, it aggravates the severe pro-oxidant state in patients on hemodialysis (31). While, the activated NADPH oxidase catalyzes the reduction of O2 to superoxide anion and then it dismutase to generate hydrogen peroxide (H2O2) (31). Notably, another cause of generation of ROS is the hemodialysis procedure (32). Hemodialysis patients manifested oxidative stress during dialysis as the consequence of the generation of oxidized-LDLs with a chronic deficiency in the antioxidant capacity (33). Tbahriti et al (34) studied the pro-oxidant status in 176 hemodialysis patients. They reported that the increased thiobarbituric acid reactive substances and lipid peroxidation and the decreased in antioxidant enzyme activity were obtained in hemodialysis patients. Mezzano et al (35) observed the increased thiobarbituric acid reactive substances and the advanced oxidation protein products in uremic patients. Reddy et al (36) studied the levels of ferric reducing ability of plasma as a measure of antioxidant potential in hemodialysis patients. They reported higher serum malondialdehyde and lower ferric reducing ability of plasma in patients with chronic renal disease.

On the other hands, the suppressed endogenous antioxidant enzymes activities and the inadequate non-enzymatic antioxidants levels play the important role in aggravating of the oxidative status (37). Nguyen-Khoa et al (38) showed that there is an inverse correlation between the duration of dialysis treatment as well as inflammatory status and plasma α-tocopherol levels. Likewise, they reported that plas-

ma ascorbate level was decreased in hemodialysis patients. Nevertheless, Hacisevki (39) found a higher superoxide dismutase activity and a lower glutathione peroxidase activity in chronic renal failure rather than those of control group. In addition, they reported that the serum malondialdehyde levels were higher in hemodialysis patients as compared to those of control group. The lower serum antioxidant enzyme activity in hemodialysis patients reflects the raised oxidative damage (39). Ahmadpoor et al (40) reported that glutathione levels, glutathione peroxidase activity was lower in dialysis patients in comparison with those of control group, but higher activity of glutathione reductase and total antioxidant capacity were noticed in maintenance dialysis patients. The depletion of glutathione in plasma indicted disturbance in antioxidant enzyme activity (40). Elshamaa et al (41) showed that the increased serum total antioxidant capacity, malondialdehyde and C reactive protein levels were obtained in patients on hemodialysis as compared to those of control group.

Antioxidant therapy on hemodialysis

Hemodialysis patients continuously undergo pro-oxidative status, thus it is required to increase antioxidant level for protection (26). Antioxidant therapy has been found to reduce oxidative stress and to modify cardiovascular disease in patients with chronic renal failure (42). There are two antioxidant defense systems including endogenous such as superoxide dismutase, catalase and glutathione peroxidase and exogenous. Extracellular antioxidants include vitamin A and C, albumin, bilirubin and uric acid preventing free radical reaction via chelating transition metal ions (43). Total antioxidant capacity is an index of antioxidant status of the body reflecting the oxidative stress (43).

Superoxide dismutase enzyme is the first line defense against damage induced by ROS (44). Additionally, glutathione peroxidase is an antioxidant enzyme produced in kidney that protects cell from oxidative injury via catalyzing the reduction of organic and hydrogen peroxides. This enzyme is considered to be a vital test to evaluate the oxidative damage in patients with chronic renal disease (45). Also, glutathione reductase contributes to antioxidant function via regenerating reduced glutathione from the oxidized glutathione form (45). Glutathione acts the important role in protecting cells from oxidative damage (45).

Vitamin C and E treatments act the important antioxidant role on hemodialysis patients (46). Notably, vitamin E increased the antioxidant potential of vitamin E via regenerating α-tocopherol (46). Vitamin E refers as the most potent lipophilic antioxidants (46). Miyazaki et al (17) studied the effects of anti-oxidative alteration during dialysis by administrating a vitamin E-coated cellulose membrane dialyzer. They showed that using vitamin E-coated membrane prevented endothelial dysfunction induced by dialysis. It was reported that administration of vitamin E in patients with chronic renal failure or hemodialysis patients not only alleviated the anti-oxidative defense (47), but also it decreased an increase in the aortic clarification index (47). Kamgar et al (29) reviewed the effects of vitamins treatment including 800 IU of vitamin E, 250 mg of vitamin C, 100 mg of vitamin B6 250 μg of vitamin B12 for 8 weeks on 37 inflammatory factors of hemodialysis patients. They reported that antioxidant administration had no significant effect on C- reactive protein and interleukin 6 levels in hemodialysis patients. One of the common disorders in hemodialysis patients is restless legs syndrome (48). Sagheb et al (25) studied the effects of antioxidant therapy including vitamin C or vitamin E on restless legs syndrome. They found that means of restless legs syndrome score in hemodialysis patients was reduced after supplementation of vitamin C or vitamin E as compared with the placebo group. Coombes and Fassett (42) reported that using α-tocopherol or vitamin C depressed oxidative stress and cardiovascular disease risk in 56 hemodialysis patients. Also, Himmelfarb et al (49) observed that oral administration of antioxidant including 666 IU tocopherol/d and 600 mg lipoic acid /d during 6 months reduced acute-phase inflammation and oxidative stress in maintenance hemodialysis patients.

