

Is Vitamin D a New Therapeutic Option in Coronary Artery Disease? Overview Data

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Coronary artery disease is the leading cause of death in developed countries. Despite the significant progress in pharmacological treatment and coronary revascularization techniques, the treatment results are still unsatisfactory. Up to now several risk factors have been identified in the cardiovascular system, but still much attention is focused on the discovery of new ones. Among the postulated is the vitamin D deficiency, which occurs in approx. 50% of the human population worldwide and, as suggested, may contribute to the increased incidence of cardiovascular disease [1-3]. Vitamin D acts on target cells by connecting to a specific receptor (VDR). In the human genome, approx. 3000 binding sites for the vitamin D receptor have been located [4], indicating the regulation of a large number of genes, estimated at about 3% of the human genome [2]. The vitamin D receptor present in most human tissues and cells has also been located in the cells of the cardiovascular system (endothelial cells, vascular smooth muscle cells, myocytes and fibroblasts); moreover, the ability of these cells has been proved in the autocrine and paracrine synthesis of active vitamin D metabolite regardless of the 25-hydroxycholecalciferol level in the body [5].

The main source of vitamin D in the body (80-90%) is its skin synthesis. Under the influence of ultraviolet radiation having a wavelength of 290-320 nm (UVB) 7dehydrocholesterol is converted to pre-vitamin D₃. The remaining 10-20% of vitamin D comes from food (daily diet, vitamin supplements). Regular exposure to UVB radiation increases the concentration of vitamin D levels in plasma, without risking the toxic effects of vitamin D on the body because its excessive amounts are converted into inactive isomers.

In the countries of Central Europe the dermal production of vitamin D under the influence of UVB radiation occurs from April to October. In autumn and winter the source of vitamin D is diet. Currently, recommended limits for exposure to sunlight may lead to increasing vitamin D deficiency [6]. Another reason for the growing epidemic of vitamin D deficiency is the aging population, as has been shown in the effectiveness of skin synthesis which weakens with body ageing; in people over 70 years of age it is four times lower than in young people with the same exposure to the sun [7,8]. Lower levels of vitamin D have also been reported within women [9,10] and patients with chronic kidney disease who are considered to be patients with a high cardiovascular risk. Another factor increasing the risk of inadequate levels of vitamin D is living in northern regions, the autumn and winter period, low physical activity, being in a nursing home, black skin colour, smoking, obesity, gastrointestinal malabsorption disorders, liver disease, use of glucocorticosteroids, immunosuppressants and also anti-retroviral therapy [11].

The study's findings show the vitamin D compound in the pathogenesis of coronary heart disease. The essence of atherosclerosis is the inflammation of the artery walls as a response to the damage of the vascular endothelium [12]. It has been shown that chronic treatment with the 25-hydroxycholecalciferol has a positive influence on endothelial cells by reducing the production of reactive oxygen compounds, stimulating production of superoxide dismutase [13],

increasing the endothelial activity of nitric oxide synthase [13,14], as well as protection against the glycosylation end product effects [15]. Anti-inflammatory effects are exerted through the inhibition of prostaglandin and cyclooxygenase-2 synthesis, and by stimulating the synthesis of cytokines with anti-inflammatory activity [16-19]. Further research is required for the yet unexplained effect of vitamin D on the process of calcification of the vascular wall. It has been shown that at low concentrations, it reduces the calcification of the middle and inner membrane of coronary arteries [20,21] and in high concentrations it stimulates the conversion of mesenchymal cells into osteoblasts and thereby contributes to the formation of calcifications in the central membrane of the artery [22] which leads to the stabilization of existing atherosclerotic plaques.

In the process of destabilization of the atherosclerotic plaque, the decisive role is played by a thin connective tissue cover, large lipid core, high activity of inflammatory cells and increased neovascularization [12]. In addition to the anti-inflammatory effect, vitamin D inhibits the conversion of macrophages into foam cells [23], reduces the neovascularization process by inhibiting the vascular endothelial growth factor and stimulating the apoptosis of epithelial cells, decreases the metalloproteinase activity responsible for the remodelling of the vascular wall and the cardiac muscle leading to the destabilization of atherosclerotic plaques [24-26].

The atherosclerotic plaque rupture is followed by the release of its lipid content, which initiates blood clotting [12]. The anticoagulant effect of vitamin D exerts by reducing the expression of the pro-coagulant tissue factor, increasing the anticoagulant production of thrombomodulin [27], and inhibition of platelet adhesion to vascular endothelial cells [28].

