REVIEW ARTICLE

Vitamin D and Heart Disease

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Abstract

Vitamin D in the past was thought to a play role constrained to calcium and bone metabolism, but in recent days its role beyond Calcium and bone metabolism is being speculated. Vitamin D has been blamed to be a contributory factor in number of cardiovascular diseases i.e. ischemic heart disease, hypertension, heart failure, and diabetes mellitus. Obtainable evidence in this regard is not very convincing, yet its role cannot be totally annulled. In this article we will make an endeavor to find out vitamin D's role in heart diseases.

Introduction

Vitamin D truly is not a vitamin, it is actually a pro-hormone. Vitamin D_3 is produced from sun exposure i.e. Ultra Violet radiation in the skin from 7-dehydrocholesterol. This is converted to 25-hydroxyvitamin D_3 (25(OH)D3]) in the liver and then to active form 1 ,25-dihydroxyvitaminD_3 (1,25(OH)2D3) in the kidney.[1] Unlike Vitamin D_3 which is produced by ultraviolet radiation in skin, Vitamin D_2 is produced commercially by irradiation of ergestoral from plants.[2] Like Vitamin D_3, Vitamin D_2 undergoes similar reaction in the liver and kidney to produce 25-hydroxyvitamin D_2 and 1,25-dihydroxyvitaminD_2 respectively.[2]

Vitamin D maintains plasma calcium and Phosphorous levels very tightly. Figure 1 which diagrammatically represents the way plasma calcium is maintained by vitamin D. Vitamin D maintains plasma calcium levels by three separate mechanisms firstly by absorption of calcium from the intestine, secondly by absorption of calcium from the kidney and lastly by absorbing calcium from bone. When plasma calcium is saturated then only bones get mineralized. Fall in calcium levels of plasma triggers secretion of parathyroid hormone, this along with Vitamin D increases calcium absorption from bone.[1]

Cardiovascular effect of vitamin D can be grouped in to three[3] first vitamin D maintain balance between pro and anti inflammatory cytokines.[4] Secondly vitamin D decreases apoptosis and induce endothelial cell proliferation[5] thirdly by association with Renin angiotensin aldosterone system[6] (Table 1).

Table 1: Proposed cardioprotective actions of vitamin D[7]

Suppression of the renin-angiotensin-aldosterone system and suppression of renin production
Reduced expression of mediators of myocardial hypertrophy (eg, atrial natriuretic pepetides) and growth factors that promote cell proliferation
Inhibition of proinflammatory cytokines (eg, interleukins)
Improvement in insulin resistance, endothelial dysfunction, and atherosclerosis

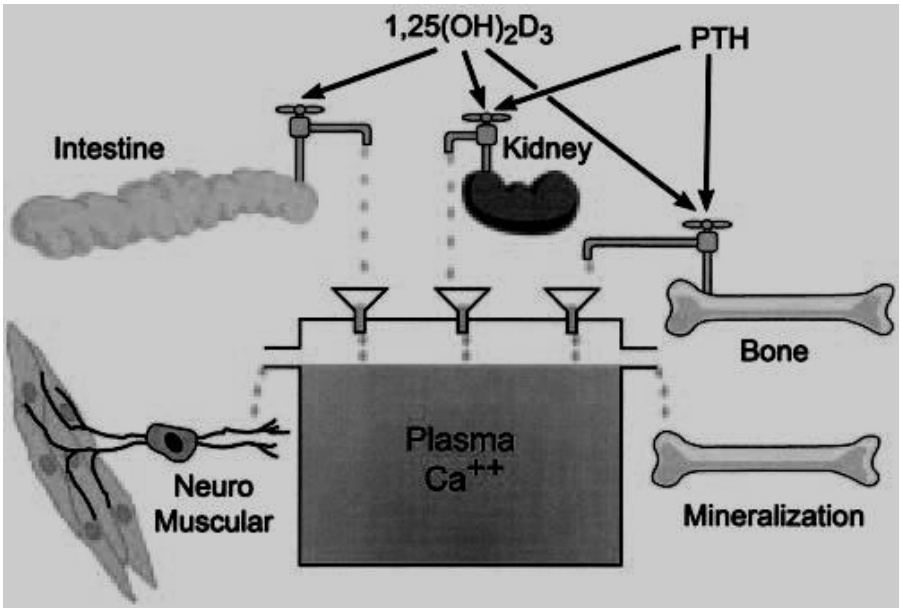

Fig. 1: Diagrammatic representation of the role of the vitamin D[1]

Measurement of Vitamin D

In clinical practice 25(OH)D is used for measuring vitamin D levels, this is because of it has longer half life, i.e. three weeks.[8,2] Cholecalciferol and 1,25(OH)2D3 have shorter half life, i.e. 24 hours and 4 to 6 hours respectively, so they are less used for measuring vitamin D.[2] Approximately 85% of 25OHD is bound to D binding protein (DBP), 15% to albumin, and 0.03% free.[9]

The measurement techniques of Vitamin D are mass spectroscopy, high performance liquid chromatography (HPLC) and immunoassay. Mass spectroscopy is used only as a reference method for other methods. HPLC methods are not used clinically because they are complex techniques. Immunoassay methods are used in routine clinical practice.[2]

The total 25(OH)D is comprised of 25(OH)D3 and 25(OH)D2. US FDA has approved tests from DiaSorin Corporation (Stillwater, MN) and IDS Ltd Tyne and Wear United Kingdom.

