The effects of vitamin D on severity of coronary artery atherosclerosis and lipid profile of cardiac patients

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Abstract

Introduction: A deficiency of 25-hydroxyvitamin D (25(OH)D) (the standard biomarker for vitamin D status) can have multiple impacts on the cardiovascular system. The aim of the study was to assess of the influence of 25(OH)D on severity of coronary atherosclerosis and lipid profile.
Material and methods: The study involved prospectively 637 patients subject to coronary catheterization. The stage of coronary atherosclerosis was assessed using the Coronary Artery Surgery Study score (CASSS). Plasma concentration of 25(OH)D was measured using an electrochemiluminescent immunoassay. The levels of total cholesterol (TC), high-density cholesterol (HDL-C) and triglycerides (TG) were measured using the enzymatic method, and the concentration of low-density cholesterol (LDL-C) was calculated with the Friedewald equation.
Results: The average level of 25(OH)D was 15.85 ng/ml. A higher level of 25(OH)D was observed in men (16.28 ng/ml vs. 15.1 ng/ml; $p = 0.027$). The study did not reveal any significant correlation between the level of 25(OH)D and severity of coronary atherosclerosis. It was observed however that the increase of 25(OH)D level results in an increased number of patients without significant lesions in the coronary arteries. In the whole group of women and men in the age group of 70–80 years an inverse relationship was observed between the level of 25(OH) and the severity of coronary atherosclerosis. The whole study group showed a statistically significant inverse correlation of the 25(OH)D level with TC ($p = 0.0057$), LDL-C ($p = 0.00037$) and TG ($p = 0.00017$).
Conclusions: Women and men over 70 years showed an inverse correlation of the 25(OH)D level and the stage of coronary atherosclerosis. Deficiency of 25(OH)D affects the levels of TC, LDL-C and TG.

Key words: vitamin D, coronary atherosclerosis, gender, lipid profile.

Introduction

Coronary atherosclerosis is the main cause of death in developed countries. In spite of important progress in medication and improvement in techniques of coronary intervention, the therapeutic outcome is still not satisfactory. So far, several risk factors of a cardiovascular event have been identified; however, much attention is still paid to finding new ones. Some people propose vitamin D deficiency, affecting 50% of the world population, which may increase occurrence of cardiovascular diseases [1–3].

The main source of vitamin D in the body (80–90%) is dermal synthesis, whereby ultraviolet radiation of 7-dehydrocholesterol is converted into pro-vitamin D_3, which is rapidly converted in the liver to form the main circulating 25-hydroxyvitamin D (25(OH)D). 25(OH)D status reflects the resources of vitamin D in the body.

Moreover, recent test results showed an independent relation between low levels of vitamin D and documented risk factors of cardiovascular event such as hypertension [4], atherogenic lipid profile [5], diabetes [6], and obesity [7]. Particularly noteworthy is the effect of vitamin D on the lipid profile. An association of high levels of total cholesterol and low-density cholesterol (LDL-C) with coronary atherosclerosis is expressly documented. It was also found that the reduction of total cholesterol and low-density lipoprotein below the recommended level significantly decreases the cardiovascular risk [8, 9]. Many studies have found an inverse relationship of 25(OH)D in serum and different cholesterol fractions [10].

Inflammation found in the wall of large and medium arteries in the course of atherosclerosis is induced in response to destruction of endothelium [11]. It was demonstrated that calcitriol is able to normalize endothelial cell function through decreased production of reactive oxygen species [12], increased activity of endothelial nitric oxide synthase [12, 13], and protection of endothelial cells from end-products of glycosylation [14]. Furthermore, it regulates proliferation, differentiation and function of immune system cells through inhibition of prostaglandin and cyclooxygenase-2 synthesis and induction of anti-inflammatory cytokines [15–18]. The influence of calcitriol on calcification of the vascular wall is unclear. In low concentrations calcitriol inhibits calcification of the tunica media and interna in coronary arteries [19, 20]. On the other hand, in high concentrations it stimulates differentiation of mesenchymal cells into osteoblasts [21].

