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Review

Antioxidant efficacy of vitamin D

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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

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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

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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, Nikooyeh 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.

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References

1. Holick MF. Vitamin D deficiency. N Engl J Med. 2007;357:266-81.
2. Bischoff-Ferrari HA, Giovannucci E, Willett WC, Dietrich T, Dawson-Hughes B. Estimation of optimal serum concentrations of 25-hydroxyvitamin D for multiple health outcomes. Am J Clin Nutr. 2006;84:18-28.
3. Dawson-Hughes B, Heaney RP, Holick MF, Lips P, Meunier PJ, Vieth R. Estimates of optimal vitamin D status. Osteoporos Int. 2005;16:713-6.
4. Martins D, Wolf M, Pan D, Zadshir A, Tareen N, Thadhani R, et al. Prevalence of cardiovascular risk factors and the serum levels of 25-hydroxyvitamin D in the United States: data from the Third National Health and Nutrition Examination Survey. Arch Intern Med. 2007;167:1159-65.
5. Norman AW. From vitamin D to hormone D: fundamentals of the vitamin D endocrine system essential for good health. Am J Clin Nutr. 2008;88(2):491S-9S.
6. Giovannucci E. Expanding roles of vitamin D. J Clin Endocrinol Metab. 2009;94:418-20.
7. Smith LL. Another cholesterol hypothesis: cholesterol as antioxidant. Free Radic Biol Med. 1991;11:47-61. PubMed
8. Sardar S, Chakraborty A, Chatterjee M. Comparative effectiveness of vitamin D3 and dietary vitamin E on peroxidation of lipids and enzymes of the hepatic antioxidant system in Sprague--Dawley rats. Int J Vitam Nutr Res. 1996;66:39-45.
9. Chiu KC, Chu A, Go VLW, Saad MF. Hypovitaminosis D is associated with insulin resistance and β cell dysfunction. Am J Clin Nutr. 2004;79:820-5.
10. Mitri J, Muraru M, Pittas A. Vitamin D and type 2 diabetes: a systematic review. Eur J Clin Nutr. 2011;65:1005-15.
11. Wang TJ, Pencina MJ, Booth SL, Jacques PF, Ingelsson E, Lanier K, et al. Vitamin D deficiency and risk of cardiovascular disease. Circulation. 2008;117:503-11.
12. Ravani P, Malberti F, Tripepi G, Pecchini P, Cutrupi S, Pizzini P, et al. Vitamin D levels and patient outcome in chronic kidney disease. Kidney Int. 2009 Jan;75:88-95.
13. Hyppönen E, Läärä E, Reunanen A, Järvelin M-R, Virtanen SM. Intake of vitamin D and risk of type 1 diabetes: a birth-cohort study. Lancet. 2001;358:1500-3.
14. Maritim A, Sanders a, Watkins rJ. Diabetes, oxidative stress, and antioxidants: a review. J Biochem Mol Toxicol. 2003;17:24-38.
15. Madamanchi NR, Vendrov A, Runge MS. Oxidative stress and vascular disease. Arterioscler Thromb Vasc Biol. 2005;25:29-38.
16. Small DM, Coombes JS, Bennett N, Johnson DW, Gobe GC. Oxidative stress, anti-oxidant therapies and chronic kidney disease. Nephrology. 2012;17:311-21.
17. Halliwell B. Free radicals and other reactive species in disease. eLS; 2005.
18. Kadiiska M, Gladen B, Baird D, Germolec D, Graham L, Parker C, et al. Biomarkers of oxidative stress study II: are oxidation products of lipids, proteins, and DNA markers of CCl 4 poisoning? Free Radic Biol Med. 2005;38:698-710.
19. Forouhi NG, Luan JA, Cooper A, Boucher BJ, Wareham NJ. Baseline serum 25-hydroxy vitamin d is predictive of future glycemic status and insulin resistance the medical research council ely prospective study 1990–2000. Diabetes. 2008;57:2619-25.
20. Ford ES, Ajani UA, McGuire LC, Liu S. Concentrations of serum vitamin D and the metabolic syndrome among US adults. Diabetes Care. 2005;28:1228-30.
21. Schöttker B, Herder C, Rothenbacher D, Perna L, Müller H, Brenner H. Serum 25-hydroxyvitamin D levels and incident diabetes mellitus type 2: a competing risk analysis in a large population-based cohort of older adults. Eur J Epidemiol. 2013;28:267-75.
22. Chiu KC, Chu A, Go VL, Saad MF. Hypovitaminosis D is associated with insulin resistance and beta cell dysfunction. Am J Clin Nutr. 2004 May;79:820-5.
23. Gradinaru D, Borsa C, Ionescu C, Margina D, Prada GI, Jansen E. Vitamin D status and oxidative stress markers in the elderly with impaired fasting glucose and type 2 diabetes mellitus. Aging Clin Exp Res. 2012;24:595-602.
24. West IC. Radicals and oxidative stress in diabetes. Diabet Med. 2000;17:171-80.
25. Schrauwen P, Hesselink MK. Oxidative capacity, lipotoxicity, and mitochondrial damage in type 2 diabetes. Diabetes. 2004;53:1412-7.
26. Goodarzi MT, Navidi AA, Rezaei M, Babahmadi-Rezaei H. Oxidative damage to DNA and lipids: correlation with protein glycation in patients with type 1 diabetes. J Clin Lab Anal. 2010;24:72-6.
27. Giacco F, Brownlee M. Oxidative stress and diabetic complications. Circ Res. 2010;107:1058-70.
28. Labudzynskyi DO, Zaitseva OV, Latyshko NV, Gudkova OO, Veliky MM. Vitamin d3 contribution to the regulation of oxidative metabolism in the liver of diabetic mice. Ukr Biochem J. 2015;87:75-90.
29. Kono K, Fujii H, Nakai K, Goto S, Kitazawa R, Kitazawa S, et al. Anti-oxidative effect of vitamin D analog on incipient vascular lesion in non-obese type 2 diabetic rats. Am J Nephrol. 2013;37:167-74.
30. Görlach A, Brandes R, Nguyen K, Amidi M, Dehghani F, Busse R. A gp91phox containing NADPH oxidase selectively expressed in endothelial cells is a major source of oxygen radical generation in the arterial wall. Circ Res. 2000;87:26-32.
31. Zhong W, Gu B, Gu Y, Groome LJ, Sun J, Wang Y. Activation of vitamin D receptor promotes VEGF and CuZn-SOD expression in endothelial cells. J Steroid Biochem Mol Biol. 2014;140:56-62.
32. Gren A. Effects of vitamin E, C and D supplementation on inflammation and oxidative stress in streptozotocin-induced diabetic mice. Int J Vitam Nutr Res. 2013;83:168-75.
33. Hamden K, Carreau S, Jamoussi K, Ayadi F, Garmazi F, Mezgenni N, et al. Inhibitory effects of 1alpha, 25dihydroxyvitamin D3 and Ajuga iva extract on oxidative stress, toxicity and hypo-fertility in diabetic rat testes. J Physiol Biochem. 2008;64:231-9.
34. Fridovich I. Superoxide dismutases. Adv Enzymol Relat