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Both were compared for estimation of total 25(OH)D. DiaSorin estimated total 25(OH)D more accurately because it measures both 25(OH)D3 and 25(OH) D2, but IDS underestimated total 25(OH)D because it underestimated 25(OH)D2.[10]

Vitamin D deficiency is defined as 25(OH)D3 of less than 11 ng/ml (20 nmol/L) and levels of 25(OH)D3 between 11 to 20ng/ml (20 to 50 nmol/L) is termed vitamin D insufficiency.[11]

Effect of Vitamin D on Lipids

In contrast to Interventional studies all cross-sectional observational studies have shown that low serum 25(OH)D is associated with dyslipidemia. Higher 25(OH)D level is positively associated with high-density lipoprotein cholesterol (HDL-C) resulting in a favourable low-density lipoprotein cholesterol (LDL-C) (or total cholesterol) to HDL-C ratio.[12,13] But Interventional Randomized Control Trials have shown contradictory results. In a meta-analysis of 12 randomized controlled trials by H, Wang et al, vitamin D supplementation lead to increased statistically significant LDL-C by 3.23 mg/dl (95% confidence interval, 0.55 to 5.90 mg/dl). There was statistically insignificant increase in Total Cholesterol 1.52 mg/dl (confidence interval -1.42 to 4.46) and a decrease in HDL-cholesterol -0.14 mg/dl (confidence interval -0.99 to 0.71) levels. Although triglyceride levels decreased -1.92 mg/dl (confidence interval -7.72 to 3.88) it was statistically not significant.[14] In a study of post menopausal women supplementation of vitamin D decreased triglyceride levels.[15] Thus contrasting results between observational and Interventional studies raises a possibility that Vitamin D may not be a causative factor of lipid abnormalities, but a marker of poor health in these high risk individuals.

Vitamin D Calcification and Atherosclerosis

The heart contracts during systole, ejected blood enters the highly elastic aorta, which distends and stores the potential energy, this stored potential energy is released during diastole thus highly elastic aorta function as energy store, this function is known as Windkessel physiology.[16] When vessels get calcified elasticity of vessels reduces leading to decreased storage of potential energy. This increases the work load on heart leading to heart failure, isolated systolic hypertension, and left ventricular hypertrophy.

Coronary artery calcification also leads to coronary artery disease.[17] Calcification of coronary arteries restrict the diastole, depending on the size and foci of calcification physical properties of atherosclerotic plaque change.[18] Spotty calcification is associated with Acute coronary syndrome whereas extensive calcification is associated with stable angina.[19]

It is well known that hypervitaminosis D increase vascular calcification. But even a low vitamin D levels lead to vascular calcification. Actions of vitamin D are inhibition of processes that are important for intimal and medial artery calcification such as pro-inflammatory cytokine release, adhesion molecule release, and proliferation and migration of vascular smooth muscle cells.[20] These functions are impaired in vitamin D deficiency thus leading vascular calcification. In a study of 195 men aged between 40 to 49 years, coronary artery calcification was 3.31 times likely to be with vitamin D deficient, after adjusting for traditional cardiovascular risk factors (odds ratio [OR] = 3.31, 95% confidence interval [CI], 1.12-9.77).[21]

Vitamin D receptor

Most of the biological actions of vitamin D are exerted through the nuclear vitamin D receptor (VDR). VDR acts as a ligand inducible transcription factor.[22] Level of VDR expression in tissue is shown to be related to atherosclerosis in animal studies. Mice deficient of VDR are associated with systemic inflammatory disease.[23] VDR deficient mice are prone to oncogene or chemocarcinogen induced tumors, high renin hypertension, cardiac hypertrophy, and increased thrombogenicity.[24]

In Cynomolgus monkeys higher concentration of VDR was associated with decreased atherosclerosis, but vitamin D levels did not correlate. Possible explanation offered was Vitamin D may have therapeutic window above and below this window there may be deleterious effect, or vitamin D levels may be altered by atherosclerosis rather than causing it.[25]

Vitamin D and cardiovascular outcome

Association of lower vitamin D levels with increased cardiovascular morbidity and mortality is shown across many studies.[26,27] Association of vitamin D deficiency with subclinical atherosclerosis is also established in studies.[28]

Supplementation of vitamin D has a little effect on cardiovascular outcome,[29] but vitamin D3 supplementation has shown to reduce all cause of mortality in hemodialysis patients.[30]

Vitamin D and Statins

Effect of Vitamin D on statins

Clinical trials have shown contrasting results with respect to effect of vitamin D on lipid level changes by statins. Logically lower vitamin D level should increase the level of statins in serum[3] because CYP3A4 enzyme responsible for metabolism of statins is induced by vitamin D.[31]

Effect of statins on vitamin D

Effect of statins on level of vitamin D has contrasting results. Statins have pleiotropic effect such as improvement in endothelial function, stabilization of atherosclerotic plaque and inhibition of vascular inflammation and oxidative stress.[32] In a study published in Cardiovascular Drugs and Therapy rosuvastatin increased the level of 25-hydroxyvitamin D and 1, 25-dihydroxyvitamin D.[33] In another study comprising non-diabetic population with dyslipidemia, atorvastatin and rosuvastatin treatment did not make significant difference in level of Vitamin D at baseline and at 12 weeks of treatment.[34]