In addition, the results of recent years show an independent compound of low vitamin D levels and documented risk factors for the cardiovascular system such as hypertension [29], atherogenic lipid profile [30], diabetes [31] and obesity [32]. As shown, the deficiency of vitamin D leads to the activation of the renin-angiotensin-aldosterone system (RAAS), while high levels of vitamin D reduces the plasma renin activity, leading to a reduction of angiotensin II concentration. This leads to a reduction in blood pressure and control of inflammatory processes in the vascular endothelium, which also reduces the

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progression of atherosclerosis [29]. Particularly noteworthy is the effect of vitamin D on the lipid profile. A compound of high levels of total cholesterol and LDL-C with coronary atherosclerosis is clearly documented. It was further found that the reduction in total cholesterol and low density lipoprotein below recommended levels significantly reduces the cardiovascular risk [33,34]. Many studies show a 25(OH)D inverse relationship in serum and different cholesterol fractions [30].

The explanation for these results may be a common metabolic pathway for vitamin D and cholesterol. Both of these are formed from a single precursor - 7dehydrocholesterol. In addition, a crucial role in their synthesis is played by 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. It has been shown that the hydroxylated derivatives of vitamin D inhibit the activity of HMG-CoA [35]. In addition, the 25-hydroxycholecalciferol can inhibit CYP51A1, which also participates in the synthesis of cholesterol. A deficiency of 25-hydroxycholecalciferol increases reductase activity and raises the CYP51A1 cholesterol levels [35]. Blocking the HMG-CoA reductase is the essence of statin activity. Moreover increased 25(OH)D levels during treatment with statins have been observed, shedding new light on the effects of these drugs [36-38]. It is believed that blocking HMG-CoA reductase for preventing the cholesterol synthesis pathway promotes the synthesis of cholecalciferol from 7-dehydrocholesterol and is responsible for at least part of the pleiotropic effect of statins. A separate issue concerns the impact of the 25(OH) level on statin therapy. It has been shown that within patients with normal serum and a slight deficiency of 25(OH)D, there is significantly greater reduction in total cholesterol levels and triglyceride levels which have been achieved during treatment with atorvastatin compared to patients with deep deficiency [39] the mechanism of this phenomenon is likely to effect CYP3A4 and requires further research. (Figure 1)

