The Role of Vitamin D in Diabetes and Cardiovascular Disease: An Updated Review of the Literature

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Received 21 June 2015; Revised 22 September 2015; Accepted 29 September 2015

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The dietary reference values for Vitamin D were set primarily considering its role in bone health, but with the discovery of Vitamin D receptors throughout body tissues, new links with other health conditions are now studied, such as for diabetes and cardiovascular diseases (CVD). This paper shall analyze and examine all new research studies carried out, especially in 2013–2015 regarding diabetes mellitus (DM) and cardiovascular diseases (CVD). Vast research has been carried out to establish strong relationship between Vitamin D serum levels, supplementation, diabetes, and CVD. However, the results from researches identified in this paper are disputable. Benefits of Vitamin D adequate levels were recognized from gestational period until later in disease developments such as diabetes and/or CVD, but since not all studies are in agreement further investigation is suggested. Researches conducting large randomized controlled trials, exploring range of supplement doses, with variable baseline serum Vitamin D levels, and inclusion of array of associated parameters, are still required to conduct large-scale analysis and draw conclusion as a risk factor. Until then it is possible to conclude that maintenance of serum Vitamin D levels holds advantageous aspects in diabetic and cardiovascular conditions, and people should strive to attain them.

1. Introduction

Vitamin D, also called calciferol, exists in two major forms: Vitamin D2 (ergocalciferol, which is largely ingested) and Vitamin D3 (cholecalciferol, which is synthesized in human body). Both forms are inactive form, which are converted into active form, exhibiting identical responses, by two enzymatic hydroxylation reactions, first in liver forming 25-hydroxyvitamin D mediated by 25-hydroxylase and second in kidney mediated by 1 α-hydroxylase forming the final activated product calcitriol (1,25 dihydroxyvitamin D). Sunshine Vitamin formerly attributed with bone health is now under rigorous investigation due to expression of Vitamin D receptors (VDR) found commonly in body tissues regulating gene transcription of many inflammatory factors and immune cells expression that could potentially contribute to chronic disease prognosis, recovery, or mortality [1].

Vitamin D RDA values were set for young and adult population to acquire certain serum levels of Vitamin D, which were supported by data on osteomalacia, and for older population the recommendations also considered the fracture risk. Based on Endocrine Society's recommendation, Vitamin D deficiency should be defined as 25(OH)D of < 20 ng/mL while Vitamin D insufficiency is now recognized as 25(OH)D of 21–29 ng/mL [2]. The recommended dietary intake (RDI) for patients with risk for Vitamin D is 400 IU/d for 0–12 months, 600 IU/d for ages 1–70 years, as well as for pregnant and lactating women, and 800 IU/d for ages 71 years and older, with measurement of 25(OH)D serum level as best indicator for Vitamin D cutaneous synthesis and total intake [1]. However, with concerns about sun exposure, committee assumed conditions of minimal exposure to sunlight to describe relationship between intake and serum 25(OH)D levels; therefore, it requires adjustment of values to populations exposure to sun. The potential contribution from body stores in their report is still uncertain [1].

Cutaneous synthesis of Vitamin D is subject to a number of limitations, as excess exposure can lead to photodegradation to avoid toxicity, or other factors, such as latitude, time of exposure, skin pigmentation, obesity, and season, can all
affect the synthesis [1]. To explain the effect of latitude on T1DM, study linking them has been carried out too recently [3]. Reasons that can attenuate endogenous production of Vitamin D through skin are generally lifestyle factors, such as air pollution, confined outdoor time, completely covering body during limited exposure time, and use of sunscreen [4]. In Korean adults, these factors further included older age, male sex, eating breakfast regularly, consumption of dairy and fatty fish, and use of Vitamin D-containing supplements in a positive correlation, whereas frequent consumption of instant noodles and sugar-sweetened beverages was linked negatively [5]. Among nonmodifiable factors are skin conditions as ichthyosis [3], and variants near genes involved in cholesterol synthesis (DHCR7), hydroxylation (CYP2R1, CYP24A1), and Vitamin D transport (GC) [6].

The central function of Vitamin D is elevation of plasma calcium and phosphate levels for bone health. However, Vitamin D receptors (VDR) are also found in nucleus of many tissues, which regulate several hundred genes throughout the body or as much as 5% of human genome [1]. Biological role of Vitamin D is plausible, as evidence from recent research in the following text shall point out relationship between insulin action and Vitamin D serum levels. The fostering mechanism could be either direct, that is, when VDR expression affects local production of 1,25(OH)2D3 in pancreatic β cells, or indirect via regulation of calcium homeostasis and calcium flux through membranes [7]. Positive effects of Vitamin D supplementation are also registered in some cases, which has further invigorated the need to investigate not only serum Vitamin D adequacy, but also the efficacy of supplements in acquiring such levels [8]. The other major investigation regarding role of Vitamin D is in development of cardiovascular diseases. Vitamin D deficiency has been found to contribute to various cardiac conditions, such as hypertension, coronary artery disease, stroke, and atherosclerosis [9–11]. Some studies consider evidence as enough to establish low Vitamin D level as CVD risk factor [12, 13], but further trials are still needed. Thus, this paper shall also identify the latest research and analysis carried out linked to serum Vitamin D levels or supplementation in cardiovascular diseases.

2. Vitamin D and Diabetes

Abundance of Vitamin D receptors in body tissue other than just in bone deviated attention from bone disease to chronic conditions. Clinical trials were performed extensively at different levels of diabetes mellitus stages to observe the role of Vitamin D status and to study efficacy of Vitamin D supplementation. Maintaining Vitamin D at adequate levels can be a useful preventive technique, since Vitamin D status in healthy adults was inversely associated with future risk of type 2 diabetes [14]. Significant negative correlation between 25(OH)D and HbA1c was also observed when compared between diabetic and nondiabetic patients [15]. Vitamin D dose in initial years of life is shown to reduce risk of future development of disease modulated by immune protective effects [16].

A meta-study by Forouhi et al. [17] found a strong inverse association between baseline 25(OH)D and incidence of type 2 diabetes. Vitamin D supplementation also improves HbA1c value for pediatrics with type 1 diabetes when treated with 300,000 IU single dose intramuscular injection of Vitamin D along with 40 mg/Kg/day of calcium divided into 2 doses [8]. A significant inverse relationship between Vitamin D status and insulin resistance (IR) was also observed, independent of adiposity, in Korean adolescents [18]. A recent meta-analysis that included 23 studies found that serum 25(OH)D was significantly lower in patients with type 1 DM than in healthy controls [19, 20]. On the other hand, not all studies support the result [21], along with limitation of another review study, it was concluded from the assessment of 17 randomized control trials and 7 longitudinal studies that Vitamin D supplementation did not improve hyperglycemia, beta cell secretion, or insulin sensitivity [22].

2.1. Supplementation Studies on Vitamin D. The review study that included 17 randomized control trials mentioned above had many limitations as most studies used daily doses less than 2000 IU to above 5000 IU of Vitamin D2 or D3. The most important limitations were the small sample groups and heterogeneity in ethnicity and baseline levels [22]. This surely highlights the need of large randomized control trials with long-term follow-up tests. Race and gender differences were also observed as far as serum Vitamin D levels and its effect in diabetes are concerned. Low 25(OH)D concentrations were found to be associated with diabetes among White but not Black people for which variation in SNP (Single Nucleotide Polymorphism) in genotype linked with either high or low Vitamin D binding protein was held accountable [23]. In newly diagnosed type 2 diabetes female patients serum 25(OH)D is associated with insulin sensitivity and β-cell function, but this association was ambiguous in males [24].