A thin layer of connective tissue, large lipid nucleus, activity of inflammatory cells and increased neovascularisation are the main factors involved in destabilization of the atherosclerotic plaque [11]. Apart from its anti-inflammatory properties, calcitriol inhibits transformation of macrophages into foam cells [22], inhibits the activity of metalloproteinases [23, 24], and negatively influences angiogenesis by inhibition of vascular endothelial growth factor (VEGF) and induction of apoptosis in epithelial cells [25].

After rupture of the atherosclerotic plaque, its lipid contents are released and the blood coagulation process is initiated [11]. Calcitriol exerts its anticoagulant activity through down-regulation of tissue factor, increased production of thrombomodulin [26] and inhibition of platelet adhesion to endothelium [27].

The aim of our study is to assess the influence of vitamin D level on the condition of coronary arteries and lipid profile of patients subject to cardiac catheterization. The obtained results can contribute to enhancement of the strategy in prevention of coronary heart disease.

Material and methods

Population

The study comprised 637 patients (415 men and 222 women) of Bielański Hospital, Cardiology Department, aged 64 ±9.7 (from 31 to 87 years old) who underwent cardiac catheterization between July 2013 and May 2015.

The study patients were selected on the basis of ambulatory diagnostics for coronary angiography for suspected coronary artery disease, and upon meeting the study's criteria.

The study excluded patients with chronic kidney disease (stages III–V) due to accompanying disorders of calcium and phosphate. Although the pathogenesis of these abnormalities is multifactorial, abnormal parathyroid hormone (PTH) secretion and vitamin D metabolism respectively seem to play a leading role in their development [28]. In addition, the study excluded patients with cancer (paraneoplastic syndromes and associated disorders of calcium-phosphate), patients with elevated markers of inflammation or fever, and those taking drugs or dietary supplements containing vitamin D or calcium. Those included in the study formed a homogeneous group in terms of diet and eating habits and length of exposure to sunlight. All the patients were treated with a statin (atorvastatin or rosuvastatin).

All the patients gave their agreement in writing to participate in the study. The test protocol was accepted by the Bioethics Committee of the Medical University of Warsaw.

Methods

All the patients were subject to cardiac catheterization using standard diagnostic catheters (access by radial or femoral artery). The severity of coronary atherosclerosis was assessed using the CASSS. Each of the three important epicardial vessels of stenosis > 70% was assigned one point. Left main coronary artery stenosis ≥ 50% was classified as 2-vessel coronary artery disease and was assigned two points. CASSS is a sum of all points reflecting one-, two-, and three-vessel coronary artery disease.

Plasma concentration of 25(OH)D was measured using the Vitamin D Total assay (ELECSYS Roche Diagnostics). This is a competitive electro-

chemiluminescence assay using a phenomenon where the identification of 25(OH)D_2 and 25(OH)D_3 used vitamin D binding protein (DBP) labeled with ruthenium. More accurate methods (using high-performance liquid chromatography or mass spectrometry) allowing for separate determination of 25(OH)D_3 and 25(OH)D_2 are expensive and used less often. It is believed that globally designated 25(OH)D_3 + 25(OH)D_2 is reasonable, given that the biological effects of these two metabolites are similar.

The 25(OH)D limit of detection was 4 ng/ml. It was considered that the optimal level of 25(OH)D is over 30 ng/ml, a slight deficiency is between 20 and 30 ng/ml, a moderate deficiency is between 10 and 20 ng/ml, and hypovitaminosis D_3 is under 10 ng/ml.

The levels of total cholesterol (TC), high-density cholesterol (HDL-C) and triglycerides (TG) were measured using the enzymatic method, and the concentration of LDL-C was calculated using the Friedewald equation.

Body mass index (BMI) was calculated to determine the degree of obesity (BMI > 30 kg/m^2). The BMI was calculated by dividing the subject's mass by the square of his or her height, expressed in metric units.