Vitamin D and statin induced myositis and myalgia

Around 10 to 15% of subjects on statin treatment develop myalgia. Statin is metabolized by CYP enzymes. CYP enzymes are induced by vitamin D. so in presence of vitamin D deficiency statin toxicity can occur. Serum vitamin D was lower in the 128 patients with myalgia on statin treatment than in the 493 asymptomatic on statin patients (28.7 6 1.2 vs 34.3 6 0.6 ng/mL P value less than 0.00001).[35] Further in this study continuation of statin with vitamin D supplementation reduced myalgia in 92% of subjects.[35]

In a meta-analysis of 7 studies, with 2420 statin-treated patients, plasma concentrations of Vitmain D was significantly lower in patients with

statin-associated myalgia, compared with patients not manifesting this side effect (weighted mean difference -9.41ng/mL; 95% confidence interval: -10.17 to -8.64; p<0.00001).[36]

Vitamin D and Hypertension

Angiotensinogen II levels are inversely related to the level of Vitamin D[37] Forman JP et al Compared individuals with sufficient 25(OH)D levels (more than 30.0 ng/mL) with those of insufficient (15.0 to 29.9 ng/mL) and deficient (less than 15.0 ng/mL) individuals and concluded that the latter had higher circulating Angiotensinogen two levels.[6]

Meta-analysis involving 47 trials vitamin D supplementation did not help in reduction of blood pressure.[38]

In patient with resistant hypertension intermittent high vitamin D3 supplementation did not reduce blood pressure and also left ventricular hypertrophy.[39] Long term supplementation of high dose vitamin D3 did not reduce systolic and diastolic blood pressure.[40]

Vitamin D and Heart Failure

Both liver and kidney failure are known to be associated with metabolic disease, but in heart failure this metabolic derangement is less defined. In patients referred for heart transplantation increased calciotropic hormones (calcitonin and parathyroid hormones) decreased level of vitamin D and osteopenia or osteoporosis was significantly observed, this was correlated with severity of heart failure.[41] In another study Vitamin D levels were similarly reduced in heart failure patients, in younger patients Calcium levels were reduced, levels of parathyroid hormone were increased and NT-proANP correlated inversely with Vitamin D.[42] Levels of high NT-proANP is a marker of severity of heart failure.

Heart failure patients develop decreased Vitamin D levels because of decreased exposure to UV radiation as these patients tend to lead a sedentary life style. Decreased absorption of vitamin D from the intestines occur in heart failure patients, this along with associated liver and renal diseases in these patients complicate it further.[7] Obesity associated with heart failure increases the deficiency of vitamin D because of sequestration in subcutaneous fat.[43]

Currently there are no clinical evidences to prove that supplementation of Vitamin D will have benefit in survival of heart failure patients.[44] Meta-analysis of seven randomized control trials revealed vitamin D supplementation was associated with significant decreases in the levels of tumor necrosis factor-α, C-reactive protein and parathyroid hormone but had no benefit in terms of left ventricular ejection fraction, N-terminal pro-B-type natriuretic peptide and 6-minute walk distance in chronic heart failure patients.[45]

Vitamin D and diabetes

Type 1 Diabetes

Type 1 Diabetes is due to immune mediated destruction of pancreatic islets cell. Vitamin D reduces the expression of MHC class antigen[46] and also Interleukin 6 production. It also induces antiapoptotic A20 protein and decreases transducing apoptotic death signals.[47]

Epidemiological studies have found higher incidence of Type 1 diabetes in subjects living at higher latitudes (at higher latitude UV radiation decreases).[48] Animal studies have demonstrated that progression to Type1 Diabetes was halted by analogues of vitamin D after initiation of autoimmune attack on pancreas.[49]

In humans observational studies with high doses of Vitamin D during first year of life has reduced type 1 diabetes incidence.[50] Cod liver oil use in early life and in third trimester reduces children's incidence of Type 1 diabetes in later life.[50]

However we do not have random controlled trials of vitamin D supplementation for prevention of type 1 diabetes.

Type 2 Diabetes

Vitamin D effects Types 2 diabetes by preventing pancreatic cell death and also by increasing calcium dependent insulin secretion.[47,51] Vitamin D deficiency increases insulin resistance by secondary hyperparathyroidism. Secondary hyperparathyroidism also leads to paradoxical increase in intracellular calcium in beta cells; this decreases glucose dependent insulin secretion, also called "calcium paradox".[52]

Vitamin D enhances insulin sensitivity by stimulating the expression of insulin receptors and/or by activating peroxisome proliferator-activated receptor-δ (PPAR- δ).[53] Vitamin D effects resistance of insulin by affecting rennin-angiotensin-aldosterone system (RAAS) levels. RAAS affects insulin resistance by NF-κB activation via NADPH oxidase.[54] Insulin resistance is also affected by intracellular calcium levels. Inflammation is thought to play important role in insulin resistance, and Vitamin D affects inflammation

