Original Article

Slow Coronary Flow and the Serum Vitamin D Level

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ABSTRACT

Background: Several studies have demonstrated an association between vitamin D deficiency and cardiovascular diseases. Slow coronary flow (SCF) is a phenomenon in coronary angiography defined as the slow (delayed) opacification of the epicardial coronary arteries with contrast agents in the absence of coronary obstruction. We sought to evaluate the level of vitamin D in SCF patients against normal coronary conditions.

Methods: This cross-sectional study was carried out on 164 patients admitted for elective coronary angiography. For 15 months, from among these patients, 82 patients with SCF and 82 patients with normal coronary arteries or mild coronary artery disease (CAD) who were matched for age and gender were selected and vitamin D levels were measured accordingly.

Results: The mean age of the patients was 56 years in the normal coronary group and 54 years in the SCF group. The mean level of vitamin D was 23.84 ng/mL in the normal coronary group and 24.29 ng/mL in the SCF group. Vitamin D deficiency was observed in 44.4% of the patients in the normal coronary group and 41.2% of the patients in the SCF group. The Mann–Whitney *U* test showed no significant difference between the 2 groups in terms of vitamin D levels ($P = 0.96$).

Conclusions: The level of vitamin D was not significantly different between our 2 groups of patients with SCF and with normal coronary arteries (or mild CAD). ***(Iranian Heart Journal 2019; 20(4): 71-78)***

KEYWORDS: Slow coronary flow, Vitamin D deficiency, Angiography

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Vitamin D is a kind of fat-soluble vitamin produced via sun exposure in the skin and acts as a steroid hormone. The liver and kidney act as intermediaries in the creation of the active form of vitamin D. [1,2]

The prevalence of vitamin D deficiency worldwide and in all populations is high. [3] The prevalence of vitamin D deficiency is about 30% to 50% in developing countries. The level of vitamin D is higher in summer and among men, individuals consuming vitamin D supplements, persons with fair skin, and those who spend more time outdoors. [4]

Several studies have shown an association between vitamin D deficiency and cardiovascular diseases—including, hypertension, myocardial infarction, heart failure, coronary artery disease (CAD), metabolic syndrome, and diabetes. [2,3,5-10]

The association between cardiovascular diseases and vitamin D deficiency may be due to endothelial dysfunction, the overactivity of the renin-angiotensin-aldosterone system (RAAS), the promotion of chronic inflammation, hyperparathyroidism, and the activity of inflammatory cytokines and their effects on the mechanisms of insulin sensitivity. [3,9,11] In some studies, the serum vitamin D level had no or weak relationships with cardiovascular diseases. [4,12-14]

Oz et al [3] found a strong association between slow coronary flow (SCF) and vitamin D insufficiency, which had not been considered in previous studies.

SCF is a phenomenon in coronary angiography defined as the slow (delayed) opacification of the epicardial coronary arteries with contrast agents in the absence of coronary obstruction (normal or near-normal coronary arteries). Its exact mechanism is unknown; however, several mechanisms have been proposed to cause SCF—including, microvascular abnormalities, diffuse atherosclerosis or occult atherosclerosis, endothelial dysfunction, vasomotor dysfunction, inflammatory processes, and platelet dysfunction. [3,15-17] Many patients with SCF experience recurrent chest pains and require coronary angiography. [3]

The prevalence of SCF in patients who undergo coronary angiography ranges from 1% to 7% in multiple studies. [15,17,18]

The Beltrame criteria for diagnosing primary SCF include

1. angiographic evidence of SCF, defined by
   a. no evidence of obstructive epicardial coronary artery disease (no lesions ≥ 40%)
   b. delayed distal vessel contrast opacification as evidenced by either thrombolysis in myocardial infarction (TIMI) 2 flow (requiring ≥ 3 beats to opacify the vessel) or a corrected TIMI count > 27 frames.
   c. delayed distal opacification in at least 1 epicardial vessel

2. exclusion of the secondary causes of SCF—including the no-reflow phenomenon, coronary emboli, coronary ectasia, and exogenous vasoconstrictor administration. [18]

In a study by Bugiardini et al, [19] a normal coronary angiography is defined as no visible disease or luminal irregularities (< 50%) as judged visually in coronary angiography. In the present study, we defined normal coronaries in accordance with the same definition in addition to the proviso that the patients had no SCF criteria in coronary angiography.

The role of vitamin D in the development of CAD is still being studied, and the existing literature has a dearth of data on the relationship between vitamin D levels and SCF.

The current study aimed to evaluate the level of vitamin D in patients with SCF compared with normal coronary arteries in coronary angiography.