Statistical analysis

The arithmetic mean and standard deviation were calculated for quantitative variables. The quantitative and percentage distributions were presented for qualitative variables. Pearson's χ^2 test was applied to check variable interdependence. Parametric tests (Student's *t*-test, Welch's test) and the non-parametric Wilcoxon signed-rank test were applied to compare two independent tests with quantitative variables. Values of $p < 0.05$ were considered as statistically significant.

Results

Men made up 65% of the patients. Hypertension was observed in 90.1%; diabetes in 29.2%; prediabetes in 6%, hyperlipidemia in 49.6%. 26.3% of the population were active tobacco smokers, whereas 16.7% of the patients mentioned smoking in the interview. Stable coronary disease was the cause of hospitalization in 67.1%, acute coronary syndrome in 32.9%. 26.6% of the patients mentioned heart failure in the past. The average BMI was 28.49 kg/m^2 (28.8 kg/m^2 in women, 29.1 kg/m^2 in men).

No significant lesions in coronary arteries were observed in 24.3% of the patients, single-vessel disease in 27.6%, two-vessel disease in 29%, and three-vessel disease in 19% of the patients.

The average level of 25(OH)D was 15.85 ng/ml (from 4.0 to 48.4 ng/ml). The optimal level was observed in just 4.9% of the patients. Severe deficiency was observed in 21% of the patients, moderate deficiency in 54%, and slight deficiency in 20%.

No statistically significant correlation between the level of 25(OH)D and the severity of coronary atherosclerosis ($p = 0.088$) was observed for the whole population. One should bear in mind, however, that the result is close to significance, and the percentage of patients with no significant lesions in coronary arteries increases with the increase of 25(OH)D level; Figure 1.

A statistically significant correlation between the level of 25(OH)D and gender ($p = 0.0033$) was observed. The average levels of 25(OH)D for women (15.1 ng/ml) were statistically significantly lower than the average levels of 25(OH)D for men (16.27 ng/ml); Figure 2.

Moreover, a significantly lower level of 25(OH)D was observed in women suffering from advanced coronary artery disease (two- and three-vessel). The average level of 25(OH)D in women with no significant lesions in the coronary arteries was 17.5 ±9 ng/ml, in the group of two- and three-vessels disease 13.4 ±6.1 ng/ml; $p = 0.0008$; Figure 3.

Men aged 70-80 years were also found to have a significantly lower level of 25(OH)D for patients suffering from two- and three-vessel coronary atherosclerosis in comparison to patients without significant lesions in coronary arteries (16.3 ±7.8 ng/ml

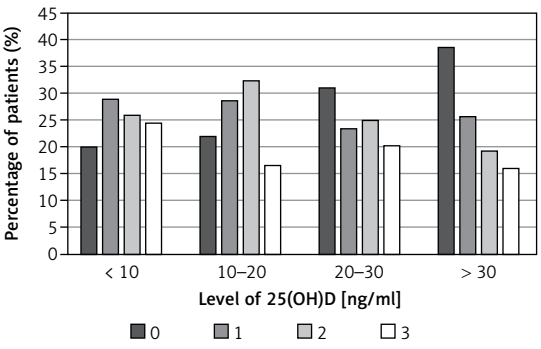

Figure 1. Correlation between the level of 25(OH)D and severity of coronary atherosclerosis (CASSS score)

