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Association between vitamin D and cardiovascular health: Myth or Fact? A narrative review of the evidence

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Abstract

Vitamin D deficiency is prevalent worldwide. Since the discovery of the expression of vitamin D receptor in ventricular cardiomyocytes, fibroblasts, and blood vessels, there has been a growing body of literature assessing the link between vitamin D status and cardiovascular health from one side, and the effect of vitamin D supplementation on prevention of cardiovascular diseases from the other side. In this review, we summarized studies highlighting the role of vitamin D on cardiovascular health, namely atherosclerosis, hypertension, heart failure, and metabolic syndrome, a recognized significant risk factor for cardiovascular diseases. Studies showed discrepancies between findings from cross-sectional and longitudinal cohorts and those from interventional trials, but also between one outcome and another. Cross-sectional studies found a strong association between low 25 hydroxyvitamin D (25(OH)D3) and acute coronary syndrome, and heart failure. These findings encouraged the promotion for vitamin D supplementation as a preventive measure for cardiovascular diseases in the elderly, namely in women. This fact, however, turned out into a myth with the results of large interventional trials that did not show any benefit from vitamin D supplementation in reducing ischemic events, heart failure or its outcomes, or hypertension. Although some clinical studies showed beneficial effect of vitamin D supplementation on insulin sensitivity and metabolic syndrome, this effect was not consistent across all studies.

Keywords

acute coronary syndrome, cardiovascular risk, diabetes, heart failure, hypertension, metabolic syndrome, ventricular hypertrophy, vitamin D

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Introduction

The 20th century was rich in scientific achievements that changed the world. Among these achievements was the discovery of vitamins. Vitamin D was the fourth vitamin to be discovered, hence its nomination "D." Since its discovery, this fat-soluble vitamin has evolved from being considered as a simple vitamin to a steroid prohormone. Because the first and pivotal potent role of vitamin D in human health was discovered by linking its deficiency to the development of rickets in children,[1] and because the vitamin D receptor (VDR) was originally discovered in the organs involved in $Ca+^{2}$ homeostasis, including the intestine, bone, kidney, and parathyroid glands,[2] it was thought for decades that the role of vitamin D is limited to musculoskeletal health. However, the discovery of VDR and the one alpha-hydroxylase in extraosseous tissues indicated possible physiological roles of vitamin D in other systems.[3] The action of 1,25 dihydroxy-vitamin D (1,25(OH)2D3) in these tissues has been associated with a

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diverse range of biological roles such as modulation of immune function, inhibition of cell growth, and induction of cell differentiation.[3] Over the last decade, vitamin D deficiency has emerged as a potential risk factor for cardiovascular diseases. There is strong evidence of the expression of VDR in ventricular cardiomyocytes and fibroblasts and in blood vessels.[4–6] Cardiomyocytes and cardiac fibroblasts also express 1α-hydroxylase at messenger RNA (mRNA) and protein levels.[7] Moreover, local production of 1,25(OH)2D3 from labeled 25 hydroxyvitamin D (25(OH) D3) substrate was observed in both endothelial and vascular smooth muscle cells *in vitro.* Animal studies provided a compelling evidence of the important role of vitamin D signaling in the cardiovascular system.[6] The first animal studies showing association between vitamin D and cardiovascular system date back to more than 15 years ago and showed that VDR knockout mouse displays hypertension, cardiac hypertrophy, and high expression in the atrial natriuretic peptide (ANP).[8] Subsequently, epidemiological studies in human showed evidence of association between 25(OH)D3 deficiency and cardiovascular diseases namely arterial stiffness, hypertension, left ventricular hypertrophy (LVH), and endothelial dysfunction in population with normal kidney function.[7] However, findings from interventional trials were not consistent.

In this article, we will review studies highlighting the role of vitamin D in cardiovascular health, namely atherosclerosis, hypertension, heart failure (HF), and metabolic syndrome (MS), a recognized significant risk factor for cardiovascular diseases.

Methodology

A thorough and comprehensive literature search was done on Medline and PubMed using the following keywords: vitamin D, cardiovascular risk, acute coronary syndrome (ACS), heart failure (HF), diabetes, Metabolic syndrome (MS), hypertension, and ventricular hypertrophy. The titles and abstracts of the papers were screened by the authors. Articles including cross-sectional and prospective cohort studies, randomized trials, review articles, case series, and meta-analysis published between 1975 and June 2022 were considered. Search was limited to articles using English language. In studies testing vitamin D supplementation, we only included studies whereby the dose was specified. Findings of the main studies are summarized in (Table 1) for observational studies and (Table 2) for interventional studies.

Vitamin D and Acute Coronary Syndrome

ACS is the leading cause of morbidity and mortality in the world, and according to a world health organization report in December 2020, ischemic heart disease is responsible for 16% of the world's total death. Epidemiological data showed an association between low 25(OH)D3 levels and myocardial infarction (MI), and this was demonstrated in both cross-sectional and large prospective cohorts. In a study of 982 patients including 394 women from Northern Argentina, Naesgaard et al.[9] showed that serum 25(OH)D3 is a 2-year predictor of all-cause mortality, cardiac death, and sudden cardiac death in ACS patients, especially in women. In addition, in their prospective observational study, they addressed the prognostic utility of 25(OH)D3 and other markers such as B-type natriuretic peptide (BNP) and high-sensitivity C-reactive protein (hsCRP) during a 5-year follow-up in patients from coastal Norway presenting with chest pain and suspected ACS. They found 25(OH)D3 to be independently related to the risk of death in females but not in males, with a significant increase in predictive value by a factor of two from the first to second quartile and from the second to third quartile.[10] The authors explained this gender difference by the lower levels of baseline 25(OH)D3 in women compared with men, specially that they did not find the same increase in risk from the third to the fourth quartile in women. This indicated that the protective effect of vitamin D depends on the 25(OH)D3 level and is only observed among those with lower baseline levels. Similarly, in the Framingham Offspring Study, another longitudinal observational cohort of 1739 study participants, without prior cardiovascular disease, and followed up for a mean of 5.4 years, low 25(OH)D3 was associated with increased rate of incident MI.[11] Suggested underlying mechanism linking low 25(OH)D3 to ACS included secondary hyperparathyroidism (HPTH). Indeed, HPTH has been associated with increased risk of cardiovascular diseases, and parathyroid hormone (PTH) level is a predictor of survival in the general aged population.[12] Other suggested mechanisms linking low vitamin D to ACS is inflammation. MI healing process involves inflammatory mechanisms triggered by local ischemia; however, it has been reported that an exuberant inflammatory reaction may paradoxically increase the extent of damage in MI. This acute repairing process is mediated by cytokines in the ischemic myocardium. In a small prospective randomized open-label single-center trial on 50 patients admitted with ACS, Arnson et al.[13] showed that vitamin D supplementation at a dose of 4000 IU daily for 5 days effectively attenuated the increase in circulating levels of inflammatory markers including interleukin (IL)-6, vascular cell adhesion protein 1 (VCAM-1) levels, and C-reactive protein (CRP). This suggested an anti-inflammatory effect of vitamin D on the vascular system mediating its possible cardio-protective properties after acute coronary event.[13] On the contrary, 1,25(OH)2D3 regulates cytokine expression by different mechanisms, either directly by targeting expression initiation or indirectly by interfering with other signaling cellular pathways. However, findings from intervention trials did not show beneficial effect of vitamin D supplementation on cardiovascular risk.[14–17] In the RECORD trial, 5292 participants

Table 1. Observational studies assessing the relationship between vitamin D and cardiovascular risk.