Significant influence was not observed on weight, fat mass, or waist circumference in a randomized double blind clinical trial with Vitamin D3 supplementation of 6000 IU of Vitamin D3/d (3 months) followed by 3000 IU/d in experimental group, and 2200 IU/d for follow-up in 6 months for both experimental and placebo groups in a recent study on type 2 diabetic obese UAE national patients [25]. Another study reported improvement in Vitamin D status and increased insulin secretion, but not insulin resistance, blood pressure, inflammation, or HbA1c in double blind randomized trial with 16 subjects in which 8 patients received 280 μg daily for 2 weeks, 140 μg daily for 10 weeks of colecalciferol [26]. A study by Heshmat et al. [27] carried out with 42 diabetic patients found no relationship between Vitamin D supplement and change in diabetes status (when observed for 3 months) with administration of single intramuscular injection of 300,000 IU of Vitamin D3, but Kuchay et al. [28] showed positive benefits of Vitamin D supplementation for 1 year on fasting plasma glucose, 2-h plasma glucose, and A1C levels with 137 subjects randomized to receive 60,000 IU for 4 weeks followed by 60,000 IU monthly of cholecalciferol. Type of Vitamin D supplement in effectiveness of supplementation was also noticed in few studies [29]. A meta-analysis of randomized control trials indicated that Vitamin D3 is more
2.2 Genetic Factors of Vitamin D Related to Diabetes. Genetic factors that may affect the Vitamin D levels in body were also explored for their link with diabetes. DHCR7 encoding 7-dehydrocholesterol reductase enzyme, which converts 7-dehydrocholesterol to cholesterol, a precursor of Vitamin D3, playing a role in endogenous production of Vitamin D was studied. Genetic variants of DHCR7 were significantly associated with increased risk of type 2 diabetes, whereas CYP2R1 was not in a Danish study with 96,423 participants genotyped [35]. Allele frequencies of 18 SNPs derived from CYP2R1, GC, and DHCR7/NADSYN1 investigated in South Asians, South-East Asians, and Arabs living in Kuwait indicated significant association between the GC (rs2282679 and rs7041), CYP2R1 (rs10741657), SNPs, and 25(OH)D levels [36]. Another European cohort (IMPROVE) based study inclusive of 3,418 individuals, of whom 929 had type 2 diabetes Single Nucleotide Polymorphisms (GC; rs2282679 and rs7041) and 7-dehydrocholesterol reductase/NAD synthetase-1 (DHCR7; rs12785878 and rs3829251), was investigated and found to have negative association with 25(OH)D levels, with differences in association significances between type 2 diabetic and nondiabetic individuals. Furthermore, rs3829251 (DHCR7) influenced progression of subclinical atherosclerosis measured in a relationship dependent on type 2 diabetes status, but independent of 25(OH)D levels [37].

Involvement of VDR in T-cells immune response to antibacterial infection, regulation of complex set of regulatory factor, and control over adverse inflammatory adaptive immunity support Vitamin D’s role in decidual immunity and possibly as future immunotherapy [38–41]. Mechanism through which Vitamin D was involved was also widely studied, and specific genes and their polymorphic conditions were discovered for Vitamin D receptors genes that accounted for some degree of risk. Vitamin D downregulates NF-κB and its downstream inflammatory cytokines expression and upregulates PPAR-α, acting as antagonist, promoting β-oxidation, and reducing triglycerides level. It increases the expression of CPT-1, a rate limiting enzyme in mitochondria, which allows for transport of free fatty acids into mitochondria for lipid oxidation, thus reducing lipid deposition [42]. Vitamin D level was negatively related with serum CRP, TNF-α and IL-6 levels and urinal inflammation factors in patients with type 1 diabetes as well [43]. Investigations exploring specific genes, involved in diabetes, commonly hold variable alleles of the same gene accountable for risk and complications in this disease. T and b, TaqI and BsmI alleles were suggested to be protective for developing TIDM in Koreans [44]. VDR FokI polymorphism is linked to TIDM [45], or to microvascular complication [46]. Study on VDR polymorphism for the whole gene indicated susceptibility for type 1 diabetes [47]. However, meta-analysis of studies since 1998 until 2013 concludes that individual VDR polymorphisms seemed not to be associated with TID risk, but haplotypes contributed significantly to disease susceptibility [48]. Further recognition sites were found on ApaI and TaqI for VDR gene in Egyptian type 1 DM patients [49]. VDR rs2228570 was also suggested as a good candidate for biomarker of diabetic retinopathy in Han Chinese T2DM patients due to the association found with the T allele [50]. Certain VDR genes were further investigated for 1692 children from DAISY cohort, and an association with type 1 diabetes progression and polymorphism of genes was concluded; however, large cohort studies are required to replicate such data [51]. Such link of genes is also discussed in regard to diabetic nephropathy [52], where ACR (Albumin-Creatinine Ratio) is linked with progression from prediabetes to diabetes [53]. Moreover, VDR polymorphism of functional SNP 2228570 C > T (FokI) of T allele can further influence the severity of metabolic syndrome in T2D patients amongst Egyptian population [54].

Vitamin D involvement in diabetic complications attenuation was also reported in some studies. An inverse and independent relationship between circulating 25(OH)D levels and the prevalence of microvascular complications in patients with type 2 diabetes was shown [55]. Low Vitamin D status is characteristically associated with advanced diabetic nephropathy [56]. Duration of diabetes and Vitamin D deficiency were independent determinants of diabetic...
A summary of studies is presented in Table 1. Consumption within normal range is considered beneficial. Vitamin D status in sufficient range holds no harm. Vitamin D supplementation usually improved the efficacy and necessity. In adults, much stronger influences on a more favorable lipid profile [75] and decreased incidence of metabolic syndrome [76], but more studies are required to establish proper causative link. Thus, mechanisms are suggested and supporting values are provided; however, science is always about experimenting and needs continuous testing to explain further. Beneficial HDL cholesterol, triglycerides,
| Study type         | Subject division                                      | Population | Vitamin D assessment/supplement                                      | Duration | Conclusion                                                                 | Citation |
|--------------------|-------------------------------------------------------|------------|---------------------------------------------------------------------|----------|----------------------------------------------------------------------------|----------|
| Cross-sectional    | Non-DM T2DM patients                                  | 100        | Vitamin D assessment & main cardiovascular risk factors             | —        | Prevalence of hypovitaminosis D was higher in diabetic patients with HbA1c, BMI, LDL, and triglycerides than Vitamin D counterparts. 25(OH)D may have an indirect effect mediated by cardiovascular risk factors on CHD | [63]     |
| Cross-sectional    | Controls Case, diabetic retinopathy                   | 110        | Vitamin D receptor gene polymorphism investigated                  | —        | Diabetes duration, systolic blood pressure, HbA1c, and AUCC-peptide, but reduced blood pressure, inflammation markers, and proteinuria levels after 6 months from baseline | [50]     |
| Prospective case-control | Control Case (deficient/insufficient serum 25(OH)D3) | 30 31      | Vitamin D supplement: case, calcitriol 0.25 μg/daily Control, no dose | 6 months | No effect on FBG, HbA1c, and AUCC-peptide, but reduced blood pressure, inflammation markers, and proteinuria levels after 6 months from baseline | [43]     |
| Case-cohort        | Control (non-GDM) Case (GDM)                           | 517        | Vitamin D assessment                                               | 8 years  | Early pregnancy Vitamin D status was found to be inversely associated with GDM | [33]     |
| Prospective cohort | White Black                                           | 8120       | Vitamin D assessment                                               | 8 years  | Risk association in Blacks No association in Whites                        | [23]     |
| Case-control       | Control Case, supplemented                            | 68 69      | Dose administration: 60,000 IU weekly for 4 weeks and then monthly  | 1 year   | Reduced HbA1c levels, FPG, and 2-h plasma glucose                          | [28]     |
| Randomized double blind | Control Subjects (DM patients)                         | 21 21      | Dose administration: intramuscular injection 300000 IU of Vitamin D3 | 3 months | Dose of Vitamin D improved plasma level but had no effect on HbA1c        | [27]     |
| Randomized double blind | Placebo Case, T2DM Vitamin D supplemented            | 42 45      | Vitamin D supplementation: phase 1 6000 IU Vitamin D3/day (3 months), phase 2 with 3000 IU Vitamin D3/day, and phase 3 both the arms unblinded and supplemented with 2200 IU Vitamin D3/day for 6 months | 1 year   | No significant influence on weight, fat mass, or waist circumference. Target levels of S-25(OH)D above 75 nmol/L in this population were not achievable | [25]     |
| Study type                  | Subject division                | Population | Vitamin D assessment/supplement | Duration | Conclusion                                           | Citation |
|-----------------------------|---------------------------------|------------|--------------------------------|----------|------------------------------------------------------|----------|
| Randomized prospective     | T1DM male (62%) Female (38%)    | 25         | Vitamin D3 (20 000 IU/week) for 6 months, either immediately or after 6 months of observation | 1 year   | Did not affect glycaemia or markers of inflammation | [21]     |
| Cross-sectional             | Female Male                     | 697        | Vitamin D assessment           | —        | Significantly decreasing trends for fasting insulin, HOMA-IR, and IFG with increasing 25(OH)D (independent of adiposity) | [18]     |
| Prospective case-control    | Control Case (diagnosed DM)     | 102        | Vitamin D assessment           | 2 years  | Controls and cases were deficient in Vitamin D, but it was significantly lower in DM patients. Significant negative correlation between 25(OH)D and HbA1c was observed | [15]     |
waist circumference, serum glucose, and low prevalence of metabolic syndrome were observed with higher Vitamin D concentration [77, 78].