METHODS

For 15 months (from September 2017 to December 2018), patients admitted to the Cardiology Department of Shafa Hospital in Kerman, Iran, for elective coronary angiography after providing consent for coronary angiography and consent to enter the study (if after the angiography, the criteria for entering the study were met) underwent coronary angiography via the standard Judkins technique. The coronary arteries were visualized in standard left and right oblique planes and using caudal and cranial angulations, at a rate of 30 frames/s.

After coronary angiography, the patients' angiography was peer-assessed by 2 independent cardiologists; and if the result of angiography was SCF (based on the Beltrame criteria) [8] or normal CAD (or mild CAD), the patients were entered into the study and the exclusion criteria were examined.

The exclusion criteria comprised previous or current use of vitamin D supplements, moderate or severe left ventricular dysfunction, liver or kidney failure, acute coronary syndrome, and malignancy.

Finally, 82 eligible patients (according to the results of coronary angiography and after an evaluation of the exclusion criteria) were placed in the SCF group and 82 patients who were matched for age and gender with the SCF group and whose angiographic result was normal coronary artery (or mild CAD) were allocated to the control group (a total of 164 patients).

First, the patients were asked about their demographic characteristics and history of diseases—including age, gender, substance abuse (eg, opium and cigarette), a history of diabetes, thyroid problems, and hypertension. The data were inserted into the data collection module.

Blood samples (10 cc of venous blood in the fasting state) were taken from the patients to measure vitamin D (25 [OH] vitamin D level). The blood samples were transferred to the laboratory and centrifuged and the level of active vitamin D was measured via the ELISA method.

This study was approved by the Medical Ethics Committee of Kerman University of Medical Sciences.

Statistical Analysis

All data were entered into SPSS, version 18, and the statistical analyses were done in 2 sections: descriptive and analytical. In the descriptive section, central and dispersion indicators were used to describe the quantitative data and tables and charts was used to describe the qualitative data. The Mann–Whitney *U* test and the Spearman correlation test were utilized to analyze the data. The significance level was a *P* value < 0.05.

RESULTS

Eighty-two patients were placed in the SCF group and 82 patients were allocated to the normal coronary group. The mean (± standard deviation) age of the patients was 56 (± 10.68) years in the normal coronary group and 54 (± 10.93) years in the SCF group. In the normal coronary group, 45 (55%) patients were women and the rest were men; and in the SCF group, 44 (54%) patients were women and the rest were men.

The number of patients with diabetes and hypertension in the normal coronary group was significantly higher than that in the SCF group: 25 patients in the normal coronary group and 13 patients in the SCF group were diabetic (P = 0.026), and 45 patients in the normal coronary group and 32 patients in the SCF group were hypertensive (P = 0.042).

The two groups did not present a significant difference in the other variables (including opium or cigarette consumption, thyroid problems, and hyperlipidemia) (Table 1).

Table 1. Frequency distribution and comparison of the variables studied in terms of the Coronary angiography results

	Variable	Normal Coronary	SCF	*P* value
Gender	woman	45(54.9)	44 (53.7)	0.875
	man	37(45.1)	38 (46.3)	
Cigarette smoking	yes	6(7.3)	10 (12.2)	0.292
	no	76(92.7)	72 (87.8)	
Opium addiction	yes	14(17.1)	18 (22.0)	0.431
	no	68(82.9)	64 (78.0)	
Diabetes	yes	25(30.5)	13 (15.9)	0.026
	no	57(69.5)	69 (84.1)	
Hypertension	yes	45(54.9)	32 (39.0)	0.042
	no	37(45.1)	50 (61.0)	
Hyperlipidemia	yes	26(31.7)	24 (29.3)	0.734
	no	56(68.3)	58 (70.7)	
Hyperthyroidism	yes	0	1 (1.2)	1*
	no	82(100.0)	81 (98.8)	
Hypothyroidism	yes	4(4.9)	2 (2.4)	0.682*
	no	78(95.1)	80 (97.6)	

*Fisher exact test
SCF, Slow coronary flow

According to the Spearman test, there was a significant positive correlation between age and serum vitamin D levels in the SCF group. With increasing age, there was a slight increase in vitamin D levels (r = 0.255, P = 0.023); however, in the normal coronary group, age and serum vitamin D levels were not statistically significant.

In the SCF group, the level of vitamin D in the diabetic patients (P = 0.021) and the hypertensive patients (P = 0.015) was higher than that in the nondiabetic and patients with normal blood pressure (Table 2). Nonetheless, in the normal coronary group, there was no significant difference in the level of vitamin D between the diabetic and hypertensive patients compared with the nondiabetic patients and those with normal blood pressure. In the SCF group, there were only 13 patients with diabetes and only 32 patients with hypertension; consequently, it appears that this conclusion is not reliable and requires more studies with a larger sample size.