Selenium is a cofactor of glutathione peroxidase enzyme that acts the vital role in protecting cell membrane against oxidative stress (50). Administration of selenium reduced oxidative and inflammatory status in chronic dialysis patients (50). The level of blood selenium and glutathione peroxidase activity was decreased in patients with end-stage renal disease (51). Richard et al (52) found the increased plasma selenium level in hemodialysis patients after intravenously injection of 50 μg of selenite for 5 weeks and then 100 μg selenite for consecutive 15 weeks. In addition, Bonomini et al (53) observed that selenite supplementation at 500 μg as orally increased the plasma selenium level after 1 month; because the level of selenium was lower in hemodialysis patients. Similarly, Koenig et al (51) reviewed the intravenously administration of 400 μg selenium three times a week on hemodialysis patients. They found that its supplementation raised selenium level in plasma after 2 weeks. Likewise, Adamowicz et al (54) studied selenium supplementation in patients with chronic renal disease and hemodialysis. They showed that selenium administration resulted in the enhanced plasma selenium level and red cell glutathione peroxiase activity. However, they found no alterations in plasma superoxide dismutase level and thiobarbituric acid reactive substances in hemodialysis patients (54). There is an inverse correlation between plasma glutathione peroxidase activity and malondialdehyde level in hemodialysis patients (54).

The lower zinc levels are associated with hemodialysis patients (55). Zinc acts the important structural role in superoxide dismutase enzyme and stabilizes membranes to diminish oxidative damage (55); thus, Roozbeh et al (56) found that zinc supplementation in hemodialysis patients led to a rise in serum zinc level and improvement in uremic signs. Mazani et al (57) studied the effects of zinc administration on antioxidant status in sixty-five hemodialysis patients. They observed the increased serum zinc and glutathione levels, total antioxidant capacity and also

superoxide dismutase activity and the reduced malondialdehyde concentration after administration of 100 mg zinc/day in hemodialysis patients (57).

Coenzyme Q10 is a cofactor in the mitochondrial electron transport chain. The reduced form of coenzyme Q10 possesses antioxidant activity (58). Bhogade et al (59) noticed that UbiQ100 administration led to a decline in lipid peroxidation and an increase in vitamin E level and erythrocyte superoxide dismutase activity in hemodialysis patients.

Castilla et al (60) reviewed the effects of concentrated red grape juice on 26 hemodialysis patients. The authors found that red grape juice treatment raised the serum antioxidant capacity and α-tocopherol level without influencing uric acid and vitamin C concentrations, but it decreased LDL concentration in hemodialysis patients. Similarly, Montazerifar et al (61) reviewed the effects of supplementation of fruit and vegetable diet in 34 hemodialysis patients. They found that antioxidant intake resulted in an increase in vitamins A and C levels and also superoxide dismutase activity after 8 weeks in hemodialysis patients. However, it was reported that intake of fruit and vegetable diet had no influence on vitamin E and malondialdehyde levels in patients with chronic kidney disease (61). Furthermore, De Paula et al (62) studied the effects of administration of 500 mg of grape powder per day on antioxidant and inflammatory biomarkers in non-diabetic hemodialysis patients. They found that grape powder supplementation increased glutathione peroxidase activity, but they did not affect C reactive protein levels.

Conclusion

Chronic renal disease is increasingly attracted the scientist' and patients attention due to its high cost and also mortality risk. The high death in maintenance hemodialysis patients is mainly resulted from the cardiovascular disease. Given the excessive ROS generation is responsible for atherosclerosis during dialysis and hence death. So, it seems that antioxidants administration could ameliorate the adverse effects of oxidative stress in hemodialysis patients.

Author's contribution

HN was the single author of the manuscript.

Conflicts of interest

The author declared no competing interests.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the author.

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