The Relationship Between Serum 25-Hydroxyvitamin D and Clinical and Subclinical Features in Hypertensive Patients with Coronary Artery Disease

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Short title: 25-Hydroxyvitamin D in hypertensive patients with coronary artery disease

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Asbtract
Background: Vitamin D deficiency increases the risk of many acute and chronic diseases such as type 1 diabetes, cardiovascular disease, several cancers, cognitive impairment, depression, pregnancy complications, autoimmune disease. This study aims to investigate the relationship between serum 25-hydroxy vitamin D and clinical and subclinical features in hypertensive patients with coronary artery disease
Methods: A cross-sectional descriptive was carried out in hypertensive patients with coronary artery stenosis by coronary.
Results: The serum 25(OH)D level was a statistically significant different between the patients with different hypertension grades. The level of 25(OH)D was highest in patients with grade I hypertension and lowest in patients with grade III hypertension. The cut-off point of 25(OH)D in predicting grade II-III hypertension was < 23.88 ng/ml; AUC = 95.9%, ($p < 0.05$). Blood cholesterol was negative correlation with serum 25(OH)D level and the correlation coefficient $r = -0.205$ with $p>0.05$. White blood cells was positive correlation with the serum 25(OH)D level and the correlation coefficient $r = 0.366$ with $p > 0.05$. Gensini score was negative correlation with serum 25(OH)D level and the correlation coefficient $r = - 0.150$ with $p > 0.05$.
Conclusion: The serum 25(OH)D level was a statistically significant difference between the patients with different hypertension grades and there was no correlation with the Gensini score.

Keywords: 25-Hydroxyvitamin D, hypertension, coronary artery disease

Introduction

Vitamin D deficiency is a major global health problem that affects not only musculoskeletal diseases such as osteopenia, fractures, osteoporosis and muscle weakness.[1] In addition, it increases the risk of many acute and chronic diseases such as type 1 diabetes, cardiovascular disease, some cancers, cognitive impairment, depression, pregnancy complications, autoimmune diseases.[2,3]

Coronary artery disease is one of the major life-threatening diseases and a major cause of death worldwide. The association between Vitamin D deficiency and coronary artery disease (CAD) has been demonstrated in many studies.[4]

Therefore, in order to contribute to the treatment and prevention of ischemic heart disease in hypertensive patients, we conducted this study to investigate the relationship between serum 25-hydroxy vitamin D and clinical and subclinical features in hypertensive patients with coronary artery disease.

Materials and Methods

Study population

A cross-sectional descriptive was carried out in hypertension patients with coronary artery stenosis determined by coronary angiography. The control group was selected with normal person.

Inclusion criteria were: (1) Patients with a history of hypertension, being treated for hypertension for > 1 year. (2) Patients with a history of chronic ischemic heart disease, myocardial infarction, ischemic stroke, peripheral artery disease. (3) Patients on admission have typical or atypical angina or dyspnea on exertion.

Exclusion criteria were: (1) Patients are taking drugs with Vitamin D, Calcium, Estrogen, Isoniazid, Thiazides diuretics; stomach acid antacids, antiepileptic drugs, Parkinson's drugs, Resin drugs group to treat dyslipidemia. (2) Patients with acute or chronic infections detected clinically and subclinically. (3) Patients who were with absorption disorders, gastric bypass surgery, known or suspected cancer, chronic kidney disease, cirrhosis, stroke, hyperparathyroidism, patient stays in one place for a long time, the patient did’nt agree to participate in the study.

Study steps

Patients admitted to the hospital were diagnosed hypertension with indications for coronary angiography will be asked about history, medical history, and clinical examination.

Coronary angiography: If coronary angiography results confirm coronary artery disease and no exclusion criteria, patients will be selected as study subjects.

Take venous blood to test the level of 25-hydroxy vitamin D.

Collect data and record in research sheets.

Statistical analysis

Data processing by medical statistical methods with SPSS 20.0 software.

Results

A total 33 patients who fullfilled the inclusion criteria were analyzed. The mean serum 25(OH)D level was 27.81 ± 8.36 mmol/l in male and 22.2 ± 7.03 ng/ml in female this difference was statistically significant (Table 1). The mean serum 25(OH)D level was 23.79 ± 6.34 ng/mL in age group ≥ 60 years and 33.42 ± 12.83 ng/ml in age group < 60 years, this difference was statistically significant (Table 2). The serum 25(OH)D level was a statistically significant different between the patients with hypertension grades, highest in grade I hypertension and lowest in grade III hypertension (Table 3).