Although some studies have shown no association between vitamin D3 and Type 2 DM, large population based by Third National Health and Nutrition Examination Survey (NHANES III) has shown inverse relation with vitamin D and diabetes.[55]

In women health study, vitamin D3 supplementation more than 511 IU/day had lesser incidence of diabetes than the 159 IU/day or less.[56] In Nurses' Health Study USA, vitamin D intake more than 800 IU/day had lesser incidence of diabetes as compared to 200 IU/day or less.[57] In a prospective study for 5years of 500 patients of pre-diabetics, weakly 20000 iu vitamin D supplementation, did not prevent occurrence of Diabetics, study concluded that larger study with pre-diabetics with established vitamin D deficiency is needed to make good conclusion.[58]

Along with vitamin D more than 800 IU/ day, calcium intake more than 1200mg/day was associated with 33% lesser incidence of Diabetes, as compared to calcium intake less than 600 IU/day and Vitamin D less than 400IU/day.[56]

Vitamin D, heart and kidney disease

Active form of vitamin D is produced by 1-α hydroxylase (CYP27B1) in the kidneys, which converts 25-hydroxyvitamin D to 1,25 hydroxyvitamin D. 1-α hydroxylase is deficient in kidney disease patients so active form of vitamin D becomes deficient. This leads to hypocalcaemia and secondary hyperparathyroidism and bone diseases.

Apart from bone disease in chronic kidney disease, patients are prone for other cardiac diseases like, ischemic

heart disease, hypertension, heart failure etc. vitamin D has pleiotropic actions, so supplementing active form of vitamin D is likely to benefit these patients.

Oral calcitriol an analog of vitamin D use is associated with lower mortality in nondialysis patients with chronic kidney disease.[59] Few studies have questioned vitamin D therapy's survival benefit in chronic kidney disease.[60]

Albuminuria

Paricalcitol a synthetic analog of vitamin D is shown to lower urine protein/creatinine ratios and lower PTH levels.[61] In another small study Paricalcitol demonstrated reduction of high-sensitivity C-reactive protein levels and 24-hour albumin excretion.[62]

In patients with diabetic nephropathy addition of 2 µg/day Paricalcitol along with RAAS inhibition reduced residual microalbuminuria.[63]

Hypertension

Chronic kidney disease patients develop hypertension due activation of RAAS. Vitamin D is known to have inhibitory affect on RAAS. It is expected that supplementing vitamin D or its analog should reduce blood pressure, but studies in this affect are notwithstanding.[64] An ongoing study may throw some light on this.[65]

Cardiovascular mortality

In hemodialysis patients low level of vitamin D was associated with increased mortality, and patients who received vitamin D supplements had lesser mortality than those who did not receive.[66]

ViDA study is expected to publish it's results in the year 2016, its data collection is completed in the year 2015. This study may answer cardiovascular outcome with vitamin D supplementation. In this study once a month 1,00,000 iu vitamin D is used.[67]

Recommendation and Contradiction of Vitamin D Supplementation

Recommendation of Vitamin D dose

Institute of Medicine (IOM) has advised 600 IU/day for adults aged 50-70 and 800 IU/day for adults aged >70 years.[68] These recommendations correspond to serum level 25(OH)D of 50 nmol/L, and is sufficient to maintain bone health in 97% of individuals. But for prevention of cancer, falls, fractures, physical functioning, and dental health, these recommendations may not be sufficient, in a review by Bischoff-Ferrari et al advantages of 25(OH)D were found at serum level of 75nmol/L and optimum level was 90nmol/L.[69] In older individuals 800-1000IU of Vitamin D supplementation is needed to maintain serum 25(OH) D level of 75nmol/L.[70]

People in temperate zones are less exposed to UV radiations; black complexion people produce lesser amount of vitamin D, and use of sunscreen, decreased outdoor physical activity, obesity all these lead to lower production of vitamin D. These factors are to be kept in mind before prescribing vitamin D.

Calcium supplementation

Calcium supplementation more than 1Gram/day in healthy postmenopausal women was associated increased incidence of vascular events.[71] Calcium supplementation along with vitamin D supplementation is associated with increased incidence of renal stones.[72]

Contradiction between Observational and Interventional Studies

Observational studies have demonstrated the association of deficiency of vitamin D with ischemic heart disease, heart failure, hypertension, and increased cardiac mortality. Apart from increased cardiac events, vitamin D deficiency is also associated with multiple sclerosis, repeated falls and cancer. But interventional studies supplementing vitamin D have not been very conclusive in demonstrating improvement in outcome. This kind of contradiction between deficiency and supplementation leads to suspicion "whether vitamin D has any role in causation of above mentioned disorders or just a poor health marker". VDR is present in most of cells apart from bone, and human genome has many sites which are responsive to VDR, these points towards possibility of pleiotropic effects of vitamin D apart from calcium and bone health.