Vitamin D supplementation might improve mortality in chronic kidney disease patients, since a study reports insulin resistance and Vitamin D deficiency as independent predictors of left ventricular hypertrophy and atherosclerosis [79]. Low 25(OH)D levels were also found to be associated with reduced incidence of CVD, much significantly for fatal cases [80]. A meta-analysis of the most well controlled randomized human trial data available however does not show benefit of Vitamin D on CVD, although small studies indicate benefits [81].

Vitamin D status was also found to have no role in the etiology of Atrial Fibrillation [82]. But augmentation index, to measure arterial stiffness, was reduced [83] in patients when supplemented (119 deficient patients randomized to receive either 50,000 international units (IU) or 100,000 IU single intramuscular Vitamin D3) and so did other mediators of arterial stiffness (62 participants received cholecalciferol 2,000 IU/day + calcium 200 mg/day, or the placebo with calcium 200 mg/day) [84]. In diabetic patients it did not show any benefits [85].

Evidence for association between Vitamin D status and ischemic stroke still remains equivocal. No association between Vitamin D status and incidence of stroke was found in some studies [86, 87], but low 25(OH)D levels as risk factor for stroke, specifically for those predisposed to high D binding protein, who thus have low bioavailability of Vitamin D, were also presented as hypothesis in one experiment with supporting outcome [10]. In Indian subjects Vitamin D deficiency was also associated with acute myocardial infarction (MI) [88]. Racial disparity was observed in heart failure cases for Vitamin D deficient patients [89]. In some conditions, such as MI, stroke, and arterial stiffness, data from recently performed experiments is not adequate to conclude, and it shall be valuable to continue recording with latest technology.

Data on blood pressure is still indecisive. In Mendelian analysis it was concluded that increased Vitamin D levels could reduce hypertension risk, but further replication of study is necessary [90]. Vitamin D supplementation for hypertensive, low Vitamin D serum levels subjects did not improve their blood pressure when given either 2800 IU of Vitamin D3 per day as oily drops \( (n = 100) \) or placebo \( (n = 100) \) for 8 weeks [91]; further controlled trial is on the way to assess the link [92]. In a review conducted on Vitamin D supplementation trials, the result was inconclusive, since randomized trials with higher Vitamin D dose are potentially required to realize specific outcome [93]. Through Mendelian randomization analysis, a causal effect of Vitamin D deficiency on increased blood pressure was suggested [94]. Studies need to be replicated in an independent, similarly powered study, as some inconsistencies were present that could be attributed to the baseline differences in 25(OH)D concentrations or blood pressure, or other sources of heterogeneity between the studies.

3.1. Supplementation Studies on Vitamin D. Vitamin D supplementation effects were investigated too, commonly to improve serum levels and to study the effect it had for target identified in research studies. Vitamin D supplementation in deficient people, free of cardiovascular risk, improved myocardial deformation parameters and epicardial fat thickness; moreover, link between Vitamin D levels and impaired left ventricular global longitudinal strain was suggested [95]. Vitamin D replacements in type 2 diabetic patients potentially have beneficial effects on cardiovascular disease risk factors too, as indicated by research on 119 type 2 diabetic patients given calcitriol 0.5 micrograms per day for 8 weeks [96]. Vitamin D deficiency is also shown through one study, to play a role in hypertension [97]. Vitamin D supplementation could aid control of systolic blood pressure, diastolic blood pressure, and mean arterial blood pressure, as concluded from study with 42 outpatients with elevated blood pressure given one capsule containing 50 000 IU of cholecalciferol weekly in intervention group [98]. Endothelial function might be impaired in healthy but Vitamin D deficient young women, which is shown to improve with 6-month replacement therapy, possibly due to immune-modulatory effects [99]. Vitamin D might also influence efficacy of drugs, as finding from study on children with lupus assessing effect of atorvastatin on carotid IMT progression reflects that serum 25(OH)D level \( \geq 20 \text{ ng/mL} \) had less carotid IMT progression from treatment [100].