Author, publication year	Study design	Study population	Outcomes	Results
Naesgaard et al.[9]	Prospective observational	588 men and 394 women, aged >18 years with suspected acute coronary syndrome	2-year all-cause mortality and cardiac mortality	Significant association seen between low 25(OH)D and 2-year total mortality and cardiac mortality
Naesgaard et al.[10]	Prospective observational	531 men and 340 women, aged >18 years, with suspected acute coronary syndrome	All-cause mortality at 2- and 7-year follow-up and cardiac death and sudden cardiac death at 2-year follow-up	40% reduction in all-cause mortality in highest compared with lowest quartile of 25(OH)D at 2 years and 34% reduction at 7-year follow-up
Wang et al.[11]	Prospective observational	Framingham Offspring Study participants (1739, 55% women, all white), without prior CV disease	Incident cardiovascular events	Individuals with 25(OH)D <15 ng/mL had a HR of 1.62 for incident cardiovascular events
Kim et al.[27]	Cross-sectional	8351 adults including 753 women from the NHANES 2001 to 2004	Relationship between and coronary artery disease, heart failure, stroke, peripheral vascular disease	Stroke and peripheral arterial disease were increased among lower 25(OH)D categories
Shane et al.[26]	Cross-sectional	79 men and 22 women with severe CHF (New York Heart Association functional class III or IV)	Relationship between mineral homeostasis and severity of CHF	Patients with more severe CHF had significantly lower 25(OH)D and 1,25(OH)2D levels
Anderson et al.[28]	Prospective longitudinal	41,504 adults (31,086 women and 10,418 men)	Incident CV risk factors and diseases, and mortality	Low 25(OH)D levels were significantly and highly associated with incident coronary artery disease, myocardial infarction, heart failure, stroke, and death
Hyppönen et al.[44]	Cross-sectional	6810 white subjects (3297 men and 3513 women), aged >45 years	Metabolic syndrome, abdominal obesity; HbA1c, blood pressure, lipid profile	Serum 25(OH)D is inversely associated with metabolic syndrome
Alagacone et al.[47]	Cross-sectional	520 adults (337 men and 183 women) between age 20 and 60 attending tertiary care center	Relationship between vitamin D deficiency and hypertension	Severe vitamin D deficiency was significantly and highly prevalent in people with hypertension compared those without hypertension
Forman et al.[54]	Prospective observational	613 men from the Health Professionals' Follow-Up Study and 1198 women from the Nurses' Health Study	Incident hypertension	Plasma 25(OH)D levels were inversely associated with risk of incident hypertension
Song and Park[94]	Prospective observational	778 postmenopausal women, aged 45–75 years, without established cardiovascular disease	Risk factors for Metabolic syndrome	**V**itamin D deficiency was associated with higher prevalence of Metabolic syndrome and its components
Karatas et al.[96]	Observational	191 women and 96 men including 94 overweight/obese with metabolic syndrome, 120 overweight/obese without metabolic syndrome, and 73 nonobese healthy subjects	Metabolic syndrome	Vitamin D deficiency was more common in overweight/obese adults than in healthy controls.

HR: hazard ratio; CV: cardiovascular ; CHF: congestive heart failure.

(85% women) with mean ± SD age of 77.5 ± 5.6 years were randomly assigned to receive vitamin D or placebo and were followed up for 3 years. Although the risk of first cardiac failure was lower in the vitamin D group than in the placebo group (adjusted hazard ratio (HR): 0.75; 95% confidence interval (CI): 0.58–0.97), there was no difference in risk of MI (HR: 0.97; 95% CI: 0.75–1.26) between groups.[17] In their meta-analyses of randomized trials

Table 2. Interventional studies assessing the effect of vitamin D on cardiovascular risk.

Author, publication year	Study design	Study population	Intervention	Outcomes	Results
Arnson et al.[13]	Randomized, open-label	11 women and 39 men with acute MI Mean age of 59.7 ± 13.4 years in the active treatment group and 61.6 ± 12.7 years in the control group	Half of the patients were randomized to vitamin D3 4000 IU daily for 5 days	Circulating levels of VCAM-1 levels, C-reactive protein, interleukin-6, .interleukin-8 levels. intercellular adhesion molecule 1, E-selectin, vascular endothelial growth factor, and tumor necrosis factor-α.	Vitamin D effectively attenuated the increase in circulating levels of inflammatory cytokines after an acute coronary event compared with control.
Scragg et al.[17]	Randomized, double-blind, placebo-controlled	5110 community-resident adults (2141 women and 2969 men) aged 50–84 years	Oral vitamin D3 in an initial dose of 200,000 IU, followed by monthly doses of 100,000 IU, or placebo for a median of 3.3 years	Incident myocardial infarction, angina, heart failure, hypertension, arrhythmias, arteriosclerosis, stroke, venous thrombosis, and death	No significant difference noted in vitamin D group compared with placebo group
Manson et al.[19]	Randomized, placebo-controlled	13,194 women aged ⩾55 years and 12,677 men aged ⩾50 years	Vitamin D3 (cholecalciferol) at a dose of 2000 IU per day	Major cardiovascular events (a composite of myocardial infarction, stroke, or death from cardiovascular causes).	Vitamin D did not lower incidence of invasive cancer or cardiovascular events
Donneyong et al.[29]	Randomized double-blind, placebo-controlled	35,983 women aged 50–79 years participating in the Women's Health Initiative	1000 mg/day of calcium plus 400 IU/day of vitamin D3 or placebo	Rates of heart failure in postmenopausal women	Calcium and vitamin D supplementation did not reduce heart failure incidence
Witham et al.[30]	Randomized, parallel group, double-blind, placebo-controlled	69 men 32 women with systolic heart failure aged ⩾70 years with 25(OH)D levels <50 nmol/L	100,000 IU of oral vitamin D2 or placebo	6-min walk, quality of life (Minnesota score), daily activity, functional limitations profile, B-type natriuretic peptide, and tumor necrosis factor-αmeasured at baseline, 10 weeks, and 20 weeks	Vitamin D supplementation did not improve functional capacity or quality of life in older patients with heart failure with vitamin D insufficiency
Djoussé et al.[31]	Randomized 2 × 2 factorial design (ancillary study of the VITAL trial)	25,871 adults (13,090 women and 12,781 men) Mean age of 67.1 ± 7.1 years	Vitamin D3 (2000 IU/day) and omega-3 fatty acids (1 g/day, including eicosapentaenoic acid (460 mg) and docosahexaenoic acid (380 mg))	Incidence of heart failure hospitalization	Interventions with vitamin D or omega-3 fatty acid supplements did not significantly reduce the first heart failure hospitalization rate after a median follow-up of 5.3 years.
Sheikh et al.[52]	Randomized, double-blind	66 men and 105 women aged 26–84 years with essential hypertension	One vitamin D pearl 50,000 U weekly or vitamin D pearl 1000 U weekly or placebo for 2 months	Systolic and diastolic blood pressure	Vitamin D3 supplementation significantly reduce the diastolic blood pressure at 1 month and the systolic blood pressure at 1 and 2 months compared with placebo