Women's health initiative study failed to demonstrates benefits of vitamin D3 supplementation in ischemic heart disease, heart failure, and cancer reduction.[73] In this study interventional arm received Calcium carbonate 1000mg/day and 400IU/day of vitamin D. IOM recommended vitamin D3 dose is 600IU/day for age below 70 years and 800 IU/day for age above 80 years.[68] For extra bone benefits of vitamin D serum level of 25(OH)D is 75 to 90nmol/L. To achieve this higher concentration Vitamin D3 should be given at dose of 800-1000IU/day. In women health initiative study mean level of 25(OH) D achieved in interventional arm was 54.1nmol/L below the expected extra bone benefits.[74] Further calcium supplementation along with vitamin D could have worsened the cardiovascular out come.[75]

In a meta-analysis, vitamin D3 supplementation unlike Vitamin D2 had favorable outcomes for cancer reduction>[76] So this could be one more reason for failure of vitamin D supplementation to show benefits in clinical trials. Vitamin D3 increases serum level of 25(OH) D 1.7 times for equimolar supplementation of vitamin D2[77] but other studies have much higher potency of vitamin D3 i.e. 4 to 5 times.[78]

VITAL Study[74]

Vitamin D and OmegA-3 Trial (VITAL) is ongoing large double-blind, placebo-controlled, randomized study with 2×2 factorial trial. Vitamin D3 [cholecalciferol], 2000 IU/day) and marine omega-3 fatty acid (Omacor® fish oil, eicosapentaenoic acid [EPA] + docosahexaenoic acid [DHA], 1 g/day) are supplemented. The primary sponsor of this study is the National Cancer Institute, and the secondary sponsor is the National Heart, Lung and Blood Institute.

The primary aim of this study is to examine whether supplementation of omega 3 fatty acids or vitamin D reduces cancer and vascular events, i.e. composite end points of stroke, myocardial infarction and cardiovascular mortality.

The secondary aim of this study is to examine site specific cancer occurrence, i.e. prostate (in men), breast (in women) and colorectal cancer. Expanded composite end points are Myocardial Infarction, stroke, coronary artery bypass, percutaneous coronary intervention, cardiovascular mortality and individual cardiovascular primary end points.

Tertiary endpoint is whether vitamin D and Omega 3 fatty supplementation

combination has any synergistic benefits on cancer and cardiovascular outcome.

More than 20000 American citizens are included in this study. Included should not have ACS, stroke, TIA CABG or PCI during enrollment into study. Participants apart from vitamin D supplements given from the study design should not take vitamin D more than 800 IU/day. Calcium consumption should not be more than 1200mg/day.

Following conditions are excluded from study renal failure or dialysis, hypercalcemia, hypo- or hyperparathyroidism, severe liver disease (cirrhosis), or sarcoidosis or other granulomatous diseases such as active chronic tuberculosis or Wegener's granulomatosis.

Follow-up period is five years. Trial started in the year 2010. Still the results are awaited. This trial has sufficient power to answer most question related Vitamin D 3 and omega 3 fatty acids

Vitamin D Toxicity

The normal 25(OH)D level is 25 to 200.[79] Vitamin D toxicity is surrounded by many controversies. Institute of medicine has set upper safe limit of vitamin D supplementation as 2000 IU/day. Hypercalcemia is sign of vitamin D toxicity. Perhaps the better is hypercalciuria. Sun exposure produces 10000 IU/day of vitamin D, so there is wide safety margin of upper safe limit Vitamin D supplementation i.e. 2000 IU/day and is sun exposure produced 10000 IU/day in subjects less exposed to sun. The incremental consumption 40 IU/day of vitamin D increases 1 nmol of 25(OH)D.[80]

The vitamin D toxicity is function free 1,25(OH)D, elevated free 1,25(OH) D plays measure role in vitamin D toxicity and hypercalcemia.[81]

Conclusion

Association of vitamin D deficiency with ischemic heart disease, hypertension, heart failure, and diabetes is shown by many observational studies, but evidence of supplementing of vitamin D, showing benefit in outcome by random control studies is lacking. This contraction could be due to under powered studies, dose of vitamin D used, associated calcium supplementation, and type of vitamin D i.e. less potent vitamin D2 versus more potent vitamin D3.

Lack of evidence from random control trials also suggest possibility of vitamin D being an innocent marker of poor health rather than the causative agent, but VDR receptor is present in most of cells which suggest role of vitamin D in extra bone and calcium metabolism.

Well designed, enough powered and rightly dosed Vitamin D Vital study and ViDA study may come out with results to prove or disprove benefits of vitamin D supplementation.

As on date before totally disbanding vitamin D supplementation from cardiology practice one has to look at available evidence of reduction of all cause mortality at least in hemodialysis patients.[66]

