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Role Of 25 Hydroxyvitamin D In Predicting Angiographic Severity Among Type 2 Diabetic Patients With Coronary Artery Disease.

Shaheena Yassir[1]*, Prabha Adhikari[2], Nivedita L Rao[3], Prashanth RM[4], Saiqa Rasool Shah[5], and Yassir M Abdulla[6].

[1]Associate Professor, Department of Biochemistry, Yenepoya Medical College, Yenepoya (Deemed to be University), Derelakatte, Mangalore 575018, Karnataka, India.
[2]Professor and HOD of Geriatric Medicine, Yenepoya Medical College Hospital, Yenepoya (Deemed to be University), Derelakatte, Mangalore 575018, Karnataka, India.
[3]Professor, Department of Biochemistry, Yenepoya Medical College, Yenepoya (Deemed to be University), Derelakatte, Mangalore 575018 Karnataka, India.
[4]Associate Professor Department of Cardiology, Yenepoya Medical College Hospital, Yenepoya (Deemed to be University), Derelakatte, Mangalore 575018, Karnataka, India.
[5]Associate Professor, Department of Biochemistry, LNCTMC Indore, LNCT Medical College & Sewakunj Hospital Indore 452012, Madhya Pradesh, India.
[6]Department of Radiodiagnosis, Srinivas Institute of Medical Sciences and Research Center, GHS Road, Mangalore 575 001, Karnataka, India.

ABSTRACT

Type 2 Diabetes Mellitus (T2DM), is one of the main risk factors of coronary artery disease (CAD). Several modifiable factors influence the cardiac function in diabetic patients. So the current study was aimed to evaluate the influence of 25 hydroxy vitamin D (25(OH)D) on the severity of coronary artery stenosis among T2DM patients. A cross sectional study was conducted on 130 T2DM patients diagnosed with CAD, aged between 35 to 65 y of both sex. Serum 25(OH)D [Chemiluminescent Immunoassay (CLIA)] was estimated in the automated instrument. Study participants were categorized based on the 25(OH)D levels as sufficient (>30 ng/mL), insufficient (21-29 ng/mL), and deficient (< 20 ng/mL) in vitamin D. Assessment of angiographic severity was done by using number of coronary vessel stenosed, Gensini score and SYNTAX score. Among the 130 study participants, only 20.7% had sufficient 25(OH)D and the remaining 35.4% and 43.1% were 25(OH)D insufficient and deficient respectively. The mean 25(OH)D was 22.92 ± 8.67. 25(OH)D was not associated with severity of angiographic findings assessed by number of vessel stenosed (p=0.132), Gensini score (p=0.864) and SYNTAX score (p=0.180). The prevalence of VDD was very high among T2DM with CAD, however, no significant association was found with severity of CAD.
Keywords: Coronary Artery Disease, 25 hydroxyvitamin D, Type 2 Diabetes Mellitus, Vitamin D deficiency.

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Corresponding author

INTRODUCTION

Diabetes mellitus (DM) is one of the major public health problems worldwide. Global estimates indicate that currently 415 million people are diagnosed with DM and is expected to increase to 642 million by 2040 [1]. Type 2 Diabetes Mellitus (T2DM) is one of the major risk factors, leading to coronary artery disease (CAD). Several modifiable factors influence the cardiac function among diabetes patients. With the discovery of vitamin D receptors in many body tissues, new links between diabetes and cardiovascular diseases (CVD) have been studied [2]. So, the current study was aimed to assess the impact of 25 hydroxy vitamin D (25(OH)D) on the severity of coronary artery stenosis in T2DM patients with CAD.

MATERIALS AND METHODS

A cross sectional study was conducted among T2DM patients undergoing angiogram/ angioplasty with known or suspected CAD and with significant angiographic findings (n=130), aged 35-65 y, of either gender.

Ethical consideration

The work proposal was approved by Yenepoya University Ethics Committee-1 (Protocol No.YEC-1/2019/106) on 4th July 2019. Participants were recruited in the study after obtaining their informed consent.

