Antioxidant efficacy of vitamin D

Zeinab Mokhtari¹, Azita Hekmatdoost¹, Mojgan Nourian²

Abstract
Vitamin D (vit D) is not only contributed to maintaining normal calcium metabolism, but also is crucial for an extensive range of non-classic actions. The antioxidant effect of vit D is between the newest suggested non-calcemic roles of this compound. According to the vit D deficiency could be related to several chronic diseases such as diabetes, cardiovascular disease and chronic kidney disease (CKD), it is proposed that vit D could involve in the development or progression of chronic diseases by modulating oxidative stress. In this review, we summarize the current evidence indicating the association between chronic diseases and oxidative stress considering the role of vit D on this relationship.

Keywords: Vitamin D, Diabetes, Cardiovascular disease, Chronic kidney disease, Oxidative stress

Introduction
Vitamin D (vit D) deficiency is a global problem (1). However, there is no agreement on standard of 25-hydroxyvitamin D serum levels, vit D deficiency is determined with most specialists as a 25-hydroxyvitamin D level of under 30 ng/mL (75 nmol/L) (2-4). The active form vit D is 1, 25-dihydroxyvitamin D3 (1, 25(OH) 2D3) that is a whole member of the endocrine system and so may involve in homeostasis of body. Vit D is not only contributed to preserving normal calcium metabolism but also is crucial for an extensive range of non-classic actions (5,6). Antioxidant effect of vit D is between the newest suggested non-calcemic roles of this compound. Having a homologous structure to cholesterol has proposed that vit D may be regarded as an antioxidant (7). In this background, in a study conducted on rats, it was found out that the antioxidant effects of vit D were similar or even further than vitamin E (8).

Increasing evidence in recent decades show that the vit D deficiency could be related to several chronic diseases, including insulin resistance and type 2 diabetes (9,10), cardiovascular complications (11), progression of chronic kidney disease (CKD) (12), and autoimmune diseases such as type 1 diabetes (13). Furthermore, several lines of evidence have shown that oxidative stress plays a key role in progression of chronic diseases such as diabetes (14), cardiovascular disease (15) and CKD (16).

Oxidative stress is defined as a significant imbalance between reactive oxygen species (ROS) production and antioxidant defenses. It induces the modifications in signaling pathways and potential tissue damage. The ROS have adverse reactions with polyunsaturated fatty acids, proteins and nucleotides that could lead to lipid peroxidation, inactivated proteins and impaired DNA and RNA. If there is no adequate defense against ROS by enzymatic and non-enzymatic antioxidants, reactive species could be damaging for cellular functions (17,18).

According to the potential role of vit D deficiency and oxidative stress in development of chronic disease, in the present review, we summarize current evidence indicating the association between chronic diseases and oxidative stress considering the role of vit D on this relationship.

Materials and Methods
While, vit D deficiency is a public health problem, the aim of this review article is to determine the antioxidant impact of vit D. 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; vitamin D, diabetes, cardiovascular disease, chronic kidney disease and oxidative stress.

Vitamin D and oxidative stress in diabetes
Several epidemiological studies show inverse associations between serum 25-hydroxyvitamin and fasting blood glucose, insulin resistance, prevalence of type 2 diabetes (19-23). Diabetes mellitus is associated with the declined antioxidant capacity and increased production of ROS through increases of lipids, proteins and DNA oxidation products, glycated biomolecules, such as advanced...
Implication for health policy/practice/research/medical education

Vitamin D (vit D) is attributed to prevention of chronic diseases such as diabetes, cardiovascular disease and chronic kidney disease by regulation of oxidative stress through following ways; induces the expression of several molecules involved in the antioxidant defense system including glutathione, glutathione peroxidase and superoxide dismutase (SOD) and suppresses the expression of NADPH oxidase.

Glycation end products (AGEs), and advanced oxidation protein products (24-26). Oxidative stress has a pivotal role in the pathogenesis of diabetes complications (27). There are several evidence supporting the antioxidant activity of vit D3 (cholecalciferol) in the oxidative stress diabetes. The results in some experimental studies implied that vit D3 administration in diabetic mice helps to diminish the ROS formation by the suppression of the gene expression of NADPH oxidase (28,29). NADPH oxidase is a main resource of ROS, and its activation contributes as a positive marker for oxidative stress (30). Vit D3 decreases the lipid peroxidation and improves the superoxide dismutase (SOD) activity in the mice (31-33). SOD is the initial line of cellular antioxidant defense in spite of the oxidative stress made by superoxide radicals (34). The antioxidant enzymes are a principal cell defense against free radical attack that protect membrane and cytosolic components against damage mediated by ROS. Some of the most important ones are SOD, catalase and glutathione (GSH) peroxidase (35).