Table 2. Comparison of vitamin D levels in terms of diabetes and hypertension in the patients with SCF

	Disease	Mean	SD	Median	Minimum	Maximum	*P* value*
Diabetes	yes	30.31	11.69	25	15	54	0.021
	no	23.13	14.05	20	5	62	
Hypertension	yes	28.60	13.54	24	10	56	0.015
	no	21.71	13.57	19	5	62	

*Mann–Whitney *U* test
SCF, Slow coronary flow

The mean (±SD) level of vitamin D in the normal coronary group was 23.84 (±13.24) ng/mL with the minimum of 6 ng/mL and the maximum of 64 ng/mL; while in the SCF group, it was 24.29 (±13.88) ng/mL with the minimum of 5 ng/mL and the maximum of 62 ng/mL. In the normal coronary group, 44.4% of the patients had vitamin D deficiency, 28.4% had suboptimal vitamin D levels, and 27.2% had normal levels of vitamin D. In the SCF group, 41.2% had vitamin D deficiency, 30.4% had sub-optimal levels, and 26.7% had normal levels of vitamin D (Table 3).

Table 3. vitamin D levels in the SCF and normal coronary arteries

			Vitamin D Level (ng/mL)			Total
			<20	20-30	30<	
Group	normal coronary	count	36	23	22	81
		% within group	44.4%	28.4%	27.2%	100.0%
	slow flow	count	33	26	21	80
		% within group	41.2%	32.5%	26.2%	100.0%
Total		count	69	49	43	161
		% within group	42.9%	30.4%	26.7%	100.0%

The results of the Kolmogorov–Smirnov test showed that the level of vitamin D did not follow a normal distribution. Regarding the non-normal distribution level of vitamin D, the Mann–Whitney *U* test was used and the result of this test showed no significant difference between the 2 groups in terms of vitamin D levels (Fig. 1 & 2 and Table 4).

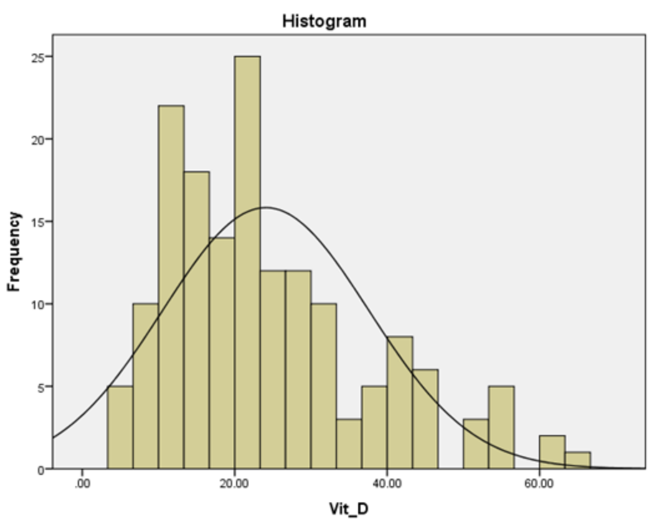

Figure 1. Non-normal distribution level of vitamin D (ng/mL)

Table 4. Comparison of vitamin D levels (ng/mL) in terms of coronary flow

Coronary Angiography	Mean	SD	Median	Minimum	Maximum	*P* value*
Normal coronary	24.87	16.11	22	6	64	0.96
Slow flow	25.47	15.62	22	5	62	

*Mann–Whitney *U* test

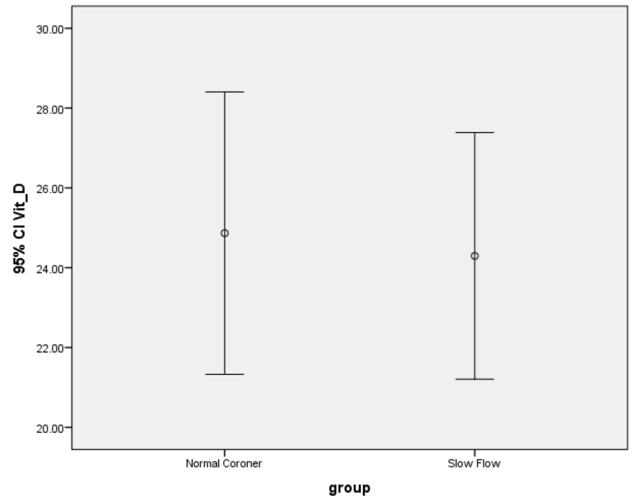

Figure 2. Comparison of vitamin D levels in terms of coronary flow

The patients in the SCF group were also evaluated for the TIMI frame count. Based on the Spearman correlation test, there was no correlation between the vitamin D level and the TIMI frame count ($r = 0.115$, $P = 0.319$).