3.2. Vitamin D's Relation to Cardiovascular Inflammatory Conditions. CVD development and progression commonly involve atherosclerosis buildup and narrowed vessels; the following trials shall indicate the link between these conditions and Vitamin D serum status. Vitamin D deficiency may lead to coronary atherosclerosis, and plaque buildup, but study does not define relationship with the composition [101]. Meta-analysis conducted for research published on “PubMed” from 2009 onwards does not conclude beneficial effect of Vitamin D on vascular reactivity [102]. To study presence of calcific atherosclerosis or obstructive coronary artery stenosis with low Vitamin D, study inclusive of 1131 individuals was conducted; however, no association was found [103]. In 375 patients undergoing coronary angiography, Vitamin D was the most significant predictor found for coronary artery disease measured by >50% stenosis in each major coronary artery [104]. To conclude link between Vitamin D levels and coronary atherosclerosis measured by coronary artery calcium, evidence is insufficient and needs further large sample studies with proper Vitamin D assessment levels and confounders adjustment (reviewed in [105]). Carotid intima media thickness (CIMT) and arterial stiffness were not associated with Vitamin D deficiency in patients with type 2 diabetes [106], with systemic lupus erythematosus [107, 108], non-diabetic males with HIV [109], amongst juvenile and adult [110], with primary hyperparathyroidism [111], or random patients admitted to internal medicine [112]. On the other hand, serum Vitamin D level was significantly, independently associated with carotid atherosclerosis in type 2 diabetes patients, since CIMT levels and proportion of
| Study type         | Subjects division | Population | Vitamin D assessment/supplement                                      | Duration | Conclusion                                                                 | Citation |
|-------------------|-------------------|------------|---------------------------------------------------------------------|----------|-----------------------------------------------------------------------------|----------|
| Prospective       | Female Male       | 28 32      | Iranian                                                              | 3 months | Did not find significant relationship between Vitamin D and P-selectin and hs-CRP levels | [120]    |
| Cross-sectional   | Postmenopausal women | 926       | Chinese                                                              | Serum 25(OH)D inversely correlated with carotid IMT | [115]    |
| Cross-sectional   | Female (43%), male (57%) | 567      | Vitamin D assessment, arterial stiffness, and carotid IMT            | Nonlinear relationship between 25(OH)D and IMT, and IMT increases slightly for 25(OH)D levels above 50 nmol/L | [117]    |
| Prospective       | 2148              | Finnish    | Vitamin D assessment & carotid IMT measurement                      | 27 years | Low Vitamin D levels were associated with increased carotid IMT in adulthood | [116]    |
| Cross-sectional   | T2DM              | 352        | Chinese                                                              | Serum Vitamin D independently associated with carotid atherosclerosis in T2D | [113]    |
| Randomized        | T2D               | 415        | Danish                                                              | Serum 25(OH)D status not associated with carotid IMT, arterial thickness, or bone health | [106]    |
| Cross-sectional   | Control Case (atherosclerosis) | 110 98   | Vitamin D assessment & coronary CT angiography                      | Relationship between low Vitamin level and coronary atherosclerosis and plaque burden, but not with morphology | [101]    |
| Randomized        | Placebo Case (atorvastatin) | 103 98   | Vitamin D assessment, carotid IMT progression, and secondary outcomes (cholesterol, LDL, and hs-CRP) | Baseline 25(OH)D levels ≥21ng/mL associated with lower baseline hs-CRP levels. Vitamin D deficiency may be involved in response to atorvastatin | [100]    |
| Randomized        | Placebo Case-supplement | 100 100  | Austria                                                              | Supplementation for hypertensive patients with low serum levels has no significant effect on blood pressure | [91]     |
| Prospective       | White (76%), Black (24%) | 12215    | Diverse                                                              | Association between Vitamin D and risk of heart failure found for both Black and White people, but in White people it also reflected incidence of heart failure | [89]     |
| Cross-sectional   | Controls Case (stroke patients) | 70 73    | Indian                                                               | Vitamin D deficiency is not linked with ischemic stroke or its risk factors | [87]     |
| Prospective       | Female Male       | 2007 1388  | Netherlands                                                          | Vitamin D status was not associated with AF incidence | [82]     |
| Study type        | Subjects division | Population | Vitamin D assessment/supplement | Duration | Conclusion                                                                                   | Citation |
|-------------------|-------------------|------------|---------------------------------|----------|-----------------------------------------------------------------------------------------------|----------|
| Cohort            | 9949              | German     | Vitamin D assessment and fatal and nonfatal CVD incidence | 5 years  | Relationship suggests that low 25(OH)D levels moderately increase risk of CVD, much strongly for fatal incidences | [80]     |
| Prospective Mendelian | 95766          | Danish     | Vitamin D assessment, genotypes for DHCR7 & CYP2R1, and mortality confounders | 5–19 years | Vitamin D concentration not associated with CVD mortality but could be result of confounding factors | [68]     |
| Cross-sectional   | Without plaque    | Chinese    | Vitamin D assessment, carotid plaque, and carotid IMT |          | Serum Vitamin D levels are inversely associated with atherosclerosis. Vitamin D is also a protective factor for increased carotid IMT amongst subjects with plaque | [11]     |
|                   | With plaque       |            |                                 |          |                                                                                               |          |
|                   | 712               |            |                                 |          |                                                                                               |          |
|                   | 289               |            |                                 |          |                                                                                               |          |
| Prospective       | 12158             |            | Vitamin D assessment, stroke incidence, and rs7041, rs4588 SNPs for D binding protein were genotyped | 20 years | Low 25(OH)D levels are risk factor for stroke, especially those predisposed to high DBP | [10]     |
carotid plaques were higher in lowest quartile of 25(OH)D than in the highest quartile [113], or in psoriasis patients with increased risk of carotid atherosclerosis, especially those with a longer history of psoriasis [114], while the first published study on healthy postmenopausal Chinese women investigating CIMT and Vitamin D also found a similar inverse relationship [115]. Low 25(OH)D level in childhood was shown to have increased risk for carotid IMT in adulthood [116]. Study investigating relationship between higher Vitamin D levels and cardiovascular risk also reports from its 567 subjects that serum levels of 50 nmol/L and above show slight increase in IMT with increasing 25(OH)D levels [117]. Hypovitaminosis D might further be involved in thoracic atherosclerosis pathogenesis too, as lower 25(OH)D was independently associated with higher aortic IMT [118]. Studies on thromboembolism do not provide conclusive result and lack large group trials; results of studies focusing on P-selectin or hs-CRP are nonsupportive [119, 120], even when considering it as risk factor to disease [121]. However, significant inverse relationship between serum 25(OH)D level and hs-CRP levels (inflammatory marker) was also detected, and it is this inflammatory process throughout the disease which plays a role in its progression [98]. Insulin-like growth factor-1 (IGF-1), which evidently counteracts vascular aging, circulates in blood when Vitamin D levels are low, according to Baltimore Longitudinal Study of Aging (BLSA) including 472 participants [122].

3.3. Genetic Factors of Vitamin D Related to Cardiovascular Diseases. Genetic factors that contribute to Vitamin D status of body were also investigated for their role in cardiovascular diseases. Single Nucleotide Polymorphisms (SNPs) in GC and DHCR7 were associated with serum levels of 25(OH)D levels, and only rs3829251 (DHCR7) influenced progression of subclinical atherosclerosis [37]. In another study inclusive of 535 individuals SNPs of CYP1A1 and CYP1B1 were identified and indicated synergistic effect on blood pressure [123]. Sixty-three male patients recruited with coronary artery disease (CAD) were genotyped for both the rs12785878 (NADSYN1) polymorphism and the rs1790349 (DHCR7). Data backs the investigated SNPs ability to predict circulating 25(OH)D levels but opposes their use as genetic markers for CAD [124]. Future studies addressing the interaction could be insightful for prevention and treatment. Many trials recognize low serum levels of Vitamin D to impact cardiovascular health negatively, whereas some still do not support, and so continuous experimentation expanding on vast range of confounders is suggestive to draw conclusion. A summary of studies is presented in Table 2.

4. Conclusion

This paper generally looked at researches or reviews conducted mostly during 2013 and mid-2015. Majority of results put forth suggest beneficial associations between Vitamin D, diabetic conditions, and cardiovascular diseases. And, the mechanisms defined propose maintenance of Vitamin D levels in desired range to prevent, delay, or control diabetes. Serum Vitamin D levels also improved cardiovascular function. All benefits of Vitamin D are concentrated in the role of this molecule in inflammation, immunity, and gene transcription. Use of supplement also proved to be beneficial, but to the extent of acquiring proper serum levels. To establish specific recommendation regarding their use still demands insight into the administered doses and duration, as in some studies Vitamin D supplementation doses were high, but for short time, whereas in others they were administered for few months in small doses. Thus, maintaining adequate Vitamin D levels is vital for chronic condition prevention, severity, and improvement.