(Continued)

Table 2. (Continued)

Author, publication year	Study design	Study population	Intervention	Outcomes	Results
Larsen et al.[55]	Randomized, placebo-controlled, double-blind	35 men and 77 women, mean age of 61 ± 10 years, with hypertension	3000 IU cholecalciferol per day or placebo	Blood pressure	Cholecalciferol did not reduce 24-h blood pressure, although central systolic blood pressure decreased significantly
Lemieux et al.[82]	Randomized, double-blind, placebo-controlled	96 participants (38.5% women), at high risk of diabetes or with newly diagnosed type 2 diabetes, aged ⩾25 years with a serum 25(OH)D ⩽55 nmol/L	Vitamin D3 5000 IU daily or placebo for 6 months	Insulin sensitivity using a 2-h hyperinsulinemic-euglycemic clamp, and HOMA index and insulin secretion after oral glucose tolerance test	Vitamin D3 supplementation did not change insulin sensitivity or insulin secretion.
Borissova et al.[83]	Open-label	27 women (10 with type 2 diabetes and 17 controls)	Cholecalciferol 1332 IU daily for 1 month	First and second phases of insulin secretion were studied during intravenous glucose tolerance test	IR improved by 21% after 1 month, but the change was not statistically significant
Gulseth et al.[84]	Randomized, placebo-controlled, double-blind	25 women and 37 men with type 2 diabetes and 25(OH)D <50 nmol/L)	Single dose of 400,000 IU oral vitamin D3 or placebo	Insulin sensitivity and insulin secretion	Vitamin D3 did not change insulin sensitivity or insulin secretion
Mousa et al.[86]	Randomized, double-blind, placebo-controlled	35 men and 19 women, overweight or obese, 25(OH)D ⩽50 nmol/L	Bolus oral dose of 100,000 IU cholecalciferol followed by 4000 IU/day or a matching placebo for 16 weeks	Insulin sensitivity and insulin secretion	Vitamin D did not improve insulin sensitivity or secretion
Fuleihan et al.[87]	Randomized, double-blind, controlled multicenter	123 women and 99 men), aged ⩾65 years, overweight, with 25(OH)D 10–30 ng/mL at baseline	Vitamin D3 20,000 IU/week or placebo, in addition, all participants received tablets containing 1000 mg calcium citrate and 600 IU vitamin D3 every day	HOMA-IR index at 1 year	Vitamin D3 at high dose did not improve HOMA-IR compared with low dose

MI: myocardial infarction; VCAM-1: vascular cell adhesion protein 1; VITAL: VITamin D and OmegA-3 TriaL; HOMA-IR: Homeostatic Model Assessment for Insulin Resistance.

including 13 studies in women, the investigators did not find an effect of vitamin D supplementation on incidence of MI events.[17] This conclusion was consistent with the findings of a more recent meta-analyses of 21 randomized clinical trials including 83,291 patients, of whom 74.4% were women, with a mean age of 65.8 ± 8.4 years.[18] The lack of benefit of vitamin D supplementation for MI prevention was further confirmed by the largest randomized controlled trial (RCT) assessing the effect of vitamin D supplementation on cardiovascular risk: the VITamin D and OmegA-3 TriaL (VITAL), a randomized, placebo-controlled 2 × 2 factorial trial of vitamin D3 (cholecalciferol, 2000 IU/day) and marine omega-3 fatty acids (1 g/day) for the prevention of cancer and cardiovascular disease in over 25,000 US men aged ⩾50 and women aged ⩾55 and that showed no beneficial effect of vitamin D on the incidence of MI after a median follow-up of 5.3 years. The treatment effect did not vary by baseline serum 25(OH)D3 levels.[19]

Vitamin D and Heart Failure

HF represents a growing social and economic burden and is the most common cause of hospitalization in elderly.[20] The increased incidence of HF in the elderly may be in part due to the aging-associated increased incidence of diabetes mellitus, hypertension, and coronary disease. Theories linking vitamin D deficiency to HF prognosis have been hypothesized. Vitamin D regulates gene expression of many genes that have a pivotal role in the progression of HF, such as cytokines genes. Indeed, vitamin D deficiency was associated with increased levels of pro-inflammatory cytokines such as IL-8 and tumor necrosis factor-α (TNF-α) and with reduced levels of anti-inflammatory cytokines, which in turn affects cardiac function and precipitates HF.[21] Furthermore, some studies showed that low vitamin D levels correlate with N-terminal pro-b-type and N-terminal pro-ANP levels, which in turn causes HF.[22] On the contrary, overloading of myocardial cells by Ca^{2+}ions due to low vitamin D levels causes impairment of contraction and relaxation of myocardial muscle, leading to inflammatory reaction and fibrosis of myocardial cells, and resulting in further dysfunction.[23] Rodman and Baker[24] showed that a depletion of endogenous vitamin D in rats resulted in profound alterations in cardiac and vascular muscle contractile function. In addition, Weishaar et al.[25] showed that these changes in cardiac and vascular muscle contractile function observed in vitamin D–deficient rats are not prevented by correction of induced hypocalcemia, and therefore, they represent a direct response to vitamin D depletion. Multiple cross-sectional studies showed an association between HF and 25(OH)D3 levels. In a small cross-sectional study of 101 subjects, 26% of subjects with HF had 25(OH)D3 levels below 15 ng/mL, with 17% of them having levels below 9 ng/mL.[26] Similarly, the large National Health and Nutrition Examination Survey (NHANES) including data from 8531 participants showed that hypovitaminosis D was present in almost 90% of patients with concomitant coronary heart disease and HF (odds ratio (OR): 3.52; 95% CI: 1.58–7.84).[27] Anderson et al.[28] prospectively analyzed a large electronic medical records database of 41,504 patient records, of which 63.6% had 25(OH)D3 levels below 30 ng/mL, and found that vitamin D deficiency was associated with significant increase in the prevalence of HF, as well as with incident HF (1.3 HR, $p < 0.0001$) for new HF development in patients with low and very low 25(OH)D3 levels). Studies assessing the role of vitamin D supplementation in reducing the incidence of HF are scarce. In the Women's Health Initiative, 35,983 postmenopausal women were randomized to receive 1000 mg/day of calcium plus 400 IU/day of vitamin D3 or placebo and were followed up for 7.1 years. Calcium and vitamin D supplementation did not reduce HF risk compared with placebo in the overall population (HR: 0.95; 95% CI: 0.82–1.09). However, subgroup analyses showed that calcium and vitamin D supplementation was associated with lower risk of HF (HR: 0.63; 95% CI: 0.4–0.8 in the low-risk subgroup).[29] In another study of 5108 adult subjects with mean baseline 25(OH)D3 concentration of 25.3 ng/mL, randomized to monthly vitamin D supplementation or placebo, and followed up for a median of 3.3 years, no significant difference was observed in the incidence of HF between the placebo and the calcium with vitamin D groups.[17] Few RCTs assessed the effect of vitamin D supplementation on the functional outcome of patients with HF. Witham et al showed vitamin D supplementation did not improve functional capacity or quality of life in older patients with systolic HF who had baseline 25(OH)D3 less than 20 ng/mL and who were randomized to receive 100,000 IU of oral vitamin D2 or placebo at baseline and at 10 weeks, and who were followed up for 20 weeks.[30] Similarly, the VITAL-HF, an ancillary study of the parent VITAL trial, including 25,000 subjects (59.6% women), with mean age of 67 ± 7 years, no significant difference in the rates of first and recurrent rates of HF hospitalization between vitamin D intervention and placebo after a median follow-up of 5.3 years was shown.[31] Rodriguez et al.[32] performed a systematic review and meta-analysis to determine whether vitamin D supplementation reduces inflammatory markers and improves health outcomes for patients with HF. Data were available for pooling from six studies (n = 1012). Vitamin D-supplemented groups had lower concentrations of TNF-α at follow-up compared with controls, but they found no differences in CRP, IL-10, or IL-6 between the vitamin D–supplemented group and the control group. However, the sample size in most studies included in this meta-analyses was small, did not report sunlight exposure, and did not take into consideration the seasonal variability, body composition, or smoking status, all of which can affect inflammatory status and/or 25(OH)D3 levels in humans. Moreover, only one study included vitamin D-deficient patients at baseline. The authors concluded that vitamin D supplementation may have specific,