Sample size calculation

The sample size x calculated for the study was based on the following formula [3]

$$\frac{Z_{1-\alpha/2} + Z_{1-\beta^2}}{1/2 \text{ Loge} \frac{1+r}{1-r}} + 3 \qquad =130$$

$Z_{1-\alpha/2} = 1.96$, $\alpha = 0.05$, $1\text{-}\beta = 20\%$, $Z_{1-\beta} = 0.84$, $r = 0.246$

The sample size of 130 is calculated as per the above formula.

Selection criteria

Diabetic patients aged between 35 to 65 y with significant angiographic findings were recruited in the study. Patients on vitamin D supplementation, chronic hepatic and renal disorder, those with insignificant angiographic findings and history of intake of drugs which can affect vitamin D metabolism within 6 weeks of study were not included in the study.

Anthropometric measurements

BMI was calculated as weight (kg) / height (m^2) and categorization of participants based on their BMI as per the WHO classification of BMI for the Asian population: Normal weight: 18.5 - 23 kg/m^2, Overweight: 23 – 27.5 kg/m^2, Obese: ≥ 27.5 kg/m^2 [4].

Biochemical investigations

Serum level of 25(OH)D was estimated on automated instrument- VITROS 5600 Integrated System using their dedicated reagent under the principle of chemiluminescent immunoassay (CLIA).

Assessment of CAD severity

The CAD severity was assessed using three methods, which includes number of stenosed vessels, Gensini scoring system and SYNTAX scoring system.

Based on the number of the stenosed vessel

The CAD severity was graded as single vessel disease, double vessel disease, and triple vessel disease, based on the number of the major epicardial vessel with significant stenosis (>50%).

Gensini scoring system

A score is given based on the degree of stenosis, and the score is then multiplied by a factor according to the site of the lesion (Gensini (1983). Gensini score risk: low < 24.5, moderate 24.5 - 68, high >68 [5].

Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery (SYNTAX) Score

All the angiographic variables pertinent to calculating the SYNTAX score were obtained by reviewing angiograms. Each coronary lesion with significan stenosis (>50%) in vessels ≥1.5mm was scored separately and summated to obtain the overall SYNTAX TM score, which was calculated using dedicated software that integrates (a) the number of lesions with their specific weighting factors based on the amount of myocardium distal to the lesion according to the score of Leaman *et al*., (1981)[39] and (b) the morphologic features of each single lesion.[127] A computer algorithm (www.syntaxscore.com) is then queried, and a summed value is produced as a total SYNTAX score. SYNTAX score risk: low < 16, moderate 16-22, high >22 [6, 7].

Study groups

Based on the 25(OH)D level, study participants were grouped as follows.

- Group 1 with vitamin D sufficient (≥ 30 ng/mL),
- Group 2 with vitamin D insufficient (20 -29 ng/mL)
- Group 3 with vitamin D are deficient (< 20 ng/mL).[8]

Statistical analysis

Statistical package SPSS vers.23 was used. Normality distribution was checked by Shapiro-Wilk test. Mean and standard deviation (SD) were used for continuous variables. Categorical variables were expressed as frequency and percentage. Categorical variables were compared using the chi-square test. Correlation was done by Spearmann correlation. p< 0.05 was considered as significant.

RESULTS

Table 1: Characteristics of the study population (N=130)

SI. No	Anthropometric variables	Categories	Anthropometric measurements
1	Age (years)		54.06 ± 7.31
2	*Gender	Male	93 (71.5%)
		Female	37 (28.5%)
3	*BMI		24.51 ± 3.54
		Normal	43 (33.07%)
		Overweight	35 (26.92%)
		Obese	52 (40.0 %)
4	Blood Pressure (mm/Hg)	Systolic	126.15 ± 12.41
		Diastolic	80 ± 6.59
5	*25 (OH) vitamin D		22.92 ± 8.67
		Group I	27 (19%)
		Group II	46 (35%)
		Group III	57 (45%)

Data is expressed as mean ± SD for continuous variables. *Categorical variables are expressed in frequency with percentage in parenthesis (%). Abbreviations used: BMI: Body mass index, WC: Waist circumference. Categorization of participants based on their BMI as per the WHO classification of BMI for the Asian population: Normal weight: 18.5 - 23 kg/m^2, Overweight: 23 – 27.5 kg/m^2, Obese: ≥ 27.5 kg/m^2, BP: Systolic: 140 mm of Hg , Diastolic: 90 mm of Hg. Group I- 25(OH) vitamin D sufficient (≥30 ng/mL), Group II- 25(OH) vitamin D insufficient (20-29 ng/mL), Group III- 25(OH) vitamin D deficient (<20 ng/mL).