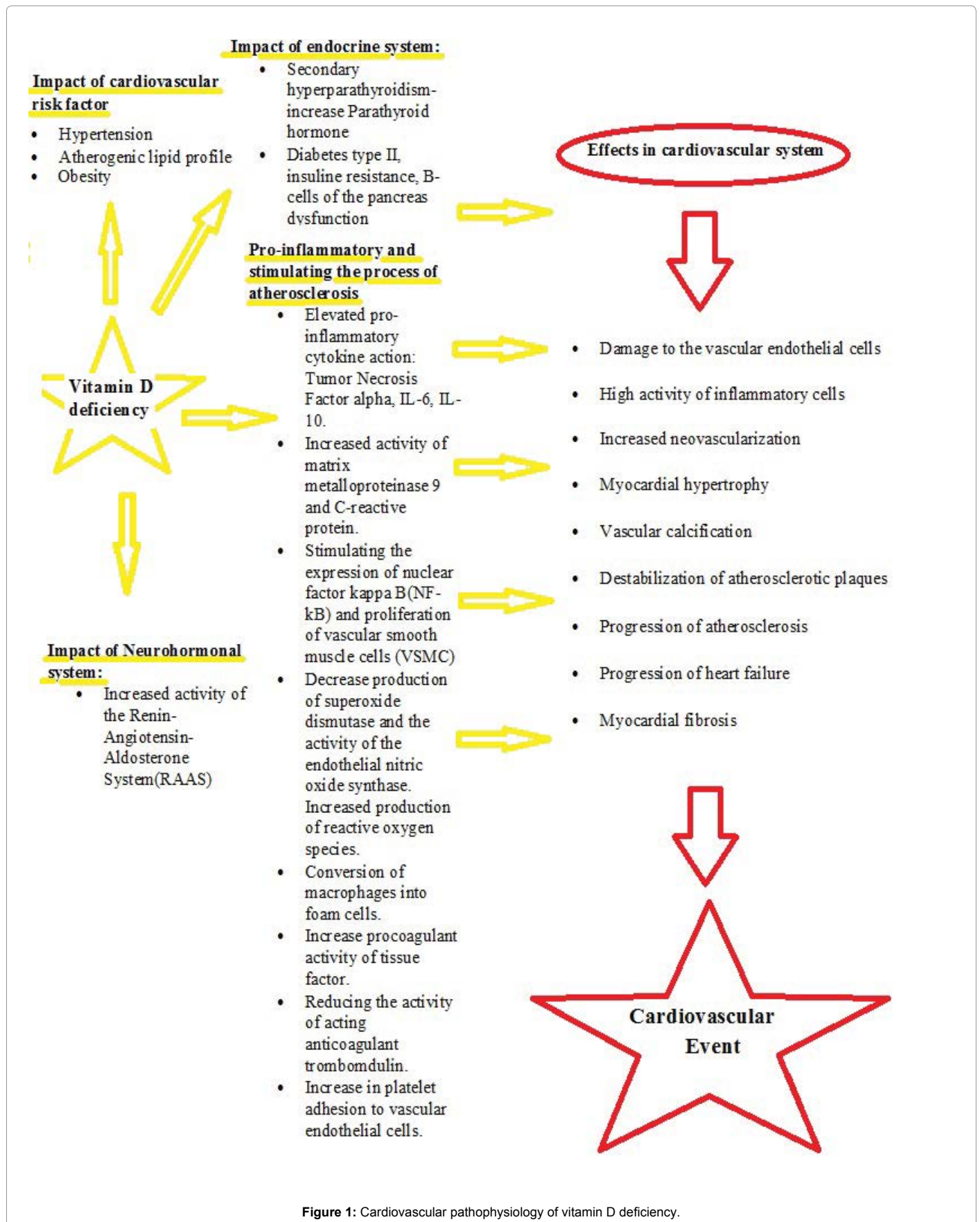
In addition to studies evaluating the effects of vitamin D on the individual processes involved in the development of coronary atherosclerosis, there is more research providing evidence of the association of vitamin D deficiency with an increased risk of adverse cardiovascular incidents. This compound was already suggested in 1981. Scragg et al. examining the relationship between the prevalence of cardiovascular disease, the time of year and geographical location suggested that increased exposure to sunlight and vitamin D may have a protective effect against cardiovascular disease [40]. In 1990, the same scientists conducted a study of 179 patients hospitalized for heart attack who had significantly lower average 25(OH)D levels compared to healthy people [40]. In 1997, Watson et al showed an inverse relationship between vitamin D levels and the amount of calcification in the coronary arteries evaluated in CT [41]. On the basis of the Framingham Offspring Study that included 1,739 participants without cardiovascular disease, it was demonstrated that people with the 25(OH)D level <15 ng/ml have 1.62 times greater risk of cardiovascular incidents, including severe myocardial infarction, coronary artery disease, CNS stroke, transient ischemic attack and heart failure, compared to the people with a level of ≥ 15 ng/ml. [42]. Also Giovannucci et al., prospectively studying 18,225 men, documented a 2.09-fold higher incidence of acute coronary syndrome within patients with low levels of 25(OH)D (≤ 15 ng/ml) compared with patients with optimal levels of 25(OH)D (>30 ng/ml), after taking into account known risk factors for cardiovascular disorders [43]. On the other hand Vacek et al. in the analysis of 10,899 patients conducted in the United States showed a significant association of vitamin D, both with hypertension, coronary artery disease, cardiomyopathy and diabetes. In addition, after taking into account a number of clinical variables, vitamin D deficiency was a strong independent predictor of all causes

of mortality ($p < 0.0001$), whereas vitamin D supplementation resulted in a significant improvement in survival ($p < 0.0001$), especially amongst patients with a documented deficiency [44]. In turn, in a multicentre study conducted in the US, which included 239 patients hospitalized for an acute coronary syndrome, deficiency of vitamin D (<30 ng/mL) was observed within almost all patients [45]. In another prospective study of 139 patients with myocardial infarction with ST-segment, elevation deficiency of vitamin D (<14 ng/mL) was observed amongst 72.7% of patients. It also showed a significant inverse correlation between the 25(OH)D level and the concentration of metalloproteinase 9 (a marker of early myocardial remodelling). Moreover, low levels of vitamin D were associated with a higher mortality of patients [46]. Interesting conclusions can be drawn studying the effects of vitamin D levels amongst patients with acute coronary syndrome on major adverse cardiac events (MACE) defined as death, hospitalization for heart failure and subsequent heart attack. The study included 1,259 patients with myocardial infarction with the average follow-up time of patients amounting to 550 days. It has been shown that 25(OH)D is an independent predictor of MACE ($p = 0.001$), primarily nonfatal MACE. While it is not a predictor of all causes of mortality. Moreover, the 25(OH)D level >7.3 ng/ml reduces the risk of nonfatal MACE by 40% within patients with acute coronary syndrome [47].