Conclusive recommendation is that further trials are necessary to establish causal risk association. Many aspects of CVD, such as stroke, blood pressure, atrial stiffnes, carotid intima, and media thickness, provide equivocal results. It is imperative to continue with large, long-term controlled trials, including range of disease confounders and properly identified baseline data to reach final stance. Further studies are required to establish causality, minimize population based genetic variance, harmonize baseline Vitamin D levels, and target specific groups. Prospective study considering changing Vitamin D levels year-round would eliminate certain limitations associated with study type reported in some cases.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

References

[1] A. C. Ross, C. L. Taylor, A. L. Yaktine, and H. B. Del Valle, Dietary Reference Intakes for Calcium and Vitamin D, National Academies Press, Washington, DC, USA, 2011.
[2] M. F. Holick, “Vitamin D status: measurement, interpretation, and clinical application,” Annals of Epidemiology, vol. 19, no. 2, pp. 73–78, 2009.
[3] S. J. Ball, A. Haynes, P. Jacoby et al., “Spatial and temporal variation in type 1 diabetes incidence in Western Australia from 1991 to 2010: increased risk at higher latitudes and over time,” Health and Place, vol. 28, pp. 194–204, 2014.
[4] D. Papandreou, P. Malindretos, Z. Karabouta, and I. Roussos, “Possible health implications and low vitamin D status during childhood and adolescence: an updated mini review,” International Journal of Endocrinology, vol. 2010, Article ID 472173, 7 pages, 2010.
[5] H. K. Joh, C. S. Lim, and B. Cho, “Lifestyle and dietary factors associated with serum 25-hydroxyvitamin D levels in Korean young adults,” Journal of Korean Medical Science, vol. 30, no. 8, pp. 1110–1120, 2015.
[6] T. J. Wang, F. Zhang, J. B. Richards et al., “Common genetic determinants of vitamin D insufficiency: a genome-wide association study,” The Lancet, vol. 376, no. 9736, pp. 180–188, 2010.
[7] S. Christakos, M. Hewison, D. G. Gardner et al., “Vitamin D: beyond bone,” Annals of the New York Academy of Sciences, vol. 1287, no. 1, pp. 45–58, 2013.
[8] S. Mohammadian, N. Fatahi, H. Zaeri, and M. A. Vakili, “Effect of vitamin D3 supplement in glycemic control of pediatrics with type 1 diabetes mellitus and vitamin D deficiency,” Journal of
C. V. Harinarayan, "Vitamin D and diabetes mellitus," Hormones, vol. 13, no. 2, pp. 163–181, 2014.

N. G. Forouhi, Z. Ye, A. P. Rickard et al., "Circulating 25-hydroxyvitamin D concentration and the risk of type 2 diabetes: results from the European Prospective Investigation into Cancer (EPIC)-Norfolk cohort and updated meta-analysis of prospective studies," Diabetologia, vol. 55, no. 8, pp. 2173–2182, 2012.

S. J. Chung, Y. A. Lee, H. Hong et al., "Inverse relationship between vitamin D status and insulin resistance and the risk of impaired fasting glucose in Korean children and adolescents: the Korean National Health and Nutrition Examination Survey (KNHANES) 2009-2010," Public Health Nutrition, vol. 17, no. 4, pp. 795–802, 2014.

R. Feng, Y. Li, G. Li et al., "Lower serum 25 (OH) D concentrations in type 1 diabetes: a meta-analysis," Diabetes Research and Clinical Practice, vol. 108, no. 3, pp. e71–e75, 2015.

E. Serra-Planas, A. Guiller, M. L. Granada et al., "High prevalence of vitamin D deficiency and lack of association with subclinical atherosclerosis in asymptomatic patients with Type 1 diabetes mellitus from a Mediterranean area," Acta Diabetologica, vol. 52, no. 4, pp. 773–779, 2015.

E. M. Shih, S. Mittelman, P. Pituikcheewanont, C. G. Azen, and R. Monzavi, "Effects of vitamin D repletion on glycemic control and inflammatory cytokines in adolescents with type 1 diabetes," Pediatric Diabetes, 2015.

N. Nigil Haroon, A. Anton, J. John, and M. Mittal, "Effect of vitamin D supplementation on glycemic control in patients with type 2 diabetes: a systematic review of interventional studies," Journal of Diabetes & Metabolic Disorders, vol. 14, no. 1, article 3, 2015.
[36] N. Elkum, F. Alkayal, F. Noronha et al., “Vitamin D insufficiency in Arabs and South Asians positively associates with polymorphisms in GC and CYP2R1 genes,” PLoS ONE, vol. 9, no. 11, Article ID e13102, 2014.

[37] R. J. Strawbridge, A. Deleskog, O. McLeod et al., “A serum 25-hydroxyvitamin D concentration-associated genetic variant in DHCR7 interacts with type 2 diabetes status to influence subclinical atherosclerosis (measured by carotid intima-media thickness),” Diabetologia, vol. 57, no. 6, pp. 1159–1172, 2014.

[38] C. L. Wagner, S. N. Taylor, A. Dawodu, D. D. Johnson, and B. W. Hollis, “Vitamin D and its role during pregnancy in attaining optimal health of mother and fetus,” Nutrients, vol. 4, no. 3, pp. 208–230, 2012.

[39] J. A. Tamblyn, M. Hewison, C. L. Wagner, J. N. Bulmer, and M. D. Kilby, “Immunological role of vitamin D at the maternal-fetal interface,” Journal of Endocrinology, vol. 224, no. 3, pp. R107–R121, 2015.

[40] C. E. Hayes, S. L. Hubler, J. R. Moore, L. E. Barta, C. E. Praska, and F. E. Nashold, “Vitamin D actions on CD4+ T cells in autoimmune disease,” Frontiers in Immunology, vol. 6, article 100, 2015.

[41] T. L. Van Belle, A. Vanherweghen, D. Feyaerts et al., “1,25-dihydroxyvitamin D3 and its analog TXS27 promote a stable regulatory T cell phenotype in T cells from type 1 diabetes patients,” PLoS ONE, vol. 9, no. 10, Article ID e90194, 2014.

[42] C. Ning, L. Liu, G. Lv et al., “Lipid metabolism and inflammation modulated by Vitamin D in liver of diabetic rats,” Lipids in Health and Disease, vol. 14, article 31, 2015.

[43] L. Mao, F. Ji, Y. Liu, W. Zhang, and X. Ma, “Calcitriol plays a protective role in diabetic nephropathy through anti-inflammatory effects,” International Journal of Clinical and Experimental Medicine, vol. 7, no. 12, pp. 5437–5444, 2014.

[44] C.-K. Cheon, H.-K. Nam, H.-K. Lee, S. Y. Kim, J. S. Song, and C. Kim, “Vitamin D receptor gene polymorphisms and type 1 diabetes mellitus in a Korean population,” Pediatrics International, 2015.

[45] Y. Morán-Auth, M. Penna-Martinez, and K. Badenhoop, “VDR FokI polymorphism is associated with a reduced T-helper cell population under vitamin D stimulation in type 1 diabetes patients,” The Journal of Steroid Biochemistry and Molecular Biology, vol. 148, pp. 184–186, 2015.

[46] Z. Liu, L. Liu, X. Chen, W. He, and X. Yu, “Associations study of vitamin D receptor gene polymorphisms with diabetic microvascular complications: a meta-analysis,” Gene, vol. 546, no. 1, pp. 6–10, 2014.