References

1. DeLuca HF. Overview of general physiologic features and functions of vitamin D. *Am J Clin Nutr* 2004; 80(6 Suppl):1689S – 96S.
2. Wootton AM. Improving the measurement of 25-hydroxyvitamin D. *Clin Biochem Rev* 2005; 26:33–6.
3. Pérez-Castrillón JL, Abad Manteca L, Vega G, et al. Vitamin D levels and lipid response to atorvastatin. *Int J Endocrinol* 2010; 320721.
4. Schleithoff SS, Zittermann A, Tenderich G, et al. Vitamin D supplementation improves cytokine profiles in patients with congestive heart failure : a double-blind , randomized. *Am J Clin Nutr* 2006; 83:754–9.
5. Xiang W, He X, Ma Y, et al. 1,25(OH)(2)D(3) influences endothelial cell proliferation, apoptosis and endothelial nitric oxide synthase expression of aorta in apolipoprotein E-deficient mice. *Zhonghua Er Ke Za Zhi* 2011; 49:829–33.
6. Forman JP, Williams JS, Fisher NDL. Plasma 25-hydroxyvitamin D and regulation of the renin-angiotensin system in humans. *Hypertension* 2010; 55:1283–8.
7. Patel R, Rizvi AA. Vitamin D deficiency in patients with congestive heart failure: mechanisms, manifestations, and management. *South Med J* 2011; 105:325–30.
8. Holick MF. ISymposium for Vitamin D and its Metabolites1Â « 2. 1990;(July):1464–9.
9. Bikle DD, Gee E, Halloran B, et al. Assessment of the Free Fraction of 25-Hydroxyvitamin D in Serum and Its Regulation by Albumin and the Vitamin D-Binding Protein. *J Clin Endocrinol Metab* 1986; 63:954–9.
10. Hollis BW. Comparison of commercially available (125) I-based RIA methods for the determination of circulating 25-hydroxyvitamin D. *Clin Chem* 2000; 46:1657–61.
11. Malabanan A, Veronikis IE, Holick MF. Redefining vitamin D insufficiency. *The Lancet* 1998; 351:805–6.
12. Jorde R, Grimnes G. Vitamin D and metabolic health with special reference to the effect of vitamin D on serum lipids. *Prog Lipid Res* 2011; 50:303–12.
13. Ponda MP, Huang XX, Odeh MA, et al. Vitamin D May Not Improve Lipid Levels: A Serial Clinical Laboratory Data Study. *Circulation* 2012 Jun 20.
14. Wang H, Xia N, Yang Y, et al. Influence of vitamin D supplementation on plasma lipid profiles: a meta-analysis of randomized controlled trials. *Lipids Health Dis* 2012; 11:42.
15. Munoz-Aguirre P, Flores M, Macias N, et al. The effect of vitamin D supplementation on serum lipids in postmenopausal women with diabetes: A randomized controlled trial. *Clin Nutr* 2015; 34:799–804.
16. Demer LL, Tintut Y. Vascular calcification: pathobiology of a multifaceted disease. *Circulation* 2008; 117:2938–48.
17. Wayhs R, Zelinger A, Raggi P. High coronary artery calcium scores pose an extremely elevated risk for hard events. *J Am Coll Cardiol* 2002; 39:225–30.
18. Wang L, Jerosch-Herold M, Jacobs DR, et al. Coronary artery calcification and myocardial perfusion in asymptomatic adults: the MESA (Multi-Ethnic Study of Atherosclerosis). *J Am Coll Cardiol* 2006; 48:1018–26.
19. Ehara S, Kobayashi Y, Yoshiyama M, et al. Spotty calcification typifies the culprit plaque in patients with acute myocardial infarction: an intravascular ultrasound study. *Circulation* 2004; 110:3424–9.
20. Schleithoff SS, Koerfer R. Vitamin D and vascular calcification. *Curr Opin Lipidol* 2007; 18:41–6.
21. Lee S, Ahuja V, Masaki K, Evans RW, Barinas-Mitchell EJM, Ueshima H, et al. A Significant Positive Association of Vitamin D Deficiency with Coronary Artery Calcification among Middle-aged Men: For the ERA JUMP Study. *J Am Coll Nutr* 2016; 1–7.
22. Kato S. The Function of Vitamin D Receptor in Vitamin D Action. *J Biochem* 2000; 127:717–22.
23. Zwerina K, Baum W, Axmann R, et al. Vitamin D receptor regulates TNF-mediated arthritis. *Ann Rheum Dis* 2011; 70:1122–9.
24. Bouillon R, Carmeliet G, Verlinden L, et al. Vitamin D and human health: lessons from vitamin D receptor null mice. *Endocr Rev* 2008; 29:726–76.
25. Schnatz PF, Nudy M, David M, et al. Coronary Artery Vitamin D Receptor Expression and Plasma Concentrations of Vitamin D: Their Association with Atherosclerosis 2013; 19:967–73.
26. Wang TJ, Pencina MJ, Booth SL, et al. Vitamin D deficiency and risk of cardiovascular disease. *Circulation* 2008; 117:503–11.
27. Grandi NC, Breitling LP, Brenner H. Vitamin D and cardiovascular disease: systematic review and meta-analysis of prospective studies. *Prev Med (Baltim)* 2010; 51:228–33.
28. Carrelli AL, Walker MD, Lowe H, et al. Vitamin D deficiency is associated with subclinical carotid atherosclerosis: the Northern Manhattan study. *Stroke* 2011; 42:2240–5.
29. Elamin MB, Abu Elnour NO, Elamin KB, et al. Vitamin D and cardiovascular outcomes: a systematic review and meta-analysis. *J Clin Endocrinol Metab* 2011; 96:1931–42.
30. Philippe AM, Sara GP. Vitamin D Supplementation and Total Mortality. *Arch Intern Med* 2007; 167:1730–7.
31. Thummel KE, Brimer C, Yasuda K, et al. Transcriptional control of intestinal cytochrome P-4503A by 1alpha,25-dihydroxy vitamin D3. *Mol Pharmacol* 2001; 60:1399–406.
32. Athyros VG, Kakafika AI, Tziomalos K, et al. Pleiotropic effects of statins--clinical evidence. *Curr Pharm Des* 2009; 15:479–89.
33. Yavuz B, Ertugrul D, Cil H, et al. Increased Levels of 25 Hydroxyvitamin D and 1,25-Dihydroxyvitamin D After Rosuvastatin Treatment: A Novel Pleiotropic Effect of Statins? *Cardiovasc Drugs Ther* 2009; 23:295–9.
34. Anagnostis P, Adamidou F, Slavakis A, et al. Comparative Effect of Atorvastatin and Rosuvastatin on 25-hydroxy-Vitamin D Levels in Non-diabetic Patients with Dyslipidaemia: A Prospective Randomized Open-label Pilot Study. *Open Cardiovasc Med J* 2014; 55–60.
35. Ahmed W, Khan N, Glueck CJ, et al. Low serum 25 (OH) vitamin D levels (<32 ng/mL) are associated with reversible myositis-myalgia in statin-treated patients. *Transl Res* 2009; 153:11–6.
36. Michalska-Kasiczak M, Sahebkar A, Mikhailidis DP, et al. Analysis of vitamin D levels in patients with and without statin-associated myalgia - a systematic review and meta-analysis of 7 studies with 2420 patients. *Int J Cardiol* 2015; 178:111–6.
37. Ajabshir S, Asif A, Nayer A. The effects of vitamin D on the renin-angiotensin system. *J Nephropathol* 2014; 3:41–3.
38. 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; 175:745–54.
39. Witham MD, Ireland S, Houston JG, et al. Vitamin D Therapy to Reduce Blood Pressure and Left Ventricular Hypertrophy