There is growing evidence linking low vitamin D levels with a higher severity of coronary atherosclerosis. Verdoia et al. in a study of 1484 patients undergoing coronary angiography, showed a significant association of vitamin D with a higher severity of coronary artery disease especially amongst patients with 25(OH)D <10 ng/mL [48]. Also, Shor et al, based on a study conducted in Israel of 101 patients undergoing coronary angiography, demonstrated a correlation between a low level of 25(OH)D and advanced coronary artery disease after taking into account variables such as gender, age, body mass index, ethnicity and smoking [49]. These results are confirmed by the study of 100 Indian patients undergoing coronary angiography which showed a higher incidence of two and three-vessel coronary heart disease amongst patients with lower 25(OH)D (<20 ng/ml) [50].

Other studies do not confirm the relationship of low 25(OH)D levels and increased mortality and morbidity from cardiovascular causes. In the NHANES III study covering more than 13,300 patients during an 8-year observation, showed no higher rate of death amongst patients with levels of 25(OH)D <17.0 ng/ml [51]. Also a Finnish study, involving 6,219 participants, showed no statistically significant correlation between vitamin D levels and risk of death from cardiovascular causes [52].

Unfortunately, up to now, only a few randomized clinical studies evaluating the effect of vitamin D supplementation on cardiovascular incidents and risk factors for coronary heart disease have been carried out. Forman et al, based on a study of 283 black patients with hypertension, who for three months received supplementation of 1000 IU of vitamin D3 per day, showed a significant decrease in systolic blood pressure without affecting diastolic pressure. The main limitation is only a three-month period of research and anti-hypertensive treatment of almost 40% of the examined patients [53]. Reduction of systolic blood pressure due to vitamin D3 supplementation in a dose of 3000 IU/day taken for 20 weeks amongst 130 German patients has also been shown by Larsen et al. [54]. However, the effect of vitamin D supplementation on blood pressure has not as yet been shown by other researchers. Witham et al examined 159 Caucasians whose average age was 77. Patients received 1000 IU/day of vitamin D3 or placebo for three months. In the group receiving vitamin D3, there was no



significant effect of supplementation on blood pressure as well as on the 24-hour measurement of blood pressure, arterial stiffness, endothelial function, cholesterol and glucose [55].

Also, there was no effect of vitamin D3 supplementation and calcium on the calcification of coronary arteries walls evaluated on the basis of the CAC score. The study included 754 postmenopausal women who were randomly assigned to receive 1000 mg per day and 400 UI/day of vitamin D3 or placebo [56]. Also Gepner et al, in a study of 114 postmenopausal women, showed no effect of supplementation with vitamin D3 (2500 UI/day for 4 months) to improve the endothelial function, arterial stiffness and inflammatory markers [57]. No effect of vitamin D2 supplementation on blood pressure, the level of E-selectin, C-reactive protein, IL-6 or CXCL-10 chemokine was demonstrated in a study of 90 women with a history of coronary heart disease [58]. In contrast, meta-analysis of 8 randomized studies carried out by Wang et al, demonstrated a small but statistically significant reduction in CVD risk in the event of supplementation of moderate to high doses of vitamin D3 compared to placebo [59]. (Table 1)

Also, the results of a meta-analysis conducted by the Elamin team, which evaluated the efficacy of compensatory vitamin D supplementation, showed no effect of cholecalciferol on the overall risk of death, stroke, myocardial infarction, levels of lipid fractions (except for a small increase in HDL-cholesterol), blood pressure or blood glucose, and it demonstrated an insignificant trend towards the reduction of mortality [60].

Interesting conclusions have been provided with a meta-analysis of 73 cohort studies (849 412 people) and 22 randomized control tests carried out by Chowdhury to estimate the association of vitamin D with mortality as a result of cardiovascular disease, cancer or other [61]. The results of this analysis indicate that there is a significant inverse correlation between the level of vitamin D and risk of death from all causes of death in general, and more specifically from coronary heart disease, lymphoma, cancer of the upper gastrointestinal tract and respiratory diseases. In all randomized research of vitamin D, supplementation administered as monotherapy did not reduce overall mortality in adults. However, a significant difference in the

reduction of mortality has been proved depending on the type of formulation of vitamin D. As shown, vitamin D3 supplementation reduced overall mortality by about 11%, while the supply of vitamin D2 supplementation had no effect on mortality.