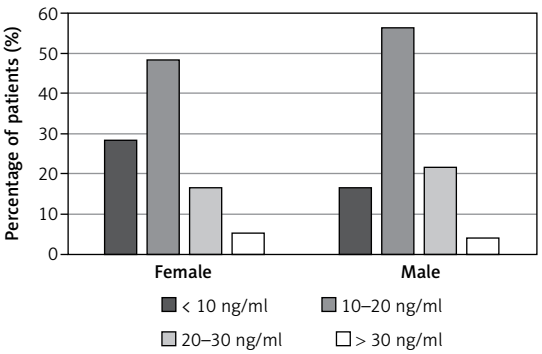

Figure 2. Correlation between the level of 25(OH)D and gender

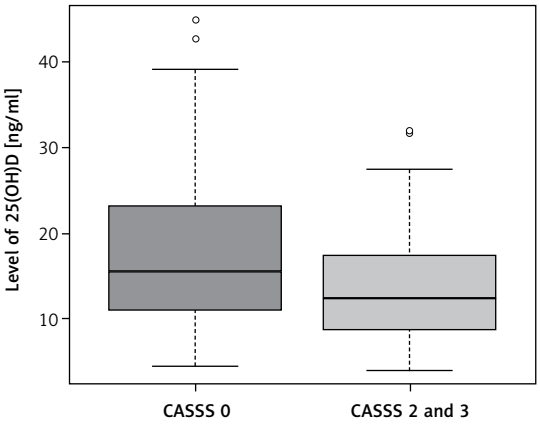

Figure 3. Correlation between the level of 25(OH)D in women without coronary atherosclerosis and with advanced coronary atherosclerosis

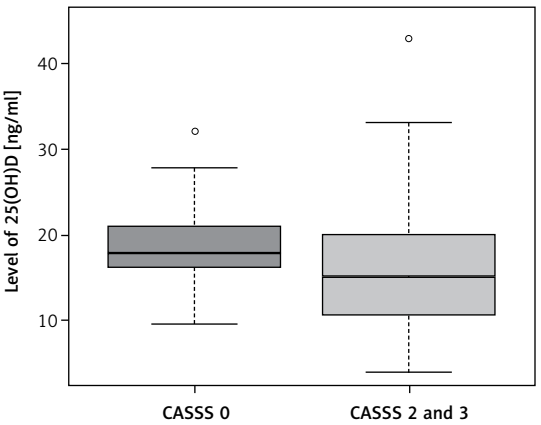

Figure 4. Correlation between the level of 25(OH)D and severity of coronary atherosclerosis in men aged 70–80 years

vs. 19.1 ±5.9 ng/ml; $p = 0.026$); Figure 4. This correlation could not be confirmed for the whole group of men.

There was no significant correlation between the level of 25(OH)D and patients' BMI ($p = 0.7$), hypertension ($p = 0.7$) or diabetes ($p = 0.87$).

However, an inverse correlation between 25(OH)D concentration and the concentrations of TC ($p = 0.0057$), LDL-C ($p = 0.00037$), and TG ($p = 0.00017$) was found, Table I. The average levels of TC, LDL-C and TG were statistically significantly lower in patients with the optimal level of 25(OH)D in comparison to patients suffering from severe vitamin D deficiency. The analysis of the results taking into consideration gender showed a statistically significant inverse correlation between 25(OH)D and TC ($p = 0.047$), LDL-C ($p = 0.0036$) and TG ($p = 0.006$) in women. In men, the only statistically significant correlation was found in relation to 25(OH)D and TG ($p = 0.029$). It should be stressed that for LDL-C, the correlation was close to statistical significance ($p = 0.052$). No

Table I. Correlation between the level of 25(OH)D and TC, LDL-C and TG

Level of 25(OH)D [ng/ml]	TC average [mg/dl]	SD	IQR	Min.	First quartile	Median	Third quartile	Max.	Number of patients
< 10	189.11	54.09	78.82	63.1	149.38	178.9	228.2	366.29	125
10–20	178.74	44.79	58.375	70.29	146.955	172	205.33	334.08	315
20–30	180.63	99.88	61.29	73.25	140.055	167.59	201.34	264.36	115
> 30	157.23	43.03	51.8725	70.02	132.40	147.5	184.27	237.9	30
Level of 25(OH)D [ng/ml]	**LDL-C average [mg/dl]**	**SD**	**IQR**	**Min.**	**First quartile**	**Median**	**Third quartile**	**Max.**	**Number of patients**
< 10	114.27	46.16	65.39	24.43	82.86	109.03	148.25	253.02	125
10–20	104.03	40.12	49.56	23.48	76.45	98.35	126.01	257.97	311
20–30	97.04	40.79	54.79	22.29	68.84	88.23	123.63	202.12	113
> 30	83.03	33.44	36.72	31.79	60.65	77.19	97.37	153.86	30
Level of 25(OH)D [ng/ml]	**TG average [mg/dl]**	**SD**	**IQR**	**Min.**	**First quartile**	**Median**	**Third quartile**	**Max.**	**Number of patients**
< 10	139.06	64.66	76.92	46.94	89.80	133.595	166.73	386.39	124
10–20	129.39	65.61	68.34	2.81	87.71	114.91	156.04	456.7	316
20–30	123.91	61.58	59.59	37.07	58.52	111.82	145.11	438.25	115
> 30	96.14	52.36	35.77	43.3	69.07	86.325	104.83	331.57	30

SD – standard deviation, IQR – interquartile range, Min. – minimum value, Max. – maximum value.