in Resistant Hypertension: Randomized, Controlled Trial. *Hypertens* 2014; 63:706–12.

40. Scragg R, Slow S, Stewart AW, et al. Long-Term High-Dose Vitamin D3 Supplementation and Blood Pressure in Healthy Adults: A Randomized Controlled Trial. *Hypertens* 2014; 64:725–30.
41. Shane E, Mancini D, Aaronson K, et al. Bone Mass, Vitamin D Deficiency, and Hyperparathyroidism in Congestive Heart Failurefn1. *Am J Med* 1997; 103:197–207.
42. Zittermann A, Schleithoff SS, Tenderich G, et al. Low vitamin D status: a contributing factor in the pathogenesis of congestive heart failure? *J Am Coll Cardiol* 2003; 41:105–12.
43. Wortsman J, Matsuoka LY, Chen TC, et al. Decreased bioavailability of vitamin D in obesity. *Am J Clin Nutr* 2000; 72:690–3.
44. Hajjar V, Depta JP, Mountis MM. Q: Does vitamin D deficiency play a role in the pathogenesis of chronic heart failure? Do supplements improve survival? *Cleve Clin J Med* 2010; 77:290–3.
45. Jiang W-L, Gu H-B, Zhang Y-F, et al. Vitamin D Supplementation in the Treatment of Chronic Heart Failure: A Meta-analysis of Randomized Controlled Trials. *Clin Cardiol* 2016; 39:56–61.
46. Hahn JH, Kuttler B, Mathieu C, et al. 1,25-Dihydroxyvitamin D3 reduces MHC antigen expression on pancreatic beta-cells in vitro. *Transplant Proc* 2014; 29:2156–7.
47. Riachy R, Vandewalle B, Moerman E, et al. 1,25-dihydroxyvitamin D3 protects human pancreatic islets against cytokine-induced apoptosis via down-regulation of the fas receptor. *Apoptosis* 2006; 11:151–9.
48. Mohr SB, Garland CF, Gorham ED, et al. The association between ultraviolet B irradiance, vitamin D status and incidence rates of type 1 diabetes in 51 regions worldwide. *Diabetologia* 2008; 51:1391–8.
49. Harinarayan CV. Vitamin D and diabetes mellitus. *Hormones (Athens)* 2014; 13:163–81.
50. Zipitis CS, Akobeng a K. Vitamin D supplementation in early childhood and risk of type 1 diabetes: a systematic review and meta-analysis. *Arch Dis Child* 2008; 93:512–7.
51. Norman AW. Vitamin D Receptor: New Assignments for an Already Busy Receptor. *Endocrinology* 2006; 147:5542–8.
52. Fujita T, Palmieri GM a. Calcium paradox disease: Calcium deficiency prompting secondary hyperparathyroidism and cellular calcium overload. *J Bone Miner Metab* 2000; 18:109–25.
53. 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; 349:248–60.
54. Wei Y, Sowers JR, Clark SE, et al. Angiotensin II-induced skeletal muscle insulin resistance mediated by NF-kappaB activation via NADPH oxidase. *Am J Physiol Endocrinol Metab* 2008; 294:E345–51.
55. Robert Scragg PMS. Serum 25-Hydroxyvitamin D, Diabetes, and Ethnicity in the Third National Health and Nutrition Examination Survey. *Diabetes Care* 2004; 27:2813–8.
56. Liu S, Song Y, Ford ES, et al. Dietary Calcium, Vitamin D, and the Prevalence of Metabolic Syndrome in Middle-Aged and Older U.S. Women. *Diabetes Care* 2005; 28:2926–32.
57. Pittas AG, Dawson-Hughes B, Li T, et al. Vitamin D and Calcium Intake in Relation to Type 2 Diabetes in Women. *Diabetes Care* 2006; 29:650–6.
58. Jorde R, Sollid ST, Svartberg J, et al. Vitamin D 20 000 IU per Week for Five Years Does Not Prevent Progression From Prediabetes to Diabetes. *J Clin Endocrinol Metab* 2016; 101:1647–55.
59. Shoben AB, Rudser KD, de Boer IH, et al. Association of oral calcitriol with improved survival in nondialyzed CKD. *J Am Soc Nephrol* 2008; 19:1613–9.
60. Tentori F, Albert JM, Young EW, et al. The survival advantage for haemodialysis patients taking vitamin D is questioned: findings from the Dialysis Outcomes and Practice Patterns Study. *Nephrol Dial Transplant* 2009; 24:963–72.