Table 2: Coronary vessel stenosis severity score and treatment modalities (N=130)

SI. No.	Angiographic findings	Severity score
Status of coronary vessel stenosis		
1	No. of coronary vessels involved	
	a) Single	37(28.4%)
	b) Double	50(38.4%)
	c) Triple	43 (33.2%)
Scoring system based on the coronary vessel stenosis		
1	*Gensini score	40.95 ± 34.01
2	*Syntax score	19.38 ± 13.30
Treatment recommended		
1	Medical management	6 (4.6%)
2	PTCA	96 (73.9%)
3	CABG	28 (21.5%)

Data for coronary vessel stenosis and treatment recommended is expressed in frequency and percentage in parenthesis (%).*Data for scoring system based on the coronary vessel stenosis is expressed as mean ± SD. Abbreviations used: PTCA – Percutaneous transluminal coronary angioplasty, CABG – coronary artery bypass grafting.

Table 3: Correlation of 25(OH) vitamin D with the angiographic score

SI.No.	Parameters	Correlation coefficient (r)	p value
1	Gensini score	0.060	0.495
2	SYNTAX score	0.100	0.257

Statistical test used

Spearman correlation expresses as 'r' value. Level of significance: *p<0.05 was considered significant, p>0.05 was considered non significant. Abbreviations used: SYNTAX -Synergy Between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery.

Table 4: Association of no. of vessels stenosed with 25(OH) vitamin D groups

SI.No.	No. of vessels stenosed	Groups based on Vitamin D status			p value
		Group I (n=27)	Group II (n=46)	Group III (n=57)	
1	Single	11 (29.7)	9 (24.3)	17 (45.9)	0.132
2	Double	5 (10.0)	20 (40.0)	25 (50.0)	
3	Triple	9 (20.9)	17 (39.5)	17 (39.5)	

Data is expressed as frequency (n) with percentage in parenthesis (%). n= number of participants in each group. Study groups: Group I- 25(OH) vitamin D sufficient (≥30 ng/mL), Group II- 25(OH) vitamin D sufficient (20-29 ng/mL), Group III- 25(OH) vitamin D deficient (<20 ng/mL). Statistical test used is Chi Square. Level of significance: *p<0.05 is considered significant. p>0.05 is considered non-significant.

Table 5: Association of Gensini and SYNTAX score with 25(OH) vitamin D groups

SI.No.	Risk score classification	Groups based on Vitamin D status			p value
		Group I (n=25)	Group II (n=46)	Group III (n=58)	
Gensini score risk					
1	Low (n= 50)	10 (20)	20 (40)	20 (40)	0.864
2	Moderate (n= 58)	11 (19)	18 (31)	29 (50)	
3	High (n=22)	4 (19)	8 (38.1)	10 (45.4)	
SYNTAX score risk					
1	Low (n=68)	9 (13.2)	24 (35.3)	35 (51.5)	0.180
2	Moderate (n=20)	3 (15)	7 (35)	10 (50)	
3	High (n=42)	13 (31)	15 (35.7)	14 (33.3)	

Data is expressed in frequency with percentage in parenthesis (%). n= number of participants in each group. Study group: Group I- 25(OH) vitamin D sufficient (≥30 ng/mL), Group II- 25(OH) vitamin D insufficient (20-29 ng/mL), Group III- 25(OH) vitamin D deficient (<20 ng/mL).Gensini score risk: low < 24.5, moderate 24.5 - 68, high >68. SYNTAX score risk: low < 16, moderate 16-22, high >22. Statistical test used is Chi Square. Level of significance: *p<0.05 is considered significant.*p>0.05 is considered non significant.