The available data is insufficient to draw definitive conclusions on the impact of vitamin D on diseases of the cardiovascular system, but the results of meta-analyses suggest that vitamin D therapy may slightly reduce overall mortality. Furthermore, some of the few randomized clinical studies have shown beneficial effects of vitamin D supplementation on the cardiovascular risk factor (e.g., hypertension). Additional studies are required to assess the potential benefits of vitamin D supplementation in the prevention of progression of coronary artery disease and adverse cardiovascular incidents, especially since vitamin D supplementation is relatively an inexpensive treatment option. Particularly noteworthy are high risk groups of cardiovascular incidents and thus the elderly, women and patients with chronic kidney disease who have had much lower vitamin D levels when compared to the general population. Perhaps our doubts dispelled the results of on-going large randomized clinical research. The biggest hopes are with the VIDA research (Vitamin D Assessment), carried out in New Zealand and VITAL (Vitamin D and Omega-3 Trial) in the United States, which, among others, are carried out to determine the effect of vitamin D supplementation on the risk of cardiovascular disease and cardiac death. Since the preliminary results are expected between 2017-2020, a few years remain with the question of whether to treat vitamin D deficiency amongst patients with heart disease. Although the recommendation of vitamin D supplementation as a method for the prophylaxis of atherosclerosis did not appear in the Scientific Societies guidelines, nevertheless, based on data indicating a synergistic effect of statins and vitamin D, many doctors are lowering the dose of statin because of the intolerance of the drug, opting for supplementation of vitamin D. The results of the available studies cannot justify vitamin supplementation in the prevention and treatment of cardiovascular diseases. The available knowledge on the impact of vitamin D on the cardiovascular system also cannot be ignored. In addition, yet unpublished results of our studies (a group of about 1,000 patients)

Author	Forman et al.	Larsen et al.	Whitham et al.	Manson et al.	Gepner et al.	Sokol et al.
Year	2013	2012	2013	2010	2012	2012
Number	283	130	159	754	114	90
Ethnic	Only Black	Only White	Only White	75% White		34% White
Age, years	51 (44–59)	61 ± 10	76,9 ± 4,8	50-59	63.9 (3.0)	55
Gender, male	98		40	Only Postmenopausal Women	Only Postmenopausal Women	57
25(OH)D, ng/mL	15.7 (10.7–23.4)	23 ± 10	18 ± 6		31.3 (10.6)	<20
Type of Vitamin D	D3	D3	D3	D3	D3	D2
Vitamin D dose (IU/day)	1000 2000 4000 or placebo	3000	100 000	400 plus 1000 mg Calcium	2500	50 000
Frequency of administration	Everyday	Everyday	Every 3 months	Everyday	Every day	Every week
Duration of the study	3 months	20 weeks	One year	7 years	4 months	12 weeks
Results	For each 1 ng/mL increase in plasma 25(OH)D, there was a significant 0.2 mmHg reduction in systolic pressure (p=0.02).	Central BP (CBP) estimated by applanation tonometry and calibrated with a standardized office BP was reduced by 7/2 mm Hg (p=0.007/0.15) vs. placebo.	No significant treatment effect was evident for any of the secondary outcomes (24-hour blood pressure, arterial stiffness, endothelial function, cholesterol level, glucose level).	Treatment with moderate doses of calcium plus vitamin D3 did not appear to alter coronary artery calcified plaque burden among postmenopausal women.	Vit. D supplementation did not improve endothelial function, arterial stiffness, or inflammation.	No significant differences in blood pressure, e-selectin, high-sensitivity c-reactive protein, IL-6 or the chemokine CXCL-10 were found with treatment.

Table 1: Overview of randomized controlled trials evaluating the effect of vitamin D supplementation on cardiovascular disease.