61. Fishbane S, Chittineni H, Packman M, et al. Oral Paricalcitol in the Treatment of Patients With CKD and Proteinuria: A Randomized Trial. *Am J Kidney Dis* 2009; 54:647–52.
62. 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; 52:249–55.
63. de Zeeuw D, Agarwal R, Amdahl M, et al. Selective vitamin D receptor activation with paricalcitol for reduction of albuminuria in patients with type 2 diabetes (VITAL study): a randomised controlled trial. *Lancet* 2010; 376:1543–51.
64. Moe SM, Saifullah A, LaClair RE, et al. A randomized trial of cholecalciferol versus doxercalciferol for lowering parathyroid hormone in chronic kidney disease. *Clin J Am Soc Nephrol* 2010; 5:299–306.
65. Thadhani R, Appelbaum E, Chang Y, et al. Vitamin D Receptor Activation and Left Ventricular Hypertrophy in Advanced Kidney Disease. *Am J Nephrol* 2011; 33:139–49.
66. Wolf M, Shah A, Gutierrez O, et al. Vitamin D levels and early mortality among incident hemodialysis patients. *Kidney Int* 2007; 72:1004–13.
67. Scragg R, Waayer D, Stewart AW, et al. The Vitamin D Assessment (ViDA) Study: design of a randomized controlled trial of vitamin D supplementation for the prevention of cardiovascular disease, acute respiratory infection, falls and non-vertebral fractures. *J Steroid Biochem Mol Biol* 2015.
68. Ross AC, Manson JE, Abrams SA, et al. The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know. *J Clin Endocrinol Metab* 2011; 96:53–8.
69. Bischoff-ferrari HA, Giovannucci E, Willett WC, et al. Estimation of optimal serum concentrations of 25-hydroxyvitamin D for multiple health outcomes 1 – 3. *Am J Clin Nutr* 2006; 25:18–28.
70. Dawson-Hughes B, Heaney R, Holick M, et al. Estimates of optimal vitamin D status. *Osteoporos Int* 2005; 16:713–6.
71. Bolland MJ, Barber PA, Doughty RN, et al. Vascular events in healthy older women receiving calcium supplementation: randomised controlled trial. *BMJ* 2008; 336:262–6.
72. Wactawski-wende J, Kotchen JM, Anderson GL, et al. Calcium plus Vitamin D Supplementation and the Risk of Colorectal Cancer. *N Engl J Med* 2006; 354:684–96.
73. Prentice RL, Pettinger MB, Jackson RD, et al. Health risks and benefits from calcium and vitamin D supplementation: Women's Health Initiative clinical trial and cohort study. *Osteoporos Int* 2013; 24:567–80.
74. Manson JE, Bassuk SS, Lee I, et al. The VITamin D and OmegA-3 TriaL (VITAL): Rationale and Design of a Large Randomized Controlled Trial of Vitamin D and Marine Omega-3 Fatty Acid Supplements for the Primary Prevention of Cancer and Cardiovascular Disease. *Contemp Clin Trials* 2013; 33:159–71.
75. Bolland MJ, Grey A, Avenell A, et al. Calcium supplements with or without vitamin D and risk of cardiovascular events: reanalysis of the Women's Health Initiative limited access dataset and meta-analysis. *BMJ* 2011; 342:d2040.
76. Chowdhury R, Kunutsor S, Vitezova A, et al. Vitamin D and risk of cause specific death: systematic review and meta-analysis of observational cohort and randomised intervention studies. *BMJ* 2014; 348:g1903.
77. Trang HM, Cole DEC, Rubin LA, et al. Evidence that vitamin D 3 increases serum 25-hydroxyvitamin D more efficiently than does vitamin D 21–3. *Am J Clin Nutr* 1998; 68:854–8.
78. Houghton LA, Vieth R. The case against ergocalciferol (vitamin D2) as a vitamin. *Am J Clin Nutr* 2006; 84:694–7.
79. Jones G. Pharmacokinetics of vitamin D toxicity 1 – 4. *Am J Clin Nutr* 2008; 88(suppl):582s–586s.
80. Vieth R. Vitamin D toxicity, policy, and science. *J Bone Miner Res* 2007; 22 Suppl 2:V64–8.
81. Pettifor JM, Bikle DD, Cavaleros M, et al. Serum Levels of Free 1,25-Dihydroxyvitamin D in Vitamin D Toxicity. *Ann Intern Med* 1995; 122:511–3.