Table 1. Mean serum 25(OH)D level by gender

Gender	Mean serum 25(OH)D (ng/ml)		p
	n	($\overline{X}$ ± SD)	
Male	18	27.81 ± 8.36	< 0.05
Female	15	22.2 ± 7.03	
Total	33	25.25 ± 8.17	

Table 2. Mean serum 25(OH)D level by age

Age	Mean serum 25 (OH)D (ng/mL)		p
	n	($\overline{X}$ ± SD)	
< 60 years	5	33.42 ± 12.83	< 0.05
≥ 60 years	28	23.79 ± 6.34	
Total	33	25.25 ± 8.17	

Table 3. Mean serum 25(OH)D level by hypertension grades

Hypertension grades	Mean serum 25 (OH)D		p
	n	$\overline{X}$ ±SD	
1	15	31.44 ± 7.06	< 0.05
2	9	23.35 ± 3.92	
3	9	16.84 ± 3.05	
Total	33	25.25 ± 8.17	

Blood cholesterol was negative correlation with serum 25(OH)D level, r = - 0.205 (p>0.05). The white blood cells count was positive correlation with the serum 25(OH)D level, r = 0.366 (p>0.05) (Table 4). In the group of patients with vitamin D deficiency, there were 18 patients with ventricular wall motion abnormality on echocardiography, accounting for 66.7% and 9 patients without ventricular wall motion abnormality, accounting for 33.3% (Table 5). In the group of patients with vitamin D deficiency, there were 4 patients with EF < 50 accounting for 14.8% and 23 patients with EF ≥ 50 accounting for 85.0% (Table 6).

Table 4. The correlation between 25 – hydroxyl vitamin D levels and several factors

Factors	n=33	
	r	p
Cholesterolemia	- 0.205	> 0.05
BMI	-0.090	> 0.05
Erythrocytes	-0.153	> 0.05
White blood cells	0.366	> 0.05
Platelet	-0.220	> 0.05
Blood Glucose	-0.166	> 0.05

Table 5. The relationship between vitamin D deficiency and regional wall motion abnormality on echocardiography

		Regional wall motion abnormal						
		Yes	%	No	%	Total	%	p
25(OH)D (ng/ml)	< 30	18	66.7	9	33.3	27	100	> 0.05
	≥ 30	4	66.7	2	33.3	6	100	
	Total	22		11		33		

Table 6. The relationship between vitamin D deficiency and ejection fraction

		EF (echocardiography)						
		< 50%	%	≥ 50%	%	Total	%	p
25(OH)D (ng/ml)	< 30	4	14.8	23	85.2	27	100	> 0.05
	≥ 30	0	0	6	100	6	100	
	Total	4		29		33		

The cut-off point of 25(OH)D was 18.8 ng/ml; AUC = 51.9%; Sensitivity 88.9%; specificity 26.67% (p>0.05). The cut-off point of 25(OH)D > 29.9 ng/ml, area ROC(AUC) = 57.1% (95% CI=0.388-0.741); Sensitivity 23.08% (95% CI 95-43.6); specificity 100% (95% CI: 59.0-100), (p>0.05) (Table 7).

Table 7. Area of the ROC curve, cut off point between 25(OH)D and severe stenosis >70% of the coronary arteries lesions

25(OH)D	Cut off point	AUC area	p	Sensitivity 95% Confidence Interval	Specificity 95% Confidence Interval
LAD	18.8	51.9	>0.05	88.9 [65.3-98.6]	26.7 [78 -55.1]
LCx	27.9	52.2	>0.05	46.7 [21.3-73.4]	77.8 [52.4-93.6]
RCA	27.95	69.4	<0.05	91.7 [61.5-99.8]	47.6 [25.7-70.2]

Discussion

Compared with some foreign studies such as Aleksova A. et al (2015) in Triese region (Italy), the mean age of 478 patients with MI was 66.7 ± 12 years old; male accounted for 69.7%.[5] Research results of Burgaz, A et al (2011) also have similar results on age and BMI.[6] According to Dziedzic et al (2017), a study in coronary artery disease patients found that the proportion of male accounted for 64.68%, the mean age was 68.1±10.3 years.[7]

However, our results were different from the study of Brondum-Jacobsen et al (2012) evaluating the level of 25(OH)D and risk factors for cardiovascular disease, the results showed mean age was 57 (49-66); female accounted for 56%.[1] The results of Roy Ambuj (2015) recorded that the group of patients with acute myocardial infarction was 51.9 ± 11.4 years old; male was 88.3%.[8] The study of Giovannucci E et al. (2008) on the concentration of 25(OH)D and risk factors for myocardial infarction in men showed that the disease age was 63.8±8.6 years.[9]

