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Review Article

Recent Insights into the Role of Vitamin B12 and Vitamin D upon Cardiovascular Mortality: A Systematic Review

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Abstract

Vitamin B12 and Vitamin D insufficiency has been observed worldwide at all stages of life. It is a major public health problem, since the pathogenesis of several chronic diseases have been attributed to low concentrations of this vitamin. The present study throws light on the causal association of Vitamin B12 to cardiovascular disorders. Several evidences suggested that vitamin D has an effect in cardiovascular diseases thereby reducing the risk. It may happen in case of gene regulation and gene expression the vitamin D receptors in various cells helps in regulation of blood pressure (through renin-angiotensin system), and henceforth modulating the cell growth and proliferation which includes vascular smooth muscle cells and cardiomyocytes functioning. The present review article is based on identifying correct mechanisms and relationships between Vitamin D and such diseases that could be important in future understanding in patient and healthcare policies. There is some reported literature about the causative association between Vitamin B12 deficiency and homocysteinemia, or its role in the development of atherosclerosis and other groups of Coronary artery disease (CAD). Numerous retrospective and prospective studies have revealed a consistent, independent relationship of mild hyper-homocysteinemia with cardiovascular disease and all-cause mortality.

Keywords: Vitamin B12; Vitamin D; Cardioprotective Action; Coronary-Artery Disease (CAD); Randomized Controlled Trials

Introduction

The major function of vitamin D is related to the maintenance and development of bone tissue. It balances the calcium and phosphorus homeostasis. The low concentrations of this vitamins have been attributed to the pathogenesis of several chronic diseases with cardiovascular risk factors, such as heart failure hypertension, peripheral arterial disease and atherosclerosis. Following the discovery of the presence of vitamin D receptors (VDR) in many cells, including cardiomyocytes, vascular smooth muscle cells (VSMC) and endothelium, several mechanisms have been proposed to explain the relationship between vitamin D and the development of cardiovascular disease. This kind of mechanisms involves association of vitamin D in the Renin angiotensin - aldosterone system and escalation and growth of VSMC.

Thromboembolism is a complex disease involving multiple risk factors including environmental and genetic factors. Over a period of time many studies have exhibited that hyperhomocysteinemia is one of the factors. Cardiovascular risk rises with either folate or vitamin B12 deficiency because folate and vitamin B12 (cyanocobalamin) are closely connected with the metabolism of homocysteine and methionine. The responsiveness of these amino acids and their elevation in clinically expressed vitamin B12 and folate deficiencies is comparatively high. In the mitochondria, Vitamin B12 helps in the regulation of the methylmalonic acid (MMA) metabolism; this is folate-independent metabolic pathway. Symptomatic Vitamin B12 deficiency in most patient's serum levels of MMA are elevated.

Moreover, irregular cases with vitamin B12 deficiency and having thrombosis have been reported drawing a close relationship between thrombosis and vitamin B12. In some of these cases vitamin B12 deficiencies were due to, intestinal mal absorption pernicious anemia, poor diet, drugs, and nitrous oxide abuse. Arterial and venous thrombotic events have been demonstrated including recurrent thrombosis and unexpected sites of thromboses such as sinus venous thrombosis, spleen and kidney infarction or portal venous thrombosis.

Vitamin B12 Function [1-14]

Vitamin B12 also known as cobalamin, comprises a number of forms including deoxy adenosyl, methyl, hydroxy-cobalamin and cyano. The cyano forms are food supplements [1]. The various other forms of cobalamin can be converted to the methyl- or 5-deoxyadenosyl forms with the help of co factors for methionine synthetase and L-methyl-malonyl-CoA mutase. Methionine synthase is an essential parameter for the synthesis of pyrimidines and purines. The reaction of methyl cobalamin which is supported by a co-factor as well as on folate, therefore a methyl group of methyl tetrahydrofolate is shifted to homocysteine to form tetrahydrofolate and methionine. The deficiency of vitamin B12 leads to the cause of megaloblastic anemia and it may also be attributed to folate deficiency too [2]. Methyl malonyl CoA to succinyl CoA by methylmalonyl CoA, having 5-deoxy adenosyl cobalamin that acts as cofactor. The accumulation of methyl malonyl CoA may be responsible for certain neurological effects in vitamin B12 deficiency [2]. Vitamin B12 in serum is protein bound known as transcobalamin's (TC). Approximately 80% of the major vitamins, is transported on the inactive TCI (also called haptocorrin). Transcobalamin II (TCII) is the active transport protein for vitamin B12, approximately forms 20% of the vitamin in the entire circulation [3]. Holo-transcobalamin (holo-TC) is TCII which is connected to cobalamin, which helps in transporting vitamin B12 to cells. A low serum vitamin B12 concentration could be attributed with a TCI deficiency, therefore TCII levels and vitamin B12 remains apposite [4].