Areas Mol Biol. 1986;58:61-97.
35. Finkel T, Holbrook NJ. Oxidants, oxidative stress and the biology of ageing. Nature. 2000;408:239-47.
36. Kanikarla-Marie P, Jain SK. 1,25(OH)2D3 inhibits oxidative stress and monocyte adhesion by mediating the upregulation of GCLC and GSH in endothelial cells treated with acetoacetate (ketosis). J Steroid Biochem Mol Biol. 2016;159:94-101.
37. Lu SC. Regulation of glutathione synthesis. Mol Aspects Med. 2009;30:42-59.
38. Jain SK, Micinski D, Huning L, Kahlon G, Bass PF, Levine SN. Vitamin D and L-cysteine levels correlate positively with GSH and negatively with insulin resistance levels in the blood of type 2 diabetic patients. Eur J Clin Nutr. 2014;68:1148-53.
39. Foroozanfard F, Jamilian M, Bahmani F, Talaee R, Talaee N, Hashemi T, et al. Calcium plus vitamin D supplementation influences biomarkers of inflammation and oxidative stress in overweight and vitamin D-deficient women with polycystic ovary syndrome: a randomized double-blind placebo-controlled clinical trial. Clin Endocrinol. 2015;83:888-94.
40. Nikooyeh B, Neyestani TR, Tayebinejad N, Alavi-Majd H, Shariatzadeh N, Kalayi A, et al. Daily intake of vitamin D- or calcium-vitamin D-fortified Persian yogurt drink (doogh) attenuates diabetes-induced oxidative stress: evidence for antioxidative properties of vitamin D. J Hum Nutr Diet. 2014;27:276-83.
41. Reis AF, Hauache OM, Velho G. Vitamin D endocrine system and the genetic susceptibility to diabetes, obesity and vascular disease. A review of evidence. Diabetes Metab. 2005;31:318-25.
42. Bouillon R, Carmeliet G, Verlinden L, van Etten E, Verstuyf A, Luderer HF, et al. Vitamin D and human health: lessons from vitamin D receptor null mice. Endocr Rev. 2008;29:726-76.
43. Wolden-Kirk H, Gysemans C, Verstuyf A, Mathieu C. Extraskeletal effects of vitamin D. Endocrinol Metab Clin North Am. 2012;41:571-94.
44. Wiseman H. Vitamin D is a membrane antioxidant. Ability to inhibit iron-dependent lipid peroxidation in liposomes compared to cholesterol, ergosterol and tamoxifen and relevance to anticancer action. FEBS Lett. 1993;326:285-8.
45. Lin AM, Chen K, Chao P. Antioxidative effect of vitamin D3 on zinc-induced oxidative stress in CNS. Ann N Y Acad Sci. 2005;1053:319-29.
46. Asemi Z, Hashemi T, Karamali M, Samimi M, Esmaillzadeh A. Effects of vitamin D supplementation on glucose metabolism, lipid concentrations, inflammation, and oxidative stress in gestational diabetes: a double-blind randomized controlled clinical trial. Am J Clin Nutr. 2013;98:1425-32.
47. Noyan T, Balaharoglu R, Komuroglu U. The oxidant and antioxidant effects of 25-hydroxyvitamin D3 in liver, kidney and heart tissues of diabetic rats. Clin Exp Med. 2005;5:31-6.
48. Andreyev AY, Kushnareva YE, Starkov A. Mitochondrial metabolism of reactive oxygen species. Biochemistry (Moscow). 2005;70:200-14.
49. Miwa S, Brand M. Mitochondrial matrix reactive oxygen species production is very sensitive to mild uncoupling. Biochem Soc Trans. 2003;31:1300-1.
50. Sun X, Zemel MB. 1Alpha,25-dihydroxyvitamin D3 modulation of adipocyte reactive oxygen species production. Obesity. 2007;15:1944-53.