but modest effects on inflammatory markers in HF but further large-scale, well-designed trials including vitamin D-deficient participants and measuring inflammatory markers and long-term clinical HF endpoints are needed.[4]

Vitamin D deficiency and Hypertension and Left ventricular Hypertrophy

VDR are expressed in the heart, vascular smooth muscle, and T cells.[4] It has been known for a long time that vitamin D deficiency is linked with renin–angiotensin–aldosterone system (RAAS),[33,34] where in vitro and animal studies found that vitamin D suppresses RAAS which is known to contribute to high blood pressure (BP).[35] This was also found in human study among 61 individuals conducted by Resnick et al.,[36] who found that plasma renin activity is inversely related to 1,25(OH)2D3 (r=–0.65) and the same was reported by Burgess et al.[37] and Tomaschitz et al.[38] Another study in individuals with balanced dietary sodium intake showed that those who were vitamin D insufficient (25(OH)D3 levels: 15.0–29.9 ng/mL) or deficient (25(OH)D3 levels <15.0 ng/mL) had significantly higher levels of angiotensin II levels when compared with those with adequate levels.[39] These animal and human data suggest that vitamin D has an inhibitory effects on RAAS system. However, vitamin D seems to play a role in increasing the influx of $Ca+^2$ into the vascular smooth muscles resulting in increased contractility, which in turn elevates BP, but at the same time increase influx of $Ca+^2$ in the juxtaglomerular cells, which in turn inhibits renin secretion. It is unclear whether vitamin D role on BP was prohypertensive or antihypertensive.[40] Some in vitro studies showed that 1,25(OH)2D3 decreases the negative effect of advanced glycation end products on the endothelium, increases nitric oxide, and hence has a beneficial antiatherosclerotic effect on endothelium.[41] Different cross-sectional studies tried to investigate the association between vitamin D and BP, majority of which showed that lower 25(OH)D3 levels were associated with higher BP and higher hypertension prevalence.[42–44] A meta-analyses investigated association between vitamin D level and hypertension, including 55,816 participants, and found that, in individuals who are not known to be hypertensive, incident hypertension was reduced by 12% for every 10 ng/mL increase of 25(OH)D3. The individuals with the highest 25(OH)D3 levels had a 30% lower risk of developing hypertension compared with individuals with the lowest levels.[45] In the large NHANES, including 15,088 participants, the OR for hypertension was 1.3 for those with 25(OH)D3 levels below 21 ng/mL compared with those with levels of 37 ng/mL or higher.[46] Another NHANES study of 2953 hypertensive subjects, 12% of which who had resistant hypertension, showed that the prevalence of vitamin D deficiency was significantly higher in resistant hypertension (61%) than controlled hypertension groups (46%).[47]

Data on the effect of vitamin D supplementation on BP in hypertensive individuals were inconsistent. A meta-analyses including 11 randomized controlled trials (RCTs) showed that vitamin D supplementation in hypertensive individuals may lower BP with a small, statistically significant decrease in diastolic blood pressure (DBP) (–3.1 mmHg; 95% CI: –5.5 to –0.6) but not in systolic blood pressure (SBP). In addition, vitamin D supplementation had no effect on BP in normotensive individuals.[48] Another meta-analysis including 28 studies, two-third of which were cross-sectional and one study was prospective, looked at the effect of vitamin D exposure on hypertension and found that pooled OR of hypertension was 0.73 (95% CI: 0.63–0.84).[49] However, a more recent systematic review of 46 trials including 4500 participants, vitamin D supplementation was found to be ineffective in lowering both SBP and DBP.[50] Similarly, a recent meta-analyses including 17 RCTs showed that vitamin D supplementation had no significant effect on BP in general but deceased SBP in those above 50 years of age and reduced both SBP and DBP in patients who have both vitamin D deficiency and hypertension.[51] A recent RCT included 208 participants with essential hypertension and vitamin D insufficiency or deficiency, who were randomized to vitamin D supplementation versus placebo and whose BP was monitored before and 1 and 2 months after supplementation. It demonstrated that vitamin D supplementation was significantly effective in reducing SBP 1 and 2 months after supplementation, and it was effective on DBP only 1 month after supplementation.[52] In a review of seven studies by Zittermann,[53] four found lower BP in healthy individuals treated with vitamin D3 supplementation and three found no effect.

The effect of vitamin D supplementation on the risk of developing hypertension was looked at in 250 African Americans who had normal BP at baseline, where participants were given either 1000 IU daily, 2000 IU e daily, 4000 IU daily, or placebo for 3 months. They found out that with higher doses of vitamin D supplementation, SBP was mildly reduced although DBP was unaffected.[54] A similar reduction in BP was noted in hypertensive individuals who received for 30 weeks 3000 IU daily of vitamin D.[54] In conclusion, lower vitamin D levels may be linked with high BP and higher risk of developing hypertension. However, different trials failed to show that vitamin D supplementation may lower BP, although additional larger randomized controlled trials are needed to better evaluate this.

Patients with end-stage renal disease frequently have abnormalities in left ventricular size and function, which usually start early in the course of chronic kidney disease and progress further as renal function deteriorates. BP and anemia contribute to this process in patients with renal failure, along with decreased 1,25(OH)2D3 leading to secondary HPTH, which in turn tends to promote hypertrophy through increased intracellular Ca^{+2} and through activation of protein kinase C which increases LVH independent of BP and may even lead to irreversible interstitial fibrosis with

collagen deposition.[55] Recent observational studies have shown that vitamin D supplementation could reduce cardiovascular death among patients on dialysis and leads to reduction in LVH.[56] Vitamin D supplementation may help in decreasing LVH through its effect on RAAS. In a small study done in patients on hemodialysis, intravenous administration of calcitriol led to significant decrease in renin and angiotensin-II levels, and a significant improvement in LVH.[57] Vitamin D deficiency may induce LVH through increasing c-myc protein involved in increasing extracellular matrix deposition.[20] In another study, it was found that low vitamin D was associated with high plasma metalloproteinase which leads to left ventricular dilation and hypertrophy and treatment with vitamin D helps to decrease plasma metalloproteinase.[58] Vitamin D also seems to have anti-inflammatory effects through reduction in inflammatory cytokines.[59] In one study, participants with chronic kidney disease who had 25(OH)D3 levels below 30 ng/mL were found to have 60% increase in the inflammatory marker, the hsCRP level, indicating subclinical inflammation, and this was reduced after 1 month of treatment with calcitriol.[60] On the contrary, other studies showed that excess vitamin D supplementation could lead to vascular calcification and increase mortality.[61] Also, excess vitamin D overdosing was found to stimulate vascular smooth muscle proliferation in another study.[62] Therefore, vitamin D supplementation may have a beneficial effect on LVH, through negatively regulating the RAAS, modulating inflammatory response to blood vessel injury, and decreasing cardiomyocyte hypertrophy and proliferation. However, vitamin D excess is often better to be avoided.