[47] J. De Azevedo Silva, R. L. Guimaraes, L. A. C. Brandao et al., “Vitamin D receptor (VDR) gene polymorphisms and age onset in type 1 diabetes mellitus,” Autoimmunity, vol. 46, no. 6, pp. 382–387, 2013.

[48] K. Tizaoui, W. Kaabachi, A. Hamzaoui, and K. Hamzaoui, “Contribution of VDR polymorphisms to type 1 diabetes susceptibility: systematic review of case-control studies and meta-analysis,” The Journal of Steroid Biochemistry and Molecular Biology, vol. 143, pp. 240–249, 2014.

[49] M. M. Kamel, S. A. Fouad, O. Salaheldin, A. E.-R. A. A. El-Razek, and A. I. A. El-Fatih, “Impact of vitamin D receptor gene polymorphisms in pathogenesis of Type-1 diabetes mellitus,” International Journal of Clinical and Experimental Medicine, vol. 7, no. 12, pp. 5505–5510, 2014.

[50] X. Zhong, Y. Du, Y. Lei, N. Liu, Y. Guo, and T. Pan, “Effects of vitamin D receptor gene polymorphism and clinical characteristics on risk of diabetic retinopathy in Han Chinese type 2 diabetes patients,” Gene, vol. 566, no. 2, pp. 212–216, 2015.

[51] B. Frederiksen, E. Liu, J. Romanos et al., “Investigation of the vitamin D receptor gene (VDR) and its interaction with protein tyrosine phosphatase, non-receptor type 2 gene (PTPN2) on risk of islet autoimmunity and type 1 diabetes: the Diabetes Autoimmunity Study in the Young (DAISY),” Journal of Steroid Biochemistry and Molecular Biology, vol. 133, no. 1, pp. 51–57, 2013.

[52] X. Wu, R. C. Davis, T. S. McMillen et al., “Genetic modulation of diabetic nephropathy among mouse strains with Ins2 Akita mutation,” Physiological Reports, vol. 2, no. 11, Article ID e12208, 2014.

[53] D. Dutta, S. Choudhuri, S. A. Mondal, S. Mukherjee, and S. Chowdhury, “Urinary albumin: creatinine ratio predicts prediabetes progression to diabetes and reversal to normoglycemia: role of associated insulin resistance, inflammatory cytokines and low vitamin D,” Journal of Diabetes, vol. 6, no. 4, pp. 316–322, 2014.

[54] A. M. H. Mackawy and M. E. H. Badawi, “Association of vitamin D and vitamin receptor gene polymorphisms with chronic inflammation, insulin resistance and metabolic syndrome components in type 2 diabetic Egyptian patients,” Meta Gene, vol. 2, pp. 540–556, 2014.

[55] G. Zoppini, A. Galletti, G. Targher et al., “Lower levels of 25-hydroxyvitamin D3 are associated with a higher prevalence of microvascular complications in patients with type 2 diabetes,” BMJ Open Diabetes Research & Care, vol. 3, no. 1, Article ID e000058, 2015.

[56] R. M. Sánchez-Hernández, C. García-Cantón, D. L. Lorenzo et al., “The specific relationship between vitamin D deficiency and diabetic nephropathy among patients with advanced chronic kidney disease: a cross-sectional study in Gran Canaria, Spain,” Clinical Nephrology, vol. 83, no. 04, pp. 218–224, 2015.

[57] N. Shimo, T. Yasuda, H. Kaneto et al., “Vitamin D deficiency is significantly associated with retinopathy in young Japanese type 1 diabetic patients,” Diabetes Research and Clinical Practice, vol. 106, no. 2, pp. e41–e43, 2014.

[58] S. Bonakdaran and N. Shoeibi, “Is there any correlation between vitamin D insufficiency and diabetic retinopathy?” International Journal of Ophthalmology, vol. 8, no. 2, pp. 326–331, 2015.

[59] X.-L. Zhang, Y.-F. Guo, Z.-X. Song, and M. Zhou, “Vitamin D prevents podocyte injury via regulation of macrophage M1/M2 phenotype in diabetic nephropathy rats,” Endocrinology, vol. 155, no. 12, pp. 4939–4950, 2014.

[60] Y. Tian, G. Lv, Y. Yang et al., “Effects of vitamin D on renal fibrosis in diabetic nephropathy model rats,” International Journal of Clinical and Experimental Pathology, vol. 7, no. 6, pp. 3028–3037, 2014.

[61] S. Goto, H. Fujii, K. Kono et al., “22-oxacalcitriol attenuates bone loss in nonobese type 2 diabetes,” Bone, vol. 74, pp. 153–159, 2015.

[62] R.-H. Chen, X.-H. Zhao, Z. Gu et al., “Serum levels of 25-hydroxyvitamin D are associated with cognitive impairment in type 2 diabetic adults,” Endocrine, vol. 45, no. 2, pp. 319–324, 2014.

[63] G. Muscogiuri, V. Nuzzo, A. Gatti et al., “Hypovitaminosis D: a novel risk factor for coronary heart disease in type 2 diabetes?” Endocrine, pp. 1–6, 2015.
[64] A. E. Riek, J. Oh, I. Darwech, C. E. Moynihan, R. R. Bruchas, and C. Bernal-Mizrachi, "25(OH) vitamin D suppresses macrophage adhesion and migration by downregulation of ER stress and scavenger receptor AI in type 2 diabetes," *Journal of Steroid Biochemistry and Molecular Biology*, vol. 144, pp. 172–179, 2014.

[65] W. Zhou and S. D. Ye, "Relationship between serum 25-hydroxyvitamin D and lower extremity arterial disease in type 2 diabetes mellitus patients and the analysis of the intervention of vitamin D," *Journal of Diabetes Research*, vol. 2015, Article ID 815949, 6 pages, 2015.

[66] B. Schöttker and H. Brenner, "Vitamin D as a resilience factor, helpful for survival of potentially fatal conditions: a hypothesis emerging from recent findings of the ESTHER cohort study and the CHANCES consortium," *Nutrients*, vol. 7, no. 5, pp. 3264–3278, 2015.

[67] R. Chowdhury, S. Kunutsor, A. Vitezova et al., "Vitamin D and risk of cause specific death: systematic review and meta-analysis of observational cohort and randomised intervention studies," *The BMJ*, vol. 348, article g9003, 2014.

[68] S. Afzal, P. Brondum-Jacobsen, S. E. Bojesen, and B. G. Nordestgaard, "Genetically low vitamin D concentrations and increased mortality: mendelian randomisation analysis in three large cohorts," *British Medical Journal*, vol. 349, Article ID g6330, 2014.

[69] H. M. Lee, M. Liu, K. Lee, Y. Luo, and N. D. Wong, "Does low vitamin D amplify the association of COPD with total and cardiovascular disease mortality?" *Clinical Cardiology*, vol. 37, no. 8, pp. 473–478, 2014.

[70] T. Skaaby, L. N. Husemoen, B. H. Thuesen et al., "Vitamin D status and chronic obstructive pulmonary disease: a prospective general population study," *PloS ONE*, vol. 9, no. 3, Article ID e90654, 2014.

[71] V. Andreás, "Vitamin D puts the brakes on angiotensin II-induced oxidative stress and vascular smooth muscle cell senescence," *Atherosclerosis*, vol. 236, no. 2, pp. 444–447, 2014.

[72] J. Oh, A. Riek, I. Darwech et al., "Deletion of macrophage vitamin d receptor promotes insulin resistance and monocyte cholesterol transport to accelerate atherosclerosis in mice," *Cell Reports*, vol. 10, no. 18, pp. 1872–1886, 2015.