Compared with some foreign studies such as Aleksova A., et al (2015), the mean concentration of 25(OH)D was 14.5 ng/mL (7.8 – 22.07); 25(OH)D concentration ≤ 20 ng/mL was more common in women with high BMI. Vitamin D deficiency < 20 ng/ml was found in 67.78% of patients and vitamin D deficiency from 21-30 ng/ml in 22.38% of patients with myocardial infarction.[5] According to Dziedzic EA, et al (2017) studied in coronary artery patients, found that patients with 25(OH)D > 30ng/l accounted for 4.8%, patients with 25(OH)D ≤ 10ng/ l accounted for 23.2%; from 10 - 20 ng/ml accounted for 49.9% and 22.3% of patients had 25(OH)D from 20-30 ng/l.[7] Roy Ambuji et al (2015) recorded that the mean concentration of (OH)D in the group of patients with acute myocardial infarction was 6.0 (3.9- 9) ng/ml and the number of patients with 25(OH) D < 10 ng/ml was 79.2%.[8]

According to Brondum-Jacobsen P., et al (2012) on 10170 patients with myocardial ischemia and myocardial infarction showed a SBP of 141 mmHg (125–154).[1] And the results of a study by Dziedzic E. A (2017) on 337 patients, showed that 92.6% of patients had hypertension in patients with coronary artery disease and type 2 diabetes.[7] According to Roy Ambuji (2015), the rate of hypertension in patients with acute myocardial infarction was 34.2%.[8]

Vitamin D may affect the renin-angiotensin system, having beneficial effects on vascular smooth muscle cells, endothelium, and cardiomyocytes. So it affects blood pressure.

The results showed that patients with 25(OH)D test < 30 ng/mL accounted for 81.8%, and group 25(OH)D normal (≥ 30 ng/mL) was 18.2%. The results show that the association of 25(OH)D concentration with hypertension was different statistically significant.

According to Martins, D (2007) a cross-sectional study examined the association between serum 25(OH)D levels and the frequency of hypertension. The study population was divided into 4 groups according to the serum 25(OH)D level. The first group (25(OH) D <21 ng/mL) showed a prevalence of hypertension of 20.46%, while the fourth group (25(OH) D ≥ 37 ng/mL) had a prevalence of hypertension was 15.10%. Comparison of these two groups showed that the odds ratio (OR) = 1.30 (95% CI: 1.13–1.48).[10]

There were many studies with similar results that 25(OH)D concentration was negative correlation with hypertension. According to a study by Bhandari SK (2011) on the levels of 25(OH)D with the rate of hypertension showed the prevalence of hypertension in the population was 24%, OR (95% Cl) of hypertension respectively 2.7 (1.4–5,2); 2.0 (1.5–2.6), and 1.3 (1.2–1,6) with concentrations of 25(OH)D <15 ng⁄mL, 15 - 29 ng ⁄mL, and 30 - 39 ng⁄mL, compared with the 40 ng ⁄mL group. Patients with a concentration of 25(OH)D (<15 ng⁄mL) had a rate of hypertension was 52.4%; 40.8% in patients with 25(OH)D levels was (15–29 ng ⁄ mL); patients with 25(OH)D concentrations of (30–39 ng ⁄ mL) and (40 ng ⁄ mL) were 27.2% and 19.4%, respectively.[11]

The results of our study on hematological indicators such as erythrocytes, white blood cells and platelets are not clear. Specifically, we commented that the mean concentration of 25(OH)D in patients with WBCs ≥ 10 G/l was 36.67 ± 14.0 ng/mL and WBCs < 10 G/l was 24.11 ± 1. 6.74 ng/mL, the difference was statistically significant between white blood cells and 25(OH)D concentration (p<0.05).

For erythrocytes, in patients with erythrocytes ≥ 4.2 T/l, the mean 25(OH)D was 24.06 ± 6.59 ng/mL and erythrocyte count < 4.2 T/l was 28.95 ± 11.66 ng/mL, the difference was not statistically significant between erythrocytes and 25(OH)D concentration (p>0.05).

For platelets, the mean levels of 25(OH)D in patients with platelets ≥ 150 G/l was 24.73 ± 8.18 ng/mL and platelets < 150 G/l was 30.49 ± 7 ,26 ng/mL, the difference was not statistically significant between platelets and 25(OH)D levels (p>0.05).