Vitamin D deficiency and Insulin Resistance

Insulin resistance (IR) is one of the main players in the pathophysiology of type 2 diabetes mellitus (T2D), and inflammation is one of the major contributors for IR,[63] where some inflammatory markers such as tumor necrosis factor, ILs, and others often lead to IR and affect islet beta cell function.[64] Since the discovery that vitamin D helps modulate inflammation and immune response and helps to reduce inflammation,[65] and VDRs are present on pancreatic beta cells, a link between vitamin D deficiency and insulin deficiency and resistance was proposed. Vitamin D deficiency was associated with decreased peripheral glucose uptake, IR, and decreased insulin secretion.[66] In addition, different studies showed that type 1 diabetes mellitus (T1D)[67] and T2D are linked with vitamin D deficiency.[68–70]

The contribution of vitamin D deficiency to IR is multifactorial. Preclinical studies conducted in rats showed that vitamin D is one of the regulators of insulin secretion and promotes pancreatic B cells survival, and its deficiency led to decreasing glucose-mediated insulin secretion in pancreatic β-cells.[69,71,72] In addition, studies in rats showed that vitamin D supplementation helped to improve glucose-mediated insulin secretion.[69,71,72] The effect of vitamin D on insulin secretion is induced directly by the presence of VDRs in pancreatic B cells as promoter of insulin gene.[73] In addition, vitamin D helps to increase cytoplasmic Ca^{+2} level in pancreatic B cells leading to insulin secretion.[74] Vitamin D does not only affect pancreatic B-cell function but also affects insulin sensitivity at the level of adipose tissue, liver, and skeletal muscle. Indeed, vitamin D deficiency was shown to be associated with down-expression of insulin receptor,[67] and vitamin D supplementation improves increased expression of this receptor.[75] 1,25(OH)2D3 might improve insulin sensitivity through the activation of Peroxisome proliferator-activated receptor delta (PPAR-δ) which is involved in the metabolism and mobilization of fatty acids in adipose tissue and skeletal muscle.[76] In addition, vitamin D in skeletal muscle increases Ca^{2+}concentration which leads to translocation of glucose transporter type 4 (GLUT4) to cell membrane and improves glucose uptake.[77] Vitamin D supplementation may improve insulin sensitivity via inhibition of RAAS.[78] Vitamin D deficiency, which often leads to secondary increase in PTH level, is also associated with IR through decreasing the number of glucose transporters (GLUT1 and GLUT4).[79] In addition, it was interesting to find that vitamin D deficiency leads to decline in mitochondrial respiration, resulting in increasing reactive oxygen species (ROS) production, which in turn leads to decreased insulin signaling pathways and decreased GLUT4 gene transcription, leading to IR as well.[80]

Whereas some clinical studies showed beneficial effect of vitamin D supplementation on improvement in insulin sensitivity,[81,82] other trials and a meta-analysis did not reveal any significant effect on glucose and insulin metabolism in obese[83–85] or overweight nondiabetic elderly subjects.[86]

Vitamin D deficiency and Metabolic Syndrome

Extensive research suggests that vitamin D deficiency is associated with MS, a metabolic disorder which includes abdominal obesity, hyperglycemia, hypertension, and dyslipidemia. Obesity is one of the most important modifiable risk factor for cardiovascular diseases. When looking at relationship between vitamin D levels and adiposity, a bidirectional association exists but the nature of relationship is not clear. Indeed, although it has been suggested that the possible lack of anti-inflammatory effects and a consequent chronic low-grade inflammation status could lead to an enhanced risk of obesity-related metabolic disorders in vitamin D deficiency, higher body mass index (BMI) has also been shown to cause deficient vitamin D status.[87] This effect was seen across different age groups and in both men and women.[87]

Several studies found an inverse association between 25(OH)D3 levels and MS.[84–88] In a systematic review of nine studies that looked at the association between vitamin D deficiency and MS in 6124 women with mean ± SD BMI of 26.9 ± 4.4 kg/m^2 (57.8% of them had vitamin D deficiency and 42.2% had normal 25(OH)D3 levels), the prevalence of MS was significantly higher among participants with vitamin D deficiency compared with those with adequate vitamin D status (34.5% vs 30.2%).[88] In addition, the prevalence of abdominal obesity, high BP, hypertriglyceridemia, and high-density lipoprotein (HDL) deficiency was higher in vitamin D-deficient women.[88–91] In another meta-analysis including 28 studies, a higher serum 25(OH)D3 levels were associated with a 51% lower risk of MS, 55% reduction in diabetes, and 33% lower risk of cardiovascular disease.[92] In a recent systematic review and meta-analyses of a total of 23 observational studies (19 cross-sectional studies and four cohort studies), Lee and Kim[93] showed that 25 nmol/L (10 ng/mL) increment in the serum 25(OH)D3 concentration was associated with 20% and 15% lower risks of MS in cross-sectional studies and cohort studies, respectively. In a study conducted in 778 Korean postmenopausal women, OR for MS was 2.4 in the lowest quartile (4.2–9.7 ng/mL), and OR was 2.2 in the lower level group (9.8–14.1 ng/mL) and 1.8 in the intermediate level group (14.3–19.8 ng/mL). In addition, the adjusted ORs for high BP and for high triglycerides in the lowest level group were 1.8 (95% CI: 1.1–2.8) and 2.7 (95% CI: 1.6–4.5), respectively.[94] A prospective study looked at incident cases of MS in 4164 adults of whom 528 (12.7%) patients developed MS; they showed that the risk of developing MS was higher in patients in the first quintile (25(OH)D3 <18 ng/mL) and second quintile (25(OH)D3: 18–23 ng/mL).[95] However, in a study by Karatas et al, an inverse association was observed between serum 25(OH)D3 concentration and triglyceride levels but no significant relationship existed with HDL-C, hypertension, and IR.[96]

Limitations

This review has some limitations. It is not a systematic review; however, a thorough literature search was performed to include the most relevant observational studies and large interventional trials. Because of the very large number of studies assessing the relationship of vitamin D status and cardiovascular risk, we did not cite all small observational studies that showed similar results. We also did not include nonpublished abstracts, and we did not search for non-English literature publications.