Vitamin B12 and Cardiovascular Disease (CVD) [5-18]

Nutritional risk factors for CVD includes hypertension, obesity and hypercholesterolemia. When tHcy concentrations gets elevated they are also considered a risk factor, although, it is obscure tHcy whether it an independent marker of the disease process or a modifiable risk factor. The research into CVD and tHcy is associated to the effects of folate supplementation with or without the incorporation of vitamins B12. The investigation on the interrelationship between CVD and vitamin B12 are restricted. Meta-analyses pertaining to the prospective studies have consistently shown correlations between tHcy and increased risk of CVD. Supplementation with vitamin B12 of doses ranging from 0.02-1 mg/d produces approximately 7% decrease in tHcy, while folate produces 10 - 30% decrease in risk.

Meta-analyses of studies assessing vitamin B12 and CVD [21-33].

Trial Type	Study Details	Main Outcomes
Meta-analysis	9 case-control studies. Assessed associations between tHcy and CVD risk.	5μM tHcy increment associated with increased risk ofCAD, OR = 1.6 (95% CI:1.4 to 1.7) for males and 1.8 (95% CI:1.3 to 1.9) for females.
Meta-analysis	30 prospective or retrospective studies assessed tHcy and CVD risk.	25% lower tHcy associated with lower risk of IHD and stroke.
Meta-analysis 7 RCTs	B vitamin supplementation and tHcy lowering, assessed effect of vitamin B12 (range 0.02-1.0mg/day).	Vitamin B12 (median dose 0.4 mg/d) - further decrease (-7%) in tHcy.
Meta-analysis 12 RCTs	Preexisting CVD or renal disease- included 3 studies of vitamin B12supplementation, with doses0.4-1.0 mg B12/day.	Reduction in stroke risk in vitamin B12 (1 mg/d) intervention OR = 0.76 (95% CI:0.59, 0.96).
Meta-analysis 8 RCTs	4 studies assessed vitamin B12 supplementation (0.018-1 mg) and stroke risk.	Reduction in stroke greater in longer trials with more tHcy lowering and no stroke history. No specific effect of vitamin B12.
Meta-analysis of 24 RCTs	Assessed CIMT: 3 with vitamin B12: 0.4-0.5 mg/d; endothelial function: 5 with B12: 6 μg-1 mg/day	↓ CIMT, ↑ FMD found in short-term not long term Trials.

Table 1:

Where μM: Micromolar; tHcy: Total Homocysteine; CAD: Coronary Artery Disease; OR: Odds Ratio; CI: Confidence Intervals; CVD: Coronary Vascular Disease; IHD: Ischemic Heart Disease; CIMT: Carotid Intima Media Thickness; FMD: Flow Mediated Dilation

The recent vitamin B supplementation trials related to the investigation of the effect of tHcy lowering and CVD did not exhibit the desired expectation in risk reduction of CVD. All of these randomized controlled trials (RCTs) involving vitamin B12 compensation (ranging from 6 µg-1 mg) in association with folate, otherwise it is difficult to determine the individual impact of vitamin B12. As there are limitations pertaining to these trials and are classified as insufficient for treatment with vitamin B12 as one of the limitations.

The analysis of the subgroups of VISP Trial in patients were found to have higher baseline vitamin B12 concentrations, best outcomes are with high dose of vitamins. Those with lower doses of vitamins have higher chances of stroke. Vitamin B12 has been shown to be a major determinant of tHcy concentrations in subjects with adequate folate status and the existence of vitamin B12 deficiency could be one reason for the lack of effect of intervention with folate

Basic vitamin D metabolism [34-52]

Sunlight-induced vitamin D synthesis in the skin accounts for about 80% of obtained vitamin D.5 Specifically, ultraviolet-B(UV-B) radiation induces the conversion of 7-dehydrocholesterol to provitamin D, which spontaneously isomerizes to vitamin D.6 This vitamin D production by sunlight exposure is particularly efficient in individuals with low levels of skin melanin. Therefore, an intriguing hypothesis suggests that in human evolution, those individuals migrating to northern regions developed a fair skin to efficiently synthesize vitamin D under conditions of less UV-B exposure, whereas those individuals residing in sunny regions have a high melanin content of the skin, which protects against sunlight induced damage.7,8 Diet makes a relatively small contribution tovitamin D status.1,5 Vitamin D can be obtained from natural foods(e.g. oily fish, eggs or UV-irradiated and sun-dried mushrooms), vitamin D-fortified food (e.g. vitamin D-fortified milk and orange juice in the United States) or vitamin D supplements.1 Two major forms of vitamin D exist: vitamin D3 (cholecalciferol), the main vitamin D form derived mainly from synthesis in the skin and from animal sources and vitamin D2 (ergocalciferol), the plant- and yeast-derived form. Unless otherwise stated, we do not differentiate between these two isoforms in this review and usually refer to vitamin D (meaning both vitamin D2 and D3) in general.

Conclusion

The systematic review study throws light on the causal association of Vitamin B12 to cardiovascular disorders that is already established. This review highlights studies that have suggested that vitamin D (particularly Vitamin D3) and its involvement in the etiopathogenesis of cardiovascular diseases and have provided evidence that it has a role in reducing cardiovascular disease risk. Identifying correct mechanisms and relationships between Vitamin D and such diseases could be an important element in relation to patient care and healthcare policies.

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Volume 2 Issue 12 December 2018