Vitamin D and Cardiovascular System
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Vitamins are organic compounds essential for growth, maintenance of health and body metabolism. As vitamins are not synthesized in body they have to be supplied in food or as supplements. Many vitamins have been studied in relation to heart. Importance of some vitamins in relation to cardiovascular system are clear e.g. thiamine deficiency leading to beri beri and heart failure. Importance of Vitamin E was controversial for some time but most of studies have now shown that vitamin E supplements have no benefits on cardiovascular or all cause mortality. In fact meta analysis of 19 clinical trials (which included 135,967 patients) showed that vitamin E supplements >400 IU/d may increase mortality and should be avoided (1). There was no cardiovascular benefit from Vitamin E supplementation in well organized study of aspirin and vitamin E supplementation which included 4495 patients both male and female and was followed for 3.6 years (2).

Recently interest has developed in Vitamin D being beneficial for cardiovascular diseases. This vitamin has been usually been associated with bones and calcium metabolism and it is well understood that vitamin D deficiency leads to rickets in children and osteomalacia and osteoporosis in adults (3). Vitamin D receptors (VDR) are widely distributed in cardiac myocytes, pancreatic beta- cells, neurons, vascular endothelial cells, immune cells in addition to being present on osteoblasts(3). So it is evident that vitamin D can have its effects on many other organs in addition to bones. Many recent studies have shown vitamin D deficiency has important role in hypertension (4), cardiac failure (5) coronary heart disease (6) and diabetes. Vitamin D deficiency seems to predispose to hypertension, diabetes and the metabolic syndrome, left ventricular hypertrophy, congestive heart failure, and chronic vascular inflammation (3,7).

Vitamin D status was assessed in 1739 Framingham Offspring Study participants in a longitudinal study. They found Vitamin D deficiency is associated with incident cardiovascular disease. There was a graded increase in cardiovascular risk across categories of 25-OH D, with multivariable-adjusted hazard ratios of 1.53 (95% confidence interval 1.00 to 2.36) for levels 10 to <15 ng/mL and 1.80 (95% confidence interval 1.05 to 3.08) for levels <10 ng/mL (P for linear trend=0.01). Further adjustment for C-reactive protein, physical activity or vitamin use did not affect the findings (8).

A prospective case control study of 18,225 men in the Health Professionals Follow-up Study was conducted in which male health professionals showed a 2-fold risk of myocardial infarction (MI) in subjects who were vitamin D deficient compared with those in the sufficient range (9).

The prevalence of vitamin D deficiency increases in proportion to distance from the equator because of oblique angles of the sun’s rays at higher latitudes which leads to atmospheric filtering of UVB radiation. Additionally, ethnic groups with darker skin require proportionally more sun exposure to synthesize equivalent amounts of vitamin D compared with white skinned ethnic group. Studies have reported higher rates of coronary heart disease and hypertension with increasing distance from the equator (10,16).

The relationship between CV risk factors and 25(OH)D levels was explored recently among the 15,088 (7186 males and 7902 females) 20 years and older subjects from
the Third National Heath And Nutrition Examination Survey (NHANES III) national cohort registry. In this cross-sectional study, 25(OH)D levels were inversely associated with hypertension, diabetes mellitus, hypertriglyceridemia, and obesity (11). Similarly, a prospective cohort study measured the vitamin D levels in 3,258 male and female German adults with mean age of 62 years who were undergoing elective cardiac catheterization. Mean follow up was for 7.7 years. Subjects in the lowest quartile for baseline serum 25-hydroxyvitamin D [25(OH)D] had a risk-adjusted 2-fold increased risk of death, especially CV death, compared with those in the highest quartile of vitamin D (12).

Vitamin D has influence on hypertension. It effects renin angiotensin aldosterone system (RAAS) thus blood pressure. Experimental studies in knockout mice confirm that the absence of vitamin D receptor activation leads to tonic up-regulation of the renin-angiotensin system, with the development of hypertension and left ventricular hypertrophy (13). Even clinical studies have shown relationship between vitamin D levels and plasma rennin activity in hypertension. (14). In a study of 100 normotensive male industrial employees with systolic blood pressure and diastolic blood pressure being main outcome measures after possible confounders were controlled for, multivariate analyses yielded an inverse, independent, and statistically significant association between calcitriol level and systolic blood pressure. A similar trend was found for the association between calcitriol and diastolic blood pressure although of borderline significance. There is an inverse association between serum calcitriol level and blood pressure. This suggests that in addition to its role in calcium homeostasis, the active metabolite of vitamin D may play a role in determining blood pressure. (15)

Additionally, ecological studies have reported higher rates of coronary heart disease and hypertension with increasing distance from the equator, a phenomenon that has been attributed to the higher prevalence of vitamin D deficiency in regions with less exposure to sunlight. (16, 17)

In view of previous reports Hsia et al randomized 36 282 postmenopausal healthy women 50 to 79 years of age at 40 clinical sites to calcium carbonate 500 mg with vitamin D 200 IU twice daily or to placebo. Cardiovascular disease was a prespecified secondary efficacy outcome. Patients were followed for 7 years. They found that calcium and vitamin D supplementation neither increased nor decreased coronary or cerebrovascular risk in this cohort. Possible explanations for negative results they say were multiple (18). a) Trial was carried out to assess the effect on fractures and not cardiovascular outcome. b) Vitamin D dosage was inadequate. c) Patients were on concurrent hormone therapy. d) Poor adherence to medication and background calcium use.