According to a study of 188 patients by Dogan et al. also showed that there was no difference in platelet count between the 2 groups with 25(OH)D concentrations of 20 ± 3 ng/ml and 30 ± 6 ng/ml.[12]

The results of our study are different from those of Park YC et al (2017).[13] In our opinion, this difference may be due to the small sample size of our study (only 33 patients). According to a study by Park YC (2017) in adults in Korea, it was found that platelet count (PC) and mean platelet volume (MPV) were correlated with blood 25(OH)D concentration.[13] Research by De Oliveira1 (2017) in the United Kingdom showed that there was a significant negative correlation between low 25(OH)D level (≤30 nmol/l) and white blood cell count (OR 1.35, 95 % CI 1.13, 1.60) in the elderly (> 50 years old).[14]

The study by Marcos-Pérez (2020) showed an negative correlation between serum 25(OH)D levels and health severity. Cancer, cardiovascular disease, hypertension, diabetes, dyslipidemia, or poor inflammatory response were more likely to occur in patients with low 25(OH)D levels. According to the research results of Forman et al. (2007), the level of (OH)D < 15ng/ml was a risk of hypertension 6.13 times higher in men and 2.67 times higher in women than those with (OH)D > 30 ng/ml.[15]

With echocardiography, it aims to investigate the movement of the heart wall, heart function as well as heart valves. When a patient has coronary artery disease,.the myocardium supplied by that coronary artery will fall into hypoxia and dyskinesia such as hypokinesia or akinesia. Echocardiography usually detects coronary artery disease at a late stage because at this time, heart wall motion abnormality have appeared. Echocardiography helps to assess the diffused of vascular remodeling, the morphology of the atherosclerotic plaques, the abnormalities and the three-dimensional structure of the blood vessels, and provides a scientific basis for the reliable measurements, thereby guiding more effective coronary interventions.

For echocardiography images, through this study, it was found that 66.7% of patients had ventricular dyskinesia in both the vitamin D deficiency group and the vitamin D enough group.

According to study by Dogan Y (2015) in Turkey showed the mean level of 25(OH)D was 20 ± 3ng/ml prone to coronary artery occlusion (CCC) according to Rentrop classification grade 0-1; while in the group of patients with 25(OH)D of 30±6 ng/ml was CCC Rentrop grade 2,3.[12] According to Dhibar DP (2016), the prevalence of vitamin D deficiency was very high in patients with coronary artery disease (CAD).[16] Vitamin D deficiency was associated with the pathogenesis of coronary artery disease.[4] Low levels of 25-hydroxyvitamin D were an independent risk factor for cardiovascular events, especially stroke and sudden cardiac death.[17] 25-hydroxyl vitamin D influencing the formation of tissues and participating in the regulation of blood pressure through the Renin-Angiotensin system and regulating the development of vascular wall cells and cardiomyocytes. There were many evidences that vitamin D deficiency adversely affects cardiac function, increasing cardiac contractility, myocardial hypertrophy and fibrosis. Receptor for 1,25-dihydroxyvitamin D found in smooth muscle, plays an important role for Vitamin D in regulating smooth muscle contraction and blood pressure. Vitamin D deficiency is also an inflammatory factor that is directly involved in the process of atherosclerosis and plaque rupture. Chronic vitamin D deficiency causes secondary hyperparathyroidism, thereby promote many adverse cardiovascular effects. Vitamin D reduces arterial stiffness and endothelial thickening by inhibiting extracellular accumulation in the vascular wall through its inhibitor effect on MMP.

Contrast selective coronary angiography is the gold standard for the diagnosis of coronary artery disease. Through this measure will know the status of the patient's coronary artery system to help diagnose coronary artery diseases such as stenosis, occlusion, dissection, thrombosis.

The results of coronary angiography in our study showed that significant coronary artery lesion occurred on all coronary arteries. Significant stenosis was found in LAD artey (66.6%), LCx artery (51.6%) and RCA artery (63.7%). The rate of moderate stenosis in LM artery was 0.06%.

Our results recorded that the number of patients with 25(OH)D test results < 30 ng/mL, those with 3-vessel stenosis accounted for 42.4%, patients with 2-vessel stenosis accounted for 36.2% and patients with 1-branch stenosis accounted for 21.2%.

Conclusion

The serum 25(OH)D level was a statistically significant different between the patients with different hypertension grades. The level of 25(OH)D was highest in patients with grade I hypertension and lowest in patients with grade III hypertension. The cut-off point of 25(OH)D in predicting grade II-III hypertension was < 23.88 ng/ml; AUC = 95.9%, ($p < 0.05$). Blood cholesterol was negative correlation with serum 25(OH)D level and the correlation coefficient $r = -0.205$ with $p>0.05$. White blood cells was positive correlation with the serum 25(OH)D level and the correlation coefficient $r = 0.366$ with $p > 0.05$.

Gensini score was negative correlation with serum 25(OH)D level and the correlation coefficient $r = -0.150$ with $p > 0.05$.

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