DISCUSSION

Vitamin D deficiency is a common medical problem in the world. Various studies have shown the inhibitory effects of vitamin D on the RAAS, coronary calcification, the proliferation of smooth muscle cells, and myocardial hypertrophy. [14] Several studies have also considered an association between vitamin D deficiency and cardiovascular diseases in recent years. [2,3, 5-10]

In a systematic review and meta-analysis study in Iran, the overall prevalence of vitamin D deficiency (vitamin D level < 20 ng/mL) was reported to be 56%. That study showed that 64% of women and 44% of men were suffering from vitamin D deficiency and, thus, recommended that strategies be devised to improve the status of vitamin D at the national level. [20]

In the present study, vitamin D deficiency < 20 ng/mL was 44.4% in the normal coronary group and 41.2% in the SCF group, which is a very high percentage. This low level of vitamin D requires special attention to the health and nutrition of the community.

The SCF phenomenon is characterized by delayed opacification of the epicardial coronary arteries with contrast agents in angiography without occlusive coronary disease; it can cause chest pains at rest or activity, hypertension, sudden cardiac death, or even acute myocardial infarction. [3,21]. The exact mechanism of SCF is still unknown, but possible mechanisms include microvascular and endothelial dysfunction and diffuse atherosclerosis. [3]

In recent years, many terms have been used to describe patients who have had chest pains due to myocardial ischemia despite normal coronary artery angiography; these terms include X syndrome, microvascular angina, and non-atherosclerotic myocardial ischemia. Patients with normal angiography and chest pains not only may have coronary microcirculation disturbances but also may be at risk in the entire coronary artery and the peripheral circulation. [19]

While highlighting the normal epicardial coronary artery in this study, we cannot conclusively state that coronary arteries were completely normal. However, it can be merely expressed, based on their appearance, that these patients did not have coronary artery stenosis and did not have the criteria considered for the SCF group.

Several studies have recently investigated the relationship between the level of vitamin D and cardiovascular diseases (and cardiovascular risk factors). The majority of these studies have shown that in patients with cardiovascular diseases, vitamin D deficiency is more prevalent. [2,3,5-11,22] Nonetheless, in some studies, the results are inconsistent or contradictory with the above studies. [4,12,13]

In the present study, we considered the relationship between the level of vitamin D and SCF in coronary artery angiography compared with normal coronary arteries (which was given no special attention in previous studies).

We found a significant positive correlation between the serum vitamin D level and age in the SCF group, with a slight increase in the vitamin D level (r = 0.255, P = 0.023) with increasing age; nevertheless, in the normal coronary group, we observed no significant correlation between age and serum vitamin D levels.

Khazaei et al [23] considered the level of vitamin D in healthy individuals. These individuals had higher levels of vitamin D; and as the age increased, so did the vitamin D level in these individuals. Nasri et al [24] evaluated the level of vitamin D in normal renal function, where there was a significant positive correlation between vitamin D levels and age. In these 2 studies, vitamin D levels increased with age, similar to those in the SCF group in our study. In neither of these studies, the relationship between age and vitamin D level was reported in patients undergoing coronary angiography. Therefore, further studies are needed to investigate the relationship between age and vitamin D levels based on the results of angiography (SCF and normal coronary).

Several studies have examined the association between vitamin D deficiency and endothelial dysfunction in different patients and have shown that vitamin D deficiency is associated with endothelial dysfunction. [25,26] However, these studies have not been performed on coronary arteries.

Oz et al [3] (2013) evaluated the TIMI frame count in coronary angiography, endothelial dysfunction, and vitamin D levels. They measured the TIMI frame count and the vitamin D level of 222 patients with normal or near-normal coronary angiography and reported that the average TIMI frame count was 20.9 ± 4 in the patients with normal levels of vitamin D (> 30 ng/mL) and 24.3 ± 4.4 in those with low levels of vitamin D (< 30ng/mL), which was statistically significant. That study showed that there was a strong correlation between vitamin D deficiency and SCF and endothelial dysfunction.

In the present study, in contrast to the study above, we found no significant difference in the level of vitamin D between the 2 groups of patients with SCF and normal coronary patients. In this study, the TIMI frame count was also calculated in SCF patients and was compared with vitamin D levels in these patients. There was no significant relationship between the frame count and the vitamin D level. These results are in contrast to the results of the study by OZ et al. [3]

In the investigation by OZ et al, [3] only 34 patients met the SCF criteria (TIMI frame count > 27). In fact, patients with a low level of vitamin D had a higher TIMI frame count, but only 34 patients (7% prevalence) had the SCF criteria in at least 1 coronary artery. In contrast, in the present study, the number of patients in the SCF group was 82, which is one of the strengths of our study.

Finally, because only a few studies have considered the level of vitamin D in SCF patients and contradictory outcomes have been obtained, we recommend that more studies be done with a larger sample size.

CONCLUSIONS

Based on the results of the current study, the level of vitamin D in the group of patients with SCF was not significantly different from that of the group with normal coronary arteries (or mild CAD).

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