According to the literature, calcitriol could enhance the pathway of ROS removal, by increasing the intracellular pool of reduced GSH, partially through upstream regulation of glutamate-cysteine ligase (GCL) and glutathione reductase (GR) genes expression (36). GCL is a key enzyme that involved in synthesis of GSH (37). A positive correlation between the vit D and GSH concentrations have been reported (38). Furthermore, Sardar et al (8) proposed that this vitamin was an antioxidant as a result of an increase in hepatic GSH amounts in rats that have gotten cholecalciferol. Results of a clinical trial showed combination of vit D and calcium supplementations made a more than reduction in malondialdehyde (MDA) plasma and a considerable increase in plasma total antioxidant capacity and GSH levels compared with calcium and vit D separately (39). However, Nikooeyeh et al (40) showed that extra calcium did not give further benefit for oxidative stress diminishing action of vit D. This difference may be to the fact that dissimilar doses of vit D treatment have been used in this studies.

Several biological activities of the 1, 25 (OH) 2D3 are accomplished by binding to a nuclear receptor, the vit D receptor (VDR) (41). Interestingly knocking down VDR removed the effective action of calcitriol as expected, thus suggesting that partially the antioxidant effects of 1, 25(OH) 2D3 are mediated by its receptor VDR (28,36).

Control of oxidative metabolism by vit D3 is involved with interactions between several nuclear coactivators or corepressors that mediate the regulation of gene transcription at the level of their interaction with receptors of hormonally active form of cholecalciferol (VDR). When binding receptors, vit D3 leads to increment in signaling and efficiently controls the rate of free radicals formation in mice liver cells (31,36,42).

In spite of this, there are evidence in literature that imply a significant antioxidant role of vit D3 in mature erythrocytes without nucleus. These results not only verify that cholecalciferol has the antioxidant effect (43), but also suggest that 1,25-dihydroxycholecalciferol could be like a direct antioxidant of membrane, via stabilizing and protecting membrane from lipid peroxidation through relations with their hydrophobic parts (44). In an in vitro study, it was suggested that vit D3 has the antioxidant effect much more than that of vitamin E, β-estradiol and melatonin (45).

Although, there is considerable evidence for protecting against oxidative stress by cholecalciferol in diabetes, but this is not confirmed well by some studies (46,47). Respiration is correlated with ROS production, thus mitochondria can generate a great portion of whole cellular ROS (48). Mild uncoupling of respiration reduces formation of mitochondrial ROS by dissipating the mitochondrial potential and proton gradient (49). Consequently, mild activation of mitochondrial uncoupling protein (UCP) might show a role in the ROS defense system. Recent evidence points toward calcitriol could inhibit UCP expression, accordingly stimulates ROS production in adipocytes (50). Furthermore, the results of another study have been indicated that vit D increased oxidative stress in human bone cells partially by stimulation of lipoxygenase enzymes (51). Though, these potential vit D stimulated oxidative stress actions remain totally hypothetical and are the issue of future study.

Vitamin D and oxidative stress in cardiovascular diseases

Considerable research indicates that there is the strong and independent relationship between vit D deficiency and incident cardiovascular events (11,52). Also, there are various interventional studies that examined the association between vit D supplementation and prevention of cardiovascular diseases (CVD) in humans (53). Based on these results, vit D should be a key role for cardiovascular health, although their detailed mechanisms remain unclear. One possible explanation for the improvement in cardiovascular health by vit D is that its effects on endothelial function may occur by protective effects against oxidative stress. Endothelial function has a pivotal role in health of cardiovascular system. Oxidative stress alters many functions of the endothelium, counting modulation of vasomotor tone and inactivation of nitric oxide by ROS (54). Tarcin et al. showed 25-hydroxyvitamin D deficiency is associated with endothelial dysfunction. When vit D is administered to hypovitaminosis D subjects, endothelial function improves. They suggest...
that this improvement in endothelial function is likely to be due to the effects of vit D replacement on lipid peroxidation (55). It was proposed that the antioxidant effect of vit D3 in human coronary artery endothelial cells may be through suppression of the expression of NADPH enzyme (56). The vasoprotective role of vit D is partially attributed to inhibition of the accumulation of AGEs in the aortic tissue. This inhibition may be caused by enhanced systemic antioxidant capacity and attenuated production of oxidative stress in the liver, the crucial organ in the circulation and metabolism of vit D (57). Although, less is known about the molecular mechanisms of antioxidants vit D activity. The Ras-mitogen activated pathway kinases (MAPKs) signaling pathway have a great action in controlling cell apoptosis following oxidative stress (58). MAPKs signaling pathway regulates cellular response to the oxidative stress controlling the expression of some transcription factors (59) for instance silent information regulator 1 (SIRT1) (60). SIRT-1 has been contributed to the vascular endothelial homeostasis (61) and inhibiting endothelial cells senescence and death attributed to oxidative stress (62,63). Polidoro et al (64), in a study conducted on human endothelial cell, found out that vit D is able to decrease the impairment after H2O2 mediated stress by the attenuation of anion superoxide yield and apoptosis. This activity was done via preventing extrinsic caspase cascade activation and the switching on MEKs/ERKs/SIRT-1 axis. This findings are in agreement with those of Uberti et al (65). As well, they reported that vit D was added to endothelium before the oxidative stress induced can enhance cell survival. The involving mechanisms contain the inhibition of ORS release and the regulation of the interaction between autophagy and apoptosis. This result is attained by preventing superoxide anion production, preserving function of mitochondria and cell viability and stimulating survival kinase (ERK) (65). Thus, vit D may effect on signaling and survival by improving oxidative stress system of endothelial cells.