[73] I. Mozos and O. Marginean, "Links between vitamin D deficiency and cardiovascular diseases," *BioMed Research International*, vol. 2015, Article ID 109275, 12 pages, 2015.

[74] A. R. Menezes, M. C. Lamb, C. J. Lavie, and J. J. Deanward, "Vitamin D and atherosclerosis," *Current Opinion in Cardiology*, vol. 29, no. 6, pp. 571–577, 2014.

[75] T. Skaaby, L. N. Husemoen, T. Martinussen et al., "Vitamin D status, filaggrin genotype, and cardiovascular risk factors: a mendelian randomization approach," *PloS ONE*, vol. 8, no. 2, Article ID e57647, 2013.

[76] T. Skaaby, L. N. Husemoen, C. Pisinger et al., "Vitamin D status and changes in cardiovascular risk factors: a prospective study of a general population," *Cardiology (Switzerland)*, vol. 123, no. 1, pp. 62–70, 2012.

[77] A. Lertratanakul, P. Wu, A. Dyer et al., "25-hydroxyvitamin D and cardiovascular disease in patients with systemic lupus erythematosus: data from a large international inception cohort," *Arthritis Care & Research*, vol. 66, no. 8, pp. 1167–1176, 2014.

[78] A. Vitezova, M. C. Zillikens, T. T. VanHerpt et al., "Vitamin D status and metabolic syndrome in the elderly: the Rotterdam study," *European Journal of Endocrinology*, vol. 172, no. 3, pp. 327–335, 2015.

[79] S. Lai, B. Coppola, M. Dimko et al., "Vitamin D deficiency, insulin resistance, and ventricular hypertrophy in the early stages of chronic kidney disease," *Renal Failure*, vol. 36, no. 1, pp. 58–64, 2014.

[80] L. Perna, B. Schöttker, B. Holleczek, and H. Brenner, "Serum 25-hydroxyvitamin D and incidence of fatal and nonfatal cardiovascular events: a prospective study with repeated measurements," *Journal of Clinical Endocrinology and Metabolism*, vol. 98, no. 12, pp. 4908–4915, 2013.

[81] P. F. Schnatz, M. Nudy, X. Jiang, J. E. Demko, and S. E. Appt, "Vitamin D deficiency and cardiovascular disease in postmenopausal women: contributions from human and non-human primate studies," *Menopause*, vol. 22, no. 5, pp. 554–563, 2015.

[82] A. Vitezova, N. S. Cartolano, J. Heeringa et al., "Vitamin D and the risk of atrial fibrillation—the rotterdam study," *PloS ONE*, vol. 10, no. 5, Article ID e0125161, 2015.

[83] C. McGreevy, M. Barry, C. Davenport et al., "The effect of vitamin D supplementation on arterial stiffness in an elderly community-based population," *Journal of the American Society of Hypertension*, vol. 9, no. 3, pp. 176–183, 2015.

[84] D. Martins, Y. Meng, N. Tareen et al., "The effect of short term vitamin d supplementation on the inflammatory and oxidative mediators of arterial stiffness," *Health*, vol. 6, no. 12, pp. 1503–1511, 2014.

[85] O.-H. Ryu, W. Chung, S. Lee, K.-S. Hong, M.-G. Choi, and H. J. Yoo, "The effect of high-dose vitamin D supplementation on insulin resistance and arterial stiffness in patients with type 2 diabetes," *Korean Journal of Internal Medicine*, vol. 29, no. 5, pp. 620–629, 2014.

[86] T. Skaaby, L. N. Husemoen, C. Pisinger et al., "Vitamin D status and incident cardiovascular disease and all-cause mortality: a general population study," *Endocrine*, vol. 43, no. 3, pp. 618–625, 2013.

[87] A. Gupta, S. Prabhakar, M. Modi, S. K. Bhadada, V. Lal, and D. Khurana, "Vitamin D status and risk of ischemic stroke in North Indian patients," *Indian Journal of Endocrinology and Metabolism*, vol. 18, no. 5, pp. 721–725, 2014.

[88] A. Roy, R. Lakshmy, M. Tarik, N. Tandon, K. S. Reddy, and D. Prabhakaran, "Independent association of severe vitamin D deficiency as a risk of acute myocardial infarction in Indians," *Indian Heart Journal*, vol. 67, no. 1, pp. 27–32, 2015.

[89] P. L. Lutsey, E. D. Michos, J. R. Misialek et al., "Race and vitamin D binding protein gene polymorphisms modify the association of 25-hydroxyvitamin D and incident heart failure: the ARIC (Atherosclerosis Risk in Communities) study," *Heart Failure*, vol. 3, no. 5, pp. 347–356, 2015.

[90] K. S. Vimalaswaran, A. Cavadino, D. J. Berry et al., "Association of vitamin D status with arterial blood pressure and hypertension risk: a mendelian randomisation study," *The Lancet Diabetes & Endocrinology*, vol. 2, no. 9, pp. 719–729, 2014.

[91] S. Pilz, M. Gaksch, K. Kienreich et al., "Effect of vitamin D binding protein gene polymorphisms on the risk of acute myocardial infarction in Europeans," *European Journal of Cardiovascular Prevention*, vol. 22, no. 2, pp. 135–142, 2015.
[93] P. F. Schnatz and J. E. Manson, “Vitamin D and cardiovascular disease: an appraisal of the evidence,” Clinical Chemistry, vol. 60, no. 4, pp. 600–609, 2014.

[94] S. K. Kunutsor, S. Burgess, P. B. Munroe, and H. Khan, “Vitamin D and high blood pressure: causal association or epiphenomenon?” European Journal of Epidemiology, vol. 29, no. 1, pp. 1–14, 2014.

[95] M. Sunbul, M. Bozbay, C. Mammadov et al., “Effect of vitamin D deficiency and supplementation on myocardial deformation parameters and epicardial fat thickness in patients free of cardiovascular risk,” The International Journal of Cardiovascular Imaging, vol. 31, no. 4, pp. 765–772, 2015.

[96] S. Bonakkadan, A. F. Nejad, V. Abdol-Reza, A. Hatemi, and M. Shakeri, “Impact of oral 1,25-dihydroxy vitamin D (calcitriol) replacement therapy on coronary artery risk factors in type 2 diabetic patients,” Endocrine, Metabolic & Immune Disorders Drug Targets, vol. 13, no. 4, pp. 295–300, 2013.

[97] K. Tomaino, K. M. Romero, C. L. Robinson et al., “Association between serum 25-hydroxy vitamin D levels and blood pressure among adolescents in two resource-limited settings in Peru,” American Journal of Hypertension, vol. 28, no. 8, pp. 1017–1023, 2015.

[98] H. Mozaffari-Khosravi, S. Loloei, M.-R. Mirjalili, and K. Bozbay, “The effect of vitamin D supplementation on blood pressure in patients with elevated blood pressure and vitamin D deficiency: a randomized, double-blind, placebo-controlled trial,” Blood Pressure Monitoring, vol. 20, no. 2, pp. 83–91, 2015.

[99] K. M. Gurses, L. Tokgozoglu, M. U. Yalcin et al., “Markers of subclinical atherosclerosis in premenopausal women with vitamin D deficiency and effect of vitamin D replacement,” Atherosclerosis, vol. 237, no. 2, pp. 784–789, 2014.