Table II. Characteristics of the examined group

Laboratory variables	Avarge	SD	Min.	Max.
25(OH)D [ng/ml]	15.85	7.34	4	48.4
BMI	28.49	5.06	16.14	54.06
Age at the time of the study	66	10.38	31	95
PTH [pg/ml]	50.88	27.33	13.2	219
Calcium in serum [mmol/l]	2.35	0.14	1.01	3.04
Phospathes in serum [mmol/l]	1.11	0.2	0.58	2.58
TC [mg/dl]	178.77	46.99	70.02	366.29
HDL [mg/dl]	48.68	14.78	8.85	113.24
LDL [mg/dl]	104.08	41.8	22.29	257.97
TG [mg/dl]	129.55	64.55	31.3	456.7
Uric acid [mg/dl]	6.2	1.76	2.58	14
Data from the medical history		**Number of patients**		
Diagnosis of unstable angina		209		
Diagnosis of stable angina		428		
Interview myocardial infarction		169		
History of prior CABG		24		
Patients with diabetes/pre-diabetes		185/38		
Active smokers or smokers in the past		167/106		

SD – standard deviation, Min. – minimum value, Max. – maximum value.

correlation of 25(OH)D and HDL-C was found for the whole population. Characteristics of the study group of patients was presented in Table II.

Discussion

There is more and more evidence that vitamin D deficiency significantly increases the risk of a cardiovascular event, and the optimal vitamin D concentration shows protective properties [29, 30]. To our knowledge this is the first study carried out on Polish patients to assess the influence of vitamin D on the severity of coronary atherosclerosis.

Vitamin D deficiency was found in 95.1% of the patients. This confirms a former analysis which found a high frequency of vitamin D deficiency in Poland [31].

In spite of the fact that there was no significant correlation between the level of 25(OH)D and the severity of coronary atherosclerosis, it should be stressed that 38.7% of the patients with the optimal level of 25(OH)D had no significant lesions in the coronary arteries, and 16.1% suffered from three-vessel coronary artery disease. The percentage of patients with no significant lesions in coronary arteries increases along with the level of vitamin D. The analysis of former studies provides various results for the effect of 25(OH)D deficiency on the condition of coronary arteries. Verdoia *et al.* carried out a study on 1484 patients subject to cardiac catheterization that showed a significant correlation between vitamin D deficiency and severity of coronary artery disease, especially in patients with 25(OH)D < 10 ng/ml [32]. The Multi-Ethnic Study of Atherosclerosis, which included 6436 patients with coronary artery disease, showed a higher risk of cardiovascular events in white people with a lower level of 25(OH)D [33]. However, Goleniewska *et al.* examined a group of 130 patients hospitalized for the first heart attack with ST-segment elevation and did not detect any correlation between the level of vitamin D and the severity of lesions in coronary arteries. However, the study showed a high percentage of vitamin D deficiency in this group of patients [34].

The analysis of our results carried out with division into genders showed a statistically significant inverse correlation between 25(OH)D and the severity of coronary atherosclerosis in women, who were found to have higher severity of coronary atherosclerosis at a lower level of 25(OH)D. Similarly, Verdoia *et al.* documented a more advanced stage of coronary atherosclerosis in female patients with a lower level of 25(OH)D [35].

Similar correlations between the level of 25(OH)D and the severity of coronary artery disease were found in men aged 70–80 years.