**Vitamin D and oxidative stress in chronic kidney disease**

There are negative associations between different indicators of oxidative stress and glomerular filtration rate (66-68). Furthermore, augmentation in oxidative stress have been correlated with longer durations of dialysis therapy (69), hence implying that oxidative stress have led to accelerate the renal damage progression by inducing cytotoxicity. ROS stimulates oxidized proteins and DNA and lipid peroxidation that causes an inflammatory cascade by inflammatory cytokines, containing, TNF-α, via the activation of NF-κB. Activated NF-κB begins signalling pathways contribute to renal fibrosis (70). The damage of functional renal tissue in CKD, leads to decline production of 25-hydroxyvitamin D 1α-hydroxylase, causes to reduce vit D3 levels (71). Patients with CKD display the great decrease in serum 25 (OH) D levels, implying an increased need for vit D in the CKD patients (72,73). Supplementation of calcitriol in CKD subjects reduced the risk of morbidity and mortality (74,75). Active vit D could attenuate glomerular injury and renal fibrosis (76,77). The molecular mechanisms behind the actions of paricalcitol in the kidney may be from diminishing oxidative stress. These effects may due, at least partially, to the inhibition of NADPH oxidase expression and enhancement in cytosolic SOD enzyme (78). After paricalcitol (VDR activators) treatment in hemodialysis patient, levels of the oxidative stress markers including MDA, nitric oxide and protein carbonyl groups were significantly reduced in serum and the level of antioxidant defenses containing GSH, catalase and SOD activity were increased (79). Another study proposed that pretreatment with vit D made to rise in SOD activity and GSH levels in renal tissue. Enhancement in renal antioxidant enzymes and reduction in renal ROS production could help to inhibit renal ischemia (80). Nevertheless, if vit D was administered in advanced stages of renal disease, there would no advantageous effects on biomarkers of oxidative stress (81). One possible mechanism was proposed for protecting against oxidative stress in nephropathy by calcitriol is the Nrf2–Keap1 pathway (82). Nuclear factor erythroid 2-related factor 2 (Nrf2) controls expression of ROS detoxifying and antioxidant agents via the antioxidant response element (ARE/EpRE). In physiological conditions, Nrf2 is sequestered in the cytoplasm by Kelch-like erythroid cell-derived protein with CNC homology (ECH)-associated protein 1 (Keap1), an actin binding repressor protein. Owing to this mechanism, Keap1 contributes to augmented oxidative stress due to negative regulation of Nrf2 and ARE/EpRE activity (83). Vit D3 could increase the expression of Nrf2 and also leads to reduce expression of Keap1 that decreases the development of nephropathy by inhibition of oxidative stress (82).

**Conclusion**

Vit D is attributed to prevention of chronic diseases such as diabetes, CVD and CKD by regulation of oxidative stress through following ways; induces the expression of several molecules involved in the antioxidant defense system including GSH, GSH peroxidase and SOD and suppresses the expression of NADPH oxidase. 1, 25-dihydroxycholecalciferol may be similar to a direct antioxidant of membrane. However, there are few in vivo studies that have examined this hypothesis. Little information is available for the molecular mechanisms of antioxidants or pro-oxidant vit D activity. Additional investigations are required to reveal the precise mechanism behind this property of cholecalciferol. It would be beneficial to the identification of possible new therapeutic plans.

**Authors’ contribution**

ZM, AH, and MN contributed to the conception of the article, literature search and interpretation, writing the article and making critical revisions related to important intellectual content of the manuscript, and final approval of the manuscript.
Conflicts of interest
The authors declared no competing interests.

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

Funding/Support
None.

References
34. Fridovich I. Superoxide dismutases. Adv Enzymol Relat
Antioxidant efficacy of vitamin D