Conclusion

In vivo and in vitro studies showed evidence for possible biological role of vitamin D deficiency in the development of cardiovascular diseases, and findings from cross-sectional studies were in line with these conclusions. These exciting findings encouraged the promotion for vitamin D supplementation as a preventive measure for cardiovascular diseases, namely in women. This fact turned out to be a myth with the results of large interventional randomized trials that did not confirm the role of vitamin D supplementation in reducing ischemic events, HF or its outcomes, or hypertension. The beneficial effect of vitamin D supplementation on insulin sensitivity and MS was not consistent across all studies. In conclusion, current evidence is insufficient to recommend vitamin D supplementation for prevention of cardiovascular diseases or related risk factors.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contribution(s)

Hala Ahmadieh: Conceptualization; Methodology; Writing—original draft; Writing—review & editing.
Asma Arabi: Methodology; Supervision; Writing—original draft; Writing—review & editing.

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References

1. O'Riordan JLH and Bijvoet OLM. Rickets before the discovery of vitamin D. *Bonekey Rep* 2014; 3: 478.
2. Haussler MR, Jurutka PW, Hsieh JC, et al. New understanding of the molecular mechanism of receptor-mediated genomic actions of the vitamin D hormone. *Bone* 1995; 17(Suppl. 2): 33S–38S.

3. Wesley J, Pike JW, Meyer MB, et al. The vitamin D receptor: contemporary genomic approaches reveal new basic and translational insights. *J Clin Invest* 2017; 127(4): 1146–1154.
4. Chen S, Glenn DJ, Ni W, et al. Expression of the vitamin D receptor is increased in the hypertrophic heart. *Hypertension* 2008; 52(6): 1106–1112.
5. Nibbelink KA, Tishkoff DX, Hershey SD, et al. 1,25(OH)2-vitamin D3 actions on cell proliferation, size, gene expression, and receptor localization, in the HL-1 cardiac myocyte. *J Steroid Biochem Mol Biol* 2007; 103(3–5): 533–537.
6. Gardner DG, Chen S and Glenn DJ. Vitamin D and the heart. *Am J Physiol Regul Integr Comp Physiol* 2013; 305(9): R969–R977.
7. Latic N and Erben RG. Vitamin D and cardiovascular disease, with emphasis on hypertension, atherosclerosis, and heart failure. *Int J Mol Sci* 2020; 21(18): 6483.
8. Xiang W, Kong J, Chen S, et al. Cardiac hypertrophy in vitamin D receptor knockout mice: role of the systemic and cardiac renin-angiotensin systems. *Am J Physiol Endocrinol Metab* 2005; 288(1): E125–E132.
9. Naesgaard PA, León De La Fuente RA, Nilsen ST, et al. Serum 25(OH)D is a 2-year predictor of all-cause mortality, cardiac death and sudden cardiac death in chest pain patients from Northern Argentina. *PLoS ONE* 2012; 7(9): e43228.
10. Naesgaard PA, Pönitz V, Aarsetoey H, et al. Prognostic utility of vitamin D in acute coronary syndrome patients in coastal Norway. *Dis Markers* 2015; 2015: 283178.
11. Wang TJ, Pencina MJ, Booth SL, et al. Vitamin D deficiency and risk of cardiovascular disease. *Circulation* 2008; 117(4): 503–511.
12. Björkman MP, Sorva AJ and Tilvis RS. Elevated serum parathyroid hormone predicts impaired survival prognosis in a general aged population. *Eur J Endocrinol* 2008; 158(5): 749–753.
13. Arnson Y, Itzhaky D, Mosseri M, et al. Vitamin D inflammatory cytokines and coronary events: a comprehensive review. *Clin Rev Allergy Immunol* 2013; 45(2): 236–247.
14. Trivedi DP, Doll R and Khaw KT. Effect of four monthly oral vitamin D3 (cholecalciferol) supplementation on fractures and mortality in men and women living in the community: randomised double blind controlled trial. *BMJ* 2003; 326(7387): 469.
15. Hsia J, Heiss G, Ren H, et al. Calcium/vitamin D supplementation and cardiovascular events. *Circulation* 2007; 115(7): 846–854.
16. Ford JA, MacLennan GS, Avenell A, et al. Cardiovascular disease and vitamin D supplementation: trial analysis, systematic review, and meta-analysis. *Am J Clin Nutr* 2014; 100(3): 746–755.
17. Scragg R, Stewart AW, Waayer D, et al. Effect of monthly high-dose vitamin D supplementation on cardiovascular disease in the vitamin D assessment study: a randomized clinical trial. *JAMA Cardiol* 2017; 2(6): 608–616.
18. Barbarawi M, Kheiri B, Zayed Y, et al. Vitamin D supplementation and cardiovascular disease risks in more than 83 000 individuals in 21 randomized clinical trials: a meta-analysis. *JAMA Cardiol* 2019; 4(8): 765–776.
19. Manson JE, Cook NR, Lee IM, et al. Vitamin D supplements and prevention of cancer and cardiovascular disease. *New Engl J Med* 2019; 380(1): 33–44.
20. Savarese G and Lund LH. Global public health burden of heart failure. *Card Fail Rev* 2017; 3(1): 7–11.
21. Meems LM, van der Harst P, van Gilst WH, et al. Vitamin D biology in heart failure: molecular mechanisms and systematic review. *Curr Drug Targets* 2011; 12(1): 29–41.
22. Hacioglu Y, Karabag T, Piskinpasa ME, et al. Impaired cardiac functions and aortic elastic properties in patients with severe vitamin D deficiency. *J Cardiovasc Echogr* 2018; 28(3): 171–176.
23. Zittermann A, Schleithoff SS and Koerfer R. Vitamin D insufficiency in congestive heart failure: why and what to do about it? *Heart Fail Rev* 2006; 11(1): 25–33.
24. Rodman JS and Baker T. Changes in the kinetics of muscle contraction in vitamin D-depleted rats. *Kidney Int* 1978; 13(3): 189–193.
25. Weishaar RE, Kim SN, Saunders DE, et al. Involvement of vitamin D3 with cardiovascular function. III. Effects on physical and morphological properties. *Am J Physiol* 1990; 258(Pt. 1): E134–E142.
26. Shane E, Mancini D, Aaronson K, et al. Bone mass, vitamin D deficiency, and hyperparathyroidism in congestive heart failure. *Am J Med* 1997; 103(3): 197–207.
27. Kim DH, Sabour S, Sagar UN, et al. Prevalence of hypovitaminosis D in cardiovascular diseases (from the National Health and Nutrition Examination Survey 2001 to 2004). *Am J Cardiol* 2008; 102(11): 1540–1544.
28. Anderson JL, May HT, Horne BD, et al. Relation of vitamin D deficiency to cardiovascular risk factors, disease status, and incident events in a general healthcare population. *Am J Cardiol* 2010; 106(7): 963–968.
29. Donneyong MM, Hornung CA, Taylor KC, et al. Risk of heart failure among postmenopausal women: a secondary analysis of the randomized trial of vitamin D plus calcium of the women's health initiative. *Circ Heart Fail* 2015; 8(1): 49–56.
30. Witham MD, Crighton LJ, Gillespie ND, et al. The effects of vitamin D supplementation on physical function and quality of life in older patients with heart failure: a randomized controlled trial. *Circ Heart Fail* 2010; 3(2): 195–201.
31. Djoussé L, Cook NR, Kim E, et al. Supplementation with vitamin D and omega-3 fatty acids and incidence of heart failure hospitalization: VITAL-heart failure. *Circulation* 2020; 141(9): 784–786.
32. Rodriguez AJ, Mousa A, Ebeling PR, et al. Effects of vitamin D supplementation on inflammatory markers in heart failure: a systematic review and meta-analysis of randomized controlled trials. *Sci Rep* 2018; 8(1): 1169.
33. Kota SK, Kota SK, Jammula S, et al. Renin-angiotensin system activity in vitamin D deficient, obese individuals with hypertension: an urban Indian study. *Indian J Endocrinol Metab* 2011; 15(Suppl. 4): S395–S401.
34. Ajabshir S, Asif A and Nayer A. The effects of vitamin D on the renin-angiotensin system. *J Nephropathol* 2014; 3(2): 41–43.
35. Li YC, Qiao G, Uskokovic M, et al. Vitamin D: a negative endocrine regulator of the renin-angiotensin system and blood pressure. *J Steroid Biochem Mol Biol* 2004; 89–90(1–5): 387–392.
36. Resnick LM, Müller FB and Laragh JH. Calcium-regulating hormones in essential hypertension. Relation to plasma renin activity and sodium metabolism. *Ann Intern Med* 1986; 105(5): 649–654.