51. Somjen D, Katzburg S, Knoll E, Sharon O, Posner GH, Stern N. Vitamin D analogs induce lipoxygenase mRNA expression and activity as well as reactive oxygen species (ROS) production in human bone cells. J Steroid Biochem Mol Biol. 2010;121:265-7.
52. Michos ED, Melamed ML. Vitamin D and cardiovascular disease risk. Curr Opin Clin Nutr Metab Care. 2008;11:7-12.
53. Zittermann A, Frisch S, Berthold HK, Götting C, Kuhn J, Kleesiek K, et al. Vitamin D supplementation enhances the beneficial effects of weight loss on cardiovascular disease risk markers. Am J Clin Nutr. 2009;89:1321-7.
54. Cai H, Harrison DG. Endothelial dysfunction in cardiovascular diseases: the role of oxidant stress. Circ Res. 2000;87:840-4.
55. Tarcin O, Yavuz DG, Ozben B, Telli A, Ogunc AV, Yuksel M, et al. Effect of vitamin D deficiency and replacement on endothelial function in asymptomatic subjects. J Clin Endocrinol Metab. 2009;94:4023-30.
56. Hirata M, Serizawa K, Aizawa K, Yogo K, Tashiro Y, Takeda S, et al. 22-Oxacalcitriol prevents progression of endothelial dysfunction through antioxidative effects in rats with type 2 diabetes and early-stage nephropathy. Nephrol Dial Transplant. 2013;28:1166-74.
57. Salum E, Kals J, Kampus P, Salum T, Zilmer K, Aunapuu M, et al. Vitamin D reduces deposition of advanced glycation end-products in the aortic wall and systemic oxidative stress in diabetic rats. Diabetes Res Clin Pract. 2013;100:243-9.
58. Martindale JL, Holbrook NJ. Cellular response to oxidative stress: signaling for suicide and survival. J Cell Physiol. 2002;192:1-15.
59. Runchel C, Matsuzawa A, Ichijo H. Mitogen-activated protein kinases in mammalian oxidative stress responses. Antioxidants & redox signaling. 2011;15:205-18.
60. Cantó C, Gerhart-Hines Z, Feige JN, Lagouge M, Noriega L, Milne JC, et al. AMPK regulates energy expenditure by modulating NAD+ metabolism and SIRT1 activity. Nature. 2009;458:1056-60.
61. Potente M, Ghaeni L, Baldessari D, Mostoslavsky R, Rossig L, Dequiedt F, et al. SIRT1 controls endothelial angiogenic functions during vascular growth. Genes Dev. 2007;21:2644-58.
62. Zu Y, Liu L, Lee MY, Xu C, Liang Y, Man RY, et al. SIRT1 promotes proliferation and prevents senescence through targeting LKB1 in primary porcine aortic endothelial cells. Circ Res. 2010;106:1384-93.
63. Alcendor RR, Gao S, Zhai P, Zablocki D, Holle E, Yu X, et al. Sirt1 regulates aging and resistance to oxidative stress in the heart. Circ Res. 2007;100:1512-21.
64. Polidoro L, Properzi G, Marampon F, Gravina GL, Festuccia C, Di Cesare E, et al. Vitamin D protects human endothelial cells from H(2)O(2) oxidant injury through the Mek/Erk-Sirt1 axis activation. J Cardiovasc Transl Res. 2013;6:221-31.
65. Uberti F, Lattuada D, Morsanuto V, Nava U, Bolis G, Vacca G, et al. Vitamin D protects human endothelial cells from oxidative stress through the autophagic and survival pathways. J Clin Endocrinol Metab. 2014;99:1367-74.
66. Dounousi E, Papavasiliou E, Makedou A, Ioannou K, Katopodis KP, Tselepis A, et al. Oxidative stress is progressively enhanced with advancing stages of CKD. Am J Kidney Dis. 2006;48:752-60.