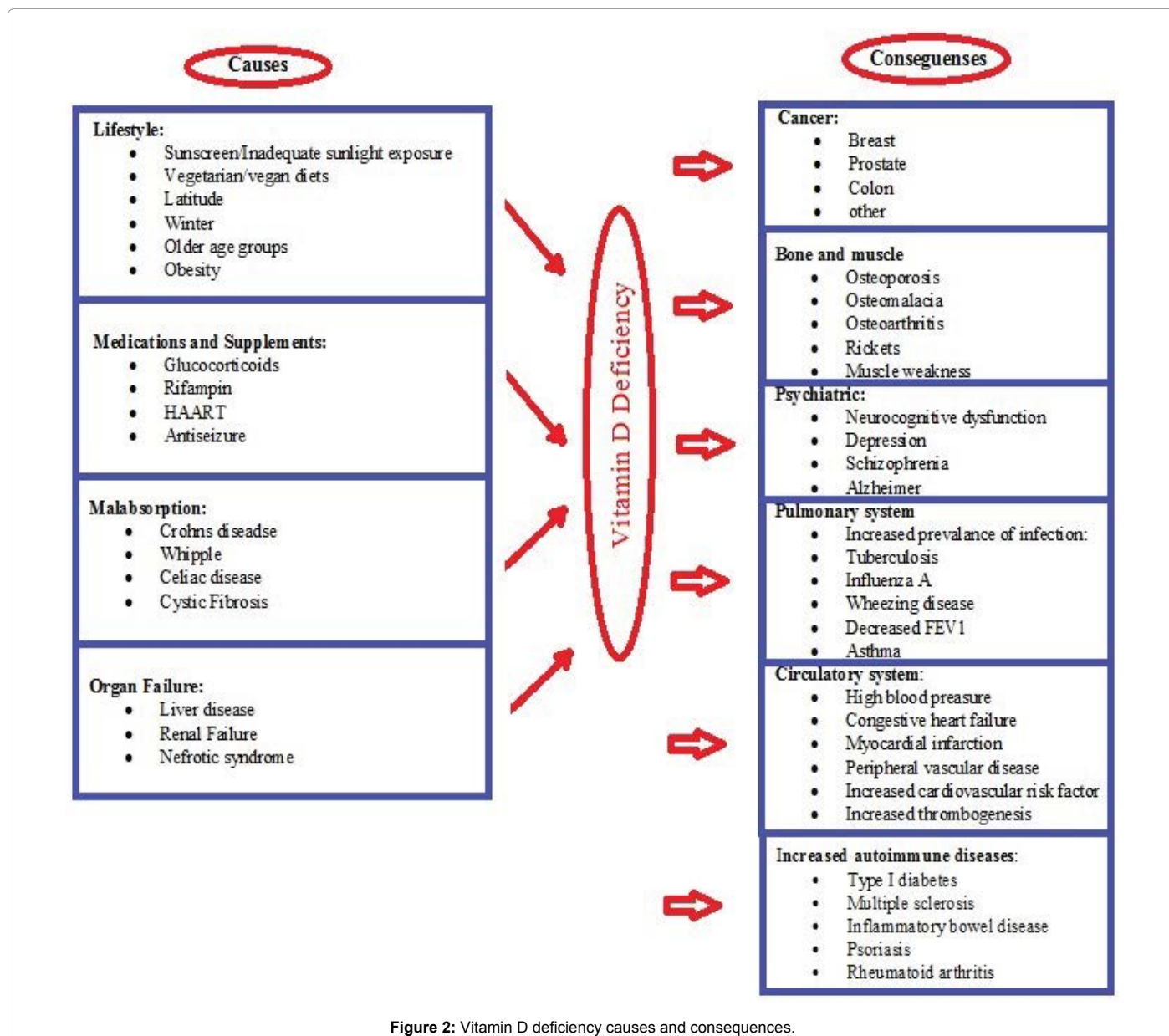


Figure 2: Vitamin D deficiency causes and consequences.

indicate the relationship of low levels of vitamin D with a higher severity of coronary atherosclerosis. Therefore, taking the decision must be weighed against the potential negative consequences of not treating vitamin D deficiency to the cost of supplementation and total risk supplementation (as a toxic dose causing a risk of hypercalcemia, it was considered to be 30,000 IU/day taken for 3 months [62]. According to the recommendations of the Institute of Medicine (IOM), the recommended daily intake of vitamin D in a dose of 600 IU/day for people up to 70 years old, to 800 IU/day for those over 70, provides safe supplementation and maintains 25(OH)D serum levels >20 ng/ml. In addition, the IOM report emphasized that there is no evidence of increased benefits at doses of 800-4000 IU/day [63] (Figure 2).

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