37. Burgess ED, Hawkins RG and Watanabe M. Interaction of 1,25-dihydroxyvitamin D and plasma renin activity in high renin essential hypertension. *Am J Hypertens* 1990; 3(12 Pt. 1): 903–905.
38. Tomaschitz A, Pilz S, Ritz E, et al. Independent association between 1,25-dihydroxyvitamin D, 25-hydroxyvitamin D and the renin-angiotensin system: the Ludwigshafen Risk and Cardiovascular Health (LURIC) study. *Clin Chim Acta* 2010; 411: 1354–1360.
39. Forman JP, Williams JS and Fisher ND. Plasma 25-hydroxyvitamin D and regulation of the renin-angiotensin system in humans. *Hypertension* 2010; 55(5): 1283–1288.
40. Beierwaltes WH. The role of calcium in the regulation of renin secretion. *Am J Physiol Renal Physiol* 2010; 298(1): F1–F11.
41. Talmor Y, Golan E, Benchetrit S, et al. Calcitriol blunts the deleterious impact of advanced glycation end products on endothelial cells. *Am J Physiol Renal Physiol* 2008; 294(5): F1059–F1064.
42. Scragg R, Sowers M and Bell C. Serum 25-hydroxyvitamin D, ethnicity, and blood pressure in the Third National Health and Nutrition Examination Survey. *Am J Hypertens* 2007; 20(7): 713–719.
43. Hintzpeter B, Mensink GB, Thierfelder W, et al. Vitamin D status and health correlates among German adults. *Eur J Clin Nutr* 2008; 62(9): 1079–1089.
44. Hyppönen E, Boucher BJ, Berry DJ, et al. 25-hydroxyvitamin D, IGF-1, and metabolic syndrome at 45 years of age: a cross-sectional study in the 1958 British Birth Cohort. *Diabetes* 2008; 57(2): 298–305.
45. Kunutsor SK, Apekey TA and Steur M. Vitamin D and risk of future hypertension: meta-analysis of 283,537 participants. *Eur J Epidemiol* 2013; 28(3): 205–221.
46. Martins D, Wolf M, Pan D, 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(11): 1159–1165.
47. Alagacone S, Verga E, Verdolini R, et al. The association between vitamin D deficiency and the risk of resistant hypertension. *Clin Exp Hypertens* 2020; 42(2): 177–180.
48. Witham MD, Nadir MA and Struthers AD. Effect of vitamin D on blood pressure: a systematic review and meta-analysis. *J Hypertens* 2009; 27(10): 1948–1954.
49. Burgaz A, Orsini N, Larsson SC, et al. Blood 25-hydroxyvitamin D concentration and hypertension: a meta-analysis. *J Hypertens* 2011; 29(4): 636–645.
50. Beveridge LA, Struthers AD, Khan F, et al. Effect of vitamin D supplementation on blood pressure: a systematic review and meta-analysis incorporating individual patient data. *JAMA Intern Med* 2015; 175(5): 745–754.
51. He S and Hao X. The effect of vitamin D3 on blood pressure in people with vitamin D deficiency: a system review and meta-analysis. *Medicine* 2019; 98(19): e15284.
52. Sheikh V, Mozaianimonfared A, Gharakhani M, et al. Effect of vitamin D supplementation versus placebo on essential hypertension in patients with vitamin D deficiency: a double-blind randomized clinical trial. *J Clin Hypertens* 2020; 22(10): 1867–1873.
53. Zittermann A. Vitamin D in preventive medicine: are we ignoring the evidence? *Br J Nutr* 2003; 89(5): 552–572.
54. Forman JP, Giovannucci E, Holmes MD, et al. Plasma 25-hydroxyvitamin D levels and risk of incident hypertension. *Hypertension* 2007; 49(5): 1063–1069.
55. Larsen T, Mose FH, Bech JN, et al. Effect of cholecalciferol supplementation during winter months in patients with hypertension: a randomized, placebo-controlled trial. *Am J Hypertens* 2012; 25(11): 1215–1222.
56. Schlüter KD, Weber M and Piper HM. Parathyroid hormone induces protein kinase C but not adenylate cyclase in adult cardiomyocytes and regulates cyclic AMP levels via protein kinase C-dependent phosphodiesterase activity. *Biochem J* 1995; 310(Pt. 2): 439–444.
57. Shoji T, Shinohara K, Kimoto E, et al. Lower risk for cardiovascular mortality in oral 1alpha-hydroxy vitamin D3 users in a haemodialysis population. *Nephrol Dial Transplant* 2004; 19(1): 179–184.
58. Park CW, Oh YS, Shin YS, et al. Intravenous calcitriol regresses myocardial hypertrophy in hemodialysis patients with secondary hyperparathyroidism. *Am J Kidney Dis* 1999; 33(1): 73–81.
59. Rahman A, Hershey S, Ahmed S, et al. Heart extracellular matrix gene expression profile in the vitamin D receptor knockout mice. *J Steroid Biochem Mol Biol* 2007; 103(3–5): 416–419.
60. Helming L, Böse J, Ehrchen J, et al. 1alpha,25-Dihydroxyvitamin D3 is a potent suppressor of interferon gamma-mediated macrophage activation. *Blood* 2005; 106(13): 4351–4358.
61. Alborzi P, Patel NA, Peterson C, et al. Paricalcitol reduces albuminuria and inflammation in chronic kidney disease: a randomized double-blind pilot trial. *Hypertension* 2008; 52(2): 249–255.
62. Goldsmith DJ, Covic A, Sambrook PA, et al. Vascular calcification in long-term haemodialysis patients in a single unit: a retrospective analysis. *Nephron* 1997; 77(1): 37–43.
63. Wu J, Garami M, Cheng T, et al. 1,25(OH)2 vitamin D3, and retinoic acid antagonize endothelin-stimulated hypertrophy of neonatal rat cardiac myocytes. *J Clin Invest* 1996; 97(7): 1577–1588.
64. Kern PA, Di Gregorio GB, Lu T, et al. Adiponectin expression from human adipose tissue: relation to obesity, insulin resistance, and tumor necrosis factor-alpha expression. *Diabetes* 2003; 52(7): 1779–1785.
65. Odegaard JI and Chawla A. Pleiotropic actions of insulin resistance and inflammation in metabolic homeostasis. *Science* 2013; 339(6116): 172–177.
66. Kunadian V, Ford GA, Bawamia B, et al. Vitamin D deficiency and coronary artery disease: a review of the evidence. *Am Heart J* 2014; 167(3): 283–291.
67. Berridge MJ. Vitamin D deficiency and diabetes. *Biochem J* 2017; 474: 1321–1332.
68. Mathieu C and Badenhoop K. Vitamin D and type 1 diabetes mellitus: state of the art. *Trends Endocrinol Metab* 2005; 16(6): 261–266.
69. Khudayar M, Nadeem A, Lodi MN, et al. The association between deficiency of vitamin D and diabetes mellitus type 2 (DMT2). *Cureus* 2022; 14(2): e22221.
70. Jumaa AM, Khalaf MA and Hassan HY. Determination of vitamin D concentration in diabetic and non diabetic men and its correlation with age. *Indian J Forensic Med Toxicol* 2021; 15: 1853–1858.