The difference of vitamin D levels in women and men is interesting and important to highlight. The study revealed significantly lower levels of 25(OH)D in women, which confirms studies of other researchers [36]. Moreover, taking into consideration the correlation between the level of 25(OH)D and the severity of coronary atherosclerosis, found in the whole group of women, the special position of vitamin D is apparent, and we hold the view that further studies need to be carried out to make recommendations in the field of supplementation in this group of patients.

It is especially important to highlight the influence of vitamin D on the lipid profile, given the fact that the correlation between the high levels of total cholesterol and LDL-C and coronary atherosclerosis is explicitly documented. Moreover, it was shown that levels of TC and LDL-C below recommended levels significantly reduce the risk of cardiovascular events [37, 38].

Our study showed inverse correlations between the 25(OH)D concentration and the concentrations of TC, LDL-C and TG in the whole examined population. The result of analysis carried out according to gender showed statistically significant inverse correlations of the level of 25(OH)D with TC, LDL-C and TG in the group of examined women. In men, however, a statistically significant correlation of 25(OH)D was found only with TG, while the correlation with LDL-C was close to statistical significance. No association between 25(OH)D and HDL-C was found both for the whole group and separately for women and men. Similar results were obtained by Garcia-Bailo *et al*. in a Canadian population [39]. Other researchers also found an inverse correlation between 25(OH)D and various lipid fractions in the serum [40].

The results described above can be explained by analyzing the metabolic pathway, common for vitamin D and cholesterol. Both these substances are formed from the common precursor of 7-dehydrocholesterol. The key role in the synthesis is played by 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMG-CoA). It was experimentally shown on various cell lines that hydroxylated derivatives of vitamin D are inhibitory to the activity of HMG-CoA reductase [41]. This effect is not observed for the active vitamin D metabolite 1,25 dihydroxycholecalciferol. Moreover, 25(OH)D can inhibit CYP51A1, which also participates in cholesterol synthesis. Deficiency of 25(OH)D increases the activity of the reductase and CYP51A1 by increasing the level of cholesterol. Blocking HMG-CoA reductase is the key function of statins. Studies of statins and increase of the 25(OH)D levels, observed during treatment with some statins, shed some light on the pleiotropic action of this medication [42–44]. It is thought that blocking HMG-CoA reductase, which prevents cholesterol synthesis, promotes the pathway of synthesis of cholecalciferol from 7-dehydrocholesterol. This reaction is responsible for some of the pleiotropic actions of statin, including bone metabolism. The influence of 25(OH)D on treatment with statins is a separate issue. It was observed that patients with the correct level of 25(OH)D as well as those with a slight deficiency showed significantly better reduction of the total cholesterol and triglyceride levels during treatment with atorvastatin in comparison to patients showing severe deficiency [45]. The mechanism behind this observation probably concerns the influence of CYP3A4 and requires further study.

Our findings were based on a single population center and would need to be verified in other, larger cohorts. In addition, although patients reported roughly comparable exposure to sunlight, we were not able to exactly determine intake of vitamin D and calcium in the diet. The study did not include the use of solar filters that significantly affect the cutaneous synthesis of vitamin D. In addition, we did not take into account the status of menopause or hormonal levels in women, and it is not possible to exclude the effect of hormones on the condition of the coronary arteries. No polymorphisms were tested for the vitamin D receptor or the level of vitamin D binding protein.

In conclusion, vitamin D deficiency was observed in 95.1% of the patients subject to cardiac catheterization. It was found that the level of 25(OH)D significantly depends on gender. An inverse correlation between the level of 25(OH)D and severity of coronary atherosclerosis was found in women and men over 70 years old. In the group of women, a statistically significant inverse correlation between 25(OH)D and TC, LDL-C and TG was found. Although the recommendations of scientific societies did not include vitamin D supplementation as a method of prevention of coronary atherosclerosis, we need additional studies to evaluate the potential benefits of vitamin D supplementation in the prevention and progression of coronary artery disease, especially considering the fact that vitamin D supplementation is an inexpensive treatment option compared with the costs of treating the effects of coronary artery disease (acute coronary events, heart failure, etc).

Conflict of interest

The authors declare no conflict of interest.

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