[100] A. B. Robinson, V. Tzaprircha, E. Yow, R. Gurion, L. E. Schanberg, and G. A. McComsey, “Vitamin D status is a determinant of atorvastatin effect on carotid intima medial thickening progression rate in children with lupus: an Atherosclerosis Prevention in Pediatric Lupus Erythematosus (APPLE) substudy,” Lupus Science & Medicine, vol. 1, no. 1, Article ID e000037, 2014.

[101] S. Satilmis, O. Celik, I. Biyik et al., “Association between serum vitamin D levels and subclinical coronary atherosclerosis and plaque burden/composition in young adult population,” Bosnian Journal of Basic Medical Sciences, vol. 15, no. 1, pp. 67–72, 2015.

[102] A. Alyami, M. J. Soares, J. L. Sherriff, and J. C. Mamo, “Vitamin D & endothelial function,” The Indian Journal of Medical Research, vol. 140, no. 4, pp. 483–490, 2014.

[103] J. S. Ho, J. J. Cannaday, C. E. Barlow, D. B. Reinhardt, W. A. Wade, and J. R. Ellis, “Low 25-OH vitamin D levels are not associated with coronary artery calcium or obstructive stenoses,” Coronary Artery Disease, vol. 26, no. 6, pp. 521–525, 2015.

[104] J. Y. Liew, S. R. Sasha, P. J. Ngu et al., “Circulating vitamin D levels are associated with the presence and severity of coronary artery disease but not peripheral arterial disease in patients undergoing coronary angiography,” Nutrition, Metabolism and Cardiovascular Diseases, vol. 25, no. 3, pp. 274–279, 2015.

[105] R. Malik, E. C. Aneni, L. Roberson et al., “Measuring coronary artery calcification: is serum vitamin D relevant?” Atherosclerosis, vol. 237, no. 2, pp. 734–738, 2014.

[106] K. Winckler, L. Tarnow, L. L. Christensen et al., “Vitamin D, carotid intima-media thickness and bone structure in patients with type 2 diabetes,” Endocrine Connections, vol. 4, no. 2, pp. 128–135, 2015.

[107] J.-Y. Jung, B.-R. Koh, C.-B. Bae, H.-A. Kim, and C.-H. Suh, “Carotid subclinical atherosclerosis is associated with disease activity but not vitamin D in Korean systemic lupus erythematosus,” Lupus, vol. 23, no. 14, pp. 1517–1522, 2014.

[108] A. N. Kiani, H. Fang, L. S. Magder, and M. Petri, “Vitamin D deficiency does not predict progression of coronary artery calcium, carotid intima-media thickness or high-sensitivity C-reactive protein in systemic lupus erythematosus,” Rheumatology, vol. 52, no. 11, Article ID ket271, pp. 2071–2076, 2013.

[109] J. Portilla, O. Moreno-Pérez, C. Serna-Candel et al., “Vitamin D insufficiency and subclinical atherosclerosis in non-diabetic males living with HIV,” Journal of the International AIDS Society, vol. 17, Article ID 18945, 2014.

[110] H. Mangge, S. Zelzer, A. Meinitzer et al., “25OH-vitamin D3 levels in obesity and metabolic syndrome—unaltered in young and not correlated to carotid IMT in all ages,” Current Pharmaceutical Design, vol. 21, no. 17, pp. 2243–2249, 2015.

[111] M. D. Walker, E. Cong, A. Kepley et al., “Association between serum 25-hydroxyvitamin D level and subclinical cardiovascular disease in primary hyperparathyroidism,” Journal of Clinical Endocrinology and Metabolism, vol. 99, no. 2, pp. 671–680, 2014.

[112] V. Carnevale, R. Minonne, A. De Matthaeis et al., “Carotid intima-media thickness is not associated with vitamin D and PTH levels in patients admitted to an Internal Medicine Department,” Endocrine, vol. 47, no. 3, pp. 833–838, 2014.

[113] R.-H. Chen, X.-Z. Jiang, Q. Jiang et al., “Correlations between serum levels of 25-hydroxyvitamin D and carotid atherosclerosis in patients with type 2 diabetes in Shanghai,” Annales d’Endocrinologie, vol. 75, no. 4, pp. 206–212, 2014.

[114] J. Orgaz-Molina, C. Magro-Checa, J. L. Rosales-Alexander et al., “Vitamin D insufficiency is associated with higher carotid intima-media thickness in psoriatic patients,” European Journal of Dermatology, vol. 24, no. 1, pp. 53–62, 2014.

[115] Y. Hao, X. Ma, Y. Luo et al., “Inverse association of serum vitamin D in relation to carotid intima-media thickness in Chinese postmenopausal women,” PLoS ONE, vol. 10, no. 3, Article ID e0122803, 2015.

[116] M. Juonala, A. Voipio, K. Pahkala et al., “Childhood 25-OH vitamin D levels and carotid intima-media thickness in adulthood: the Cardiovascular risk in young Finns study,” The Journal of Clinical Endocrinology & Metabolism, vol. 100, no. 4, pp. 1469–1476, 2015.

[117] S. C. Van Dijk, E. Sohl, C. Oudshoorn et al., “Non-linear associations between serum 25-OH vitamin D and indices of arterial stiffness and arteriosclerosis in an older population,” Age and Ageing, vol. 44, no. 1, pp. 136–142, 2015.

[118] G. Y. Kalkan, M. Gür, N. Y. Koyunsever et al., “Serum 25-hydroxyvitamin D level and aortic intima-media thickness in patients without clinical manifestation of atherosclerotic cardiovascular disease,” Journal of Clinical Laboratory Analysis, vol. 29, no. 4, pp. 305–311, 2015.

[119] K. Gholami, A. H. Talasaz, T. Entezari-Maleki et al., “The effect of high-dose vitamin D3 on soluble P-selectin and hs-CRP level in patients with venous thromboembolism: a randomized clinical trial,” Clinical and Applied Thrombosis/Hemostasis, 2015.

[120] T. Entezari-Maleki, A. H. Talasaz, M. Salarifar et al., “Plasma vitamin D status and its correlation with risk factors of thrombosis: P-selectin and hs-CRP level in patients with venous thromboembolism: the first study of iranian population,” Iranian Journal of Pharmaceutical Research, vol. 13, no. 1, pp. 319–327, 2014.
[121] A. R. Folsom, N. S. Roetker, W. D. Rosamond et al., "Serum 25-hydroxyvitamin D and risk of venous thromboembolism: the Atherosclerosis Risk in Communities (ARIC) Study," *Journal of Thrombosis and Haemostasis*, vol. 12, no. 9, pp. 1455–1460, 2014.

[122] P. Ameri, M. Canepa, P. Fabbi et al., "Vitamin D modulates the association of circulating insulin-like growth factor-1 with carotid artery intima-media thickness," *Atherosclerosis*, vol. 236, no. 2, pp. 418–425, 2014.

[123] H. Y. Park, J. H. Kim, S. Bae, Y. Y. Choi, J. Y. Park, and Y.-C. Hong, "Interaction effect of serum 25-hydroxyvitamin D levels and CYP1A1, CYP1B1 polymorphisms on blood pressure in an elderly population," *Journal of Hypertension*, vol. 33, no. 1, pp. 69–76, 2015.

[124] M. A. Abu El Maaty, S. I. Hassanein, H. M. Sleem, and M. Z. Gad, "Effect of polymorphisms in the NADSYN1/DHCR7 locus (rs12785878 and rs1790349) on plasma 25-hydroxyvitamin D levels and coronary artery disease incidence," *Journal of Nutrigenetics and Nutrigenomics*, vol. 6, no. 6, pp. 327–335, 2014.