Increased levels of 25 hydroxyvitamin D and 1, 25-Dihydroxyviamin D were seen after treatment with rosuvastatin therapy which could be a novel pleotropic effect of rosuvastatin and possible mechanism of benefits of rosuvastatin (19). Another study evaluated the possible effect of atorvastatin on vitamin D levels in patients with acute ischemic heart disease. Eighty-three patients (52 men and 31 women) with an acute coronary syndrome (75 with acute myocardial infarction and 8 with unstable angina) were included. It was found that atorvastatin increases vitamin D levels. This increase could explain some of the beneficial effects of atorvastatin that are unrelated to cholesterol levels (20).
Recently a study including 1,61,808 participants from the Women's Health Initiative clinical trials (68,132 subjects in 3 overlapping trials of hormone therapy, dietary modification, and calcium and vitamin D supplements) and an observational study (93,676 subjects). Detailed data were collected on multivitamin use at baseline and follow-up time points. Study enrollment occurred between 1993 and 1998; the women were followed up for a median of 8.0 years in the clinical trials and 7.9 years in the observational study. Disease end points were collected through 2005. The Women's Health Initiative study concluded that multivitamin use has little or no influence on the risk of common cancers, CVD, or total mortality in postmenopausal women (21).

Another study in U.S. tested the association of low 25(OH)D levels with all-cause, cancer, and cardiovascular disease (CVD) mortality in 13,331 nationally representative adults 20 years or older from the Third National Health and Nutrition Examination Survey (NHANES III) linked mortality files. Participant vitamin D levels were collected from 1988 through 1994, and individuals were passively followed for mortality through 2000. The lowest quartile of 25(OH)D level (<17.8 ng/mL) was independently associated with all-cause mortality in the general population (22).

How vitamin D deficiency mediates accelerated cardiovascular disease in patients with diabetes mellitus, was investigated by studying effects of active vitamin D on macrophage cholesterol deposition. Macrophages were obtained from 76 obese, diabetic, hypertensive patients with vitamin D deficiency (25-hydroxyvitamin D <80 nmol/L; group A) and 4 control groups obese, diabetic, hypertensive patients with normal vitamin D (group B; n=15). Results identify reduced vitamin D receptor signaling as a potential mechanism underlying increased foam cell formation and accelerated cardiovascular disease in diabetic subjects. (23)

In a study conducted in Germany 25-hydroxyvitamin D [25(OH)D] levels were measured in 3299 Caucasian patients who were routinely referred to coronary angiography. It was found that low levels of 25(OH)D and 1,25-dihydroxyvitamin D are associated with prevalent myocardial dysfunction, deaths due to heart failure, and sudden cardiac death (SCD) (24)

A new observational study by Dr Tami L Bair (Intermountain Medical Center, Murray, UT) was reported at the American Heart Association 2009 Scientific Sessions. Bair and colleagues followed more than 27,000 people 50 years or older with no history of cardiovascular disease for just over a year and found that those with very low levels of vitamin D (<15 ng/mL) were 77% more likely to die, 45% more likely to develop coronary artery disease, and 78% more likely to have a stroke than those with normal levels (>30 ng/mL). Those deficient in vitamin D were also twice as likely to develop heart failure as those with normal levels. They concluded that even a moderate deficiency of vitamin D was associated with developing coronary artery disease, heart failure, stroke, and death. (25)

Fresh studies are being taken up to answer these contradictory results of previous studies regarding vitamin D and cardiovascular outcomes. Two large trials are eagerly awaited at present.

One is NIH sponsored Vitamin D and Omega-3 Trial (VITAL) study. It will study whether 2000 IU vitamin D and/or 1 g of fish oil (omega-3 fatty-acid supplementation) can reduce the risk of developing heart disease, stroke, or cancer.
in 20 000 men and women. It is supposed to begin in January 2010. For VITAL, women need to be over age 65 to enter the study; men need to be over age 60. Participants will be randomized to one of four groups: daily vitamin D (2000 IU) and fish oil (1 g); daily vitamin D and fish-oil placebo; daily vitamin-D placebo and fish oil; or daily vitamin-D placebo and fish-oil placebo.

Another is The Thiazolidinedione Intervention with Vitamin D Evaluation (TIDE) study is being coordinated by researchers at McMaster University, Hamilton, ON. This trial is looking at rosiglitazone versus pioglitazone in people with type 2 diabetes at risk of heart disease, but also has a vitamin D versus placebo arm. The primary outcome for the vitamin D arm will be cancer, but there are a number of secondary cardiovascular end points.

We hope these trials (VITAL and TIDE) will make us wiser about role of vitamin D in cardiovascular diseases.

Right now evidence in favor of vitamin D being beneficial for cardiovascular system is stronger than evidence for other vitamins. But the right advice for patients at present is to have regular exercise, decrease weight, avoid smoking and increase fresh fruit and vegetables in routine diet. It is not as of yet wise to advise vitamins for prevention of cardiac diseases as the patients overall have tendency to jump to vitamins and neglect essential medication.

References:


Conflict of Interest: None.
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