71. Norman AW, Frankel JB, Heldt AM, et al. Vitamin D deficiency inhibits pancreatic secretion of insulin. *Science* 1980; 209(4458): 823–825.
72. Cade C and Norman AW. Vitamin D3 improves impaired glucose tolerance and insulin secretion in the vitamin D-deficient rat in vivo. *Endocrinology* 1986; 119(1): 84–90.
73. Tanaka Y, Seino Y, Ishida M, et al. Effect of vitamin D3 on the pancreatic secretion of insulin and somatostatin. *Acta Endocrinol* 1984; 105(4): 528–533.
74. Johnson JA, Grande JP, Roche PC, et al. Immunohistochemical localization of the 1,25(OH)2D3 receptor and calbindin D28k in human and rat pancreas. *Am J Physiol* 1994; 267(3 Pt. 1): E356–E360.
75. Draznin B, Lewis D, Houlder N, et al. Mechanism of insulin resistance induced by sustained levels of cytosolic free calcium in rat adipocytes. *Endocrinology* 1989; 125(5): 2341–2349.
76. Maestro B, Campión J, Dávila N, et al. Stimulation by 1,25-dihydroxyvitamin D3 of insulin receptor expression and insulin responsiveness for glucose transport in U-937 human promonocytic cells. *Endocr J* 2000; 47(4): 383–391.
77. Dunlop TW, Väisänen S, Frank C, et al. The human peroxisome proliferator-activated receptor delta gene is a primary target of 1alpha,25-dihydroxyvitamin D3 and its nuclear receptor. *J Mol Biol* 2005; 349(2): 248–260.
78. Wright DC, Hucker KA, Holloszy JO, et al. Ca2+ and AMPK both mediate stimulation of glucose transport by muscle contractions. *Diabetes* 2004; 53(2): 330–335.
79. Yuan W, Pan W, Kong J, et al. 1,25-dihydroxyvitamin D3 suppresses renin gene transcription by blocking the activity of the cyclic AMP response element in the renin gene promoter. *J Biol Chem* 2007; 282(41): 29821–29830.
80. Ni Z, Smogorzewski M and Massry SG. Effects of parathyroid hormone on cytosolic calcium of rat adipocytes. *Endocrinology* 1994; 135(5): 1837–1844.
81. Rains JL and Jain SK. Oxidative stress, insulin signaling, and diabetes. *Free Rad Biol Med* 2011; 50(5): 567–575.
82. Lemieux P, Weisnagel SJ, Caron AZ, et al. Effects of 6-month vitamin D supplementation on insulin sensitivity and secretion: a randomised, placebo-controlled trial. *Eur J Endocrinol* 2019; 181(3): 287–299.
83. Borissova AM, Tankova T, Kirilov G, et al. The effect of vitamin D3 on insulin secretion and peripheral insulin sensitivity in type 2 diabetic patients. *Int J Clin Pract* 2003; 57(4): 258–261.
84. Gulseth HL, Wium C, Angel K, et al. Effects of vitamin D supplementation on insulin sensitivity and insulin secretion in subjects with type 2 diabetes and vitamin D deficiency: a randomized controlled trial. *Diabetes Care* 2017; 40(7): 872–878.
85. Jamka M, Woźniewicz M, Jeszka J, et al. The effect of vitamin D supplementation on insulin and glucose metabolism in overweight and obese individuals: systematic review with meta-analysis. *Sci Rep* 2015; 5: 16142.
86. Mousa A, Naderpoor N, de Courten MP, et al. Vitamin D supplementation has no effect on insulin sensitivity or secretion in vitamin D-deficient, overweight or obese adults: a randomized placebo-controlled trial. *Am J Clin Nutr* 2017; 105(6): 1372–1381.
87. Fuleihan GEH, Baddoura R, Habib RH, et al. Effect of vitamin D replacement on indexes of insulin resistance in overweight elderly individuals: a randomized controlled trial. *Am J Clin Nutr* 2016; 104(2): 315–323.
88. Vimaleswaran KS, Berry DJ, Lu C, et al. Causal relationship between obesity and vitamin D status: bi-directional Mendelian randomization analysis of multiple cohorts. *PLoS Med* 2013; 10(2): e1001383.
89. Maroufi NF, Pezeshgi P, Mortezania Z, et al. Association between vitamin D deficiency and prevalence of metabolic syndrome in female population: a systematic review. *Horm Mol Biol Clin Investig* 2020; 41(4): 33.
90. Baynes KC, Boucher BJ, Feskens EJ, et al. Vitamin D, glucose tolerance and insulinaemia in elderly men. *Diabetologia* 1997; 40(3): 344–347.
91. Ford ES, Ajani UA, McGuire LC, et al. Concentrations of serum vitamin D and the metabolic syndrome among U.S. adults. *Diabetes Care* 2005; 28(5): 1228–1230.
92. Parker J, Hashmi O, Dutton D, et al. Levels of vitamin D and cardiometabolic disorders: systematic review and meta-analysis. *Maturitas* 2010; 65(3): 225–236.
93. Lee K and Kim J. Serum vitamin D status and metabolic syndrome: a systematic review and dose-response meta-analysis. *Nutr Res Pract* 2021; 15(3): 329–345.
94. Song HR and Park CH. Low serum vitamin D level is associated with high risk of metabolic syndrome in post-menopausal women. *J Endocrinol Invest* 2013; 36(10): 791–796.
95. Gagnon C, Lu ZX, Magliano DJ, et al. Low serum 25-hydroxyvitamin D is associated with increased risk of the development of the metabolic syndrome at five years: results from a national, population-based prospective study (The Australian Diabetes, Obesity and Lifestyle Study: AusDiab). *J Clin Endocrinol Metab* 2012; 97(6): 1953–1961.
96. Karatas S, Hekimsoy Z and Dinc G. Vitamin D levels in overweight/obese adults with and without metabolic syndrome. *J Endocrinol Metab* 2013; 3: 47–56.