67. Terawaki H, Yoshimura K, Hasegawa T, Matsuyama Y, Negawa T, Yamada K, et al. Oxidative stress is enhanced in correlation with renal dysfunction: examination with the redox state of albumin. Kidney Int. 2004;66:1988-93.
68. Forbes JM, Coughlan MT, Cooper ME. Oxidative stress as a major culprit in kidney disease in diabetes. Diabetes. 2008;57:1446-54.
69. Nguyen-Khoa T, Massy ZA, De Bandt JP, Kebede M, Salama L, Lambrey G, et al. Oxidative stress and haemodialysis: role of inflammation and duration of dialysis treatment. Nephrol Dial Transplant. 2001;16:335-40.
70. Greiber S, Muller B, Daemisch P, Pavenstadt H. Reactive oxygen species alter gene expression in podocytes: induction of granulocyte macrophage-colony-stimulating factor. J AM Soc Nephrol. 2002;13:86-95.
71. Christakos S, Ajibade DV, Dhawan P, Fechner AJ, Mady LJ. Vitamin D: metabolism. Rheum Dis Clin North Am. 2012;38:1-11.
72. Levin A, Bakris G, Molitch M, Smulders M, Tian J, Williams L, et al. Prevalence of abnormal serum vitamin D, PTH, calcium, and phosphorus in patients with chronic kidney disease: results of the study to evaluate early kidney disease. Kidney Int. 2007;71:31-8.
73. González EA, Sachdeva A, Oliver DA, Martin KJ. Vitamin D insufficiency and deficiency in chronic kidney disease. Am J Nephrol. 2004;24:503-10.
74. Kovesdy CP, Ahmadzadeh S, Anderson JE, Kalantar-Zadeh K. Association of activated vitamin D treatment and mortality in chronic kidney disease. Arch Intern Med. 2008;168:397-403.
75. Tentori F, Hunt W, Stidley C, Rohrscheib M, Bedrick E, Meyer K, et al. Mortality risk among hemodialysis patients receiving different vitamin D analogs. Kidney Int. 2006;70:1858-65.
76. Tan X, Li Y, Liu Y. Therapeutic role and potential mechanisms of active Vitamin D in renal interstitial fibrosis. J Steroid Biochem Mol Biol. 2007;103:491-6.
77. Makibayashi K, Tatematsu M, Hirata M, Fukushima N, Kusano K, Ohashi S, et al. A vitamin D analog ameliorates glomerular injury on rat glomerulonephritis. Am J Pathol. 2001;158:1733-41.
78. Finch JL, Suarez EB, Husain K, Ferder L, Cardema MC, Glenn DJ, et al. Effect of combining an ACE inhibitor and a VDR activator on glomerulosclerosis, proteinuria, and renal oxidative stress in uremic rats. Am J Physiol Renal Physiol. 2012;302:F141-9.
79. Izquierdo MJ, Cavia M, Muniz P, de Francisco AL, Arias M, Santos J, et al. Paricalcitol reduces oxidative stress and inflammation in hemodialysis patients. BMC Nephrol. 2012;13:159.
80. Sezgin G, Öztürk G, Güney Ş, Sinanoğlu O, Tunçdemir M. Protective effect of melatonin and 1, 25-dihydroxyvitamin D3 on renal ischemia–reperfusion injury in rats. Ren Fail. 2013;35:374-9.
81. Thethi TK, Bajwa MA, Ghanim H, Jo C, Weir M, Goldfine AB, et al. Effect of paricalcitol on endothelial function and inflammation in type 2 diabetes and chronic kidney disease. J Diabetes Complications. 2015;29:433-7.
82. Nakai K, Fujii H, Kono K, Goto S, Kitazawa R, Kitazawa S, et al. Vitamin D activates the Nrf2-Keap1 antioxidant pathway and ameliorates nephropathy in diabetic rats. Am J Hypertens. 2014;27:586-95.
83. Kobayashi M, Yamamoto M. Molecular mechanisms activating the Nrf2-Keap1 pathway of antioxidant gene regulation. Antioxid Redox Signal. 2005;7:385-94.