DISCUSSION

The current study aimed to evaluate the influence of 25(OH)D on the angiographic severity in T2DM patients diagnosed with CAD, found no significant effect of 25(OH)D on angiographic severity. However, the mean 25(OH)D level was as low as 22.92 ± 8.67 ng/mL. Only 19% (27/130) had sufficient 25(OH)D, where as 35% (46/130) and 45% (57/130) were insufficient and deficient in 25(OH)D, respectively (Table 1). Hypovitaminosis D at varying prevalence rates are reported earlier among diabetic patients. The prevalence of low vitamin D levels was higher among diabetics and individuals with prediabetes as compared to non diabetic controls [9-12]. Consequently a low vitamin D status was assumed to be involved in the occurence and also progression of T2DM. This was supported by various experimental and clinical studies which showed an enhanced IR and an impaired secretion of insulin in the β cells of pancreas, in the presence of hypovitaminosis D [13, 14]. Knezevic *et al.*, (2017) [15], found that patients with acute coronary syndrome (ACS) had low levels of vitamin D, but the diabetic patients had the lowest level. So, in this current study, we tried to explore different methods to assess angiographic severity, to assess its association with 25(OH)D.

The current study assessed angiographic severity by various methods such as, number of vessels stenosed, Gensini score and SYNTAX score. Majority (71.6%) of the participants had complex vessel disease ie., 38.4% with double vessel stenosis and 33.2 % with triple vessel disease (Table 2). One of the most effective tools for grading the severity of coronary artery lesions and predicting the long term adverse CVD events, is the SYNTAX score. A high SYNTAX score predicts more complex and worse prognosis, among patients undergoing percutaneous coronary intervention (PCI) [16]. Neverthless, no significant correlation of 25(OH)D was found with Genisini and SYNTAX scoring system (Table 3). There was no significant association of 25(OH)D seen with any of the risk score assessed (Table 4 and Table 5).

Dhibar *et al.,* (2016) [17], in their cross sectional study, reported high prevalence of VDD among CAD, but did not correlate with the severity of CAD. Safi *et al.,* (2018) [18], conducted a correlational study among suspected CAD patients. The SYNTAX score and serum vitamin D levels did not, however, show a significant inverse correlation (r=-0.037, p=0.67). Nepal *et al.,* (2021) [19], reported that vitamin D levels among patients with angiographic normal coronary artery and angiographic proven CAD were 25.94 ± 11.63 ng/mL and 26.07 ±12.90 ng/mL respectively (p=0.97). There was no association of VDD with severity of angiographic proven CAD (p>0.05). This finding was in consensus with the findings of present study.

Nevertheless, there are also conflicting findings suggesting a connection between CAD and serum vitamin D levels. According to Aleksova et al. (2020) [20], the adjusted risks for the primary end-point (time to first major event) were similar for T2DM and VDD. In comparison to patients without hypovitaminosis

D or diabetes, the adjusted hazard ratio for the primary composite end-point in patients with hypovitaminosis D and T2DM was 1.69 (95%CI 1.25–2.29, p=0.001). Dziedzic *et al.,* (2021) [21] found that women with more severe coronary atherosclerosis had significantly lower serum 25(OH)D level (p=0.0001) . Vitamin D (β = −0.02; p=0.016), hypertension (β = 0.44; *p*=0.025), age (β = 0.02; p=0.003), and past history of myocardial infarction (MI) (β = 0.63; p<0.0001), were shown as Coronary Artery Surgery Study Score (CASSS) determinants. Age, dyslipidemia, and past history of MI were significantly found to determine the vitamin D level (all p<0.05). Siddiki *et al.,* (2021) [22], found mean age as 55.9±10.7 y and majority (83.1%) of the patients were males which was similar to the present study. Among acute coronary syndrome patients, they found a significant negative correlation (r=-0.479; p=0.001) between serum vitamin D and Gensini score. Somunco *et al*., (2020) [23], reported that MI patients with hyperuricemia and VDD had more multivessel disease (24.1% vs 8.5%), and a higher SYNTAX score and Gensini score as compared with the control group (13.9 ± 8.0 vs. 9.5 ± 6.3, 54.8 ± 24.0 vs. 40.5 ± 19.9, respectively). In MI patients, the co-occurrence of hyperuricemia and VDD seems to be a reliable indicator of severe CAD.

CONCLUSION

The prevalence of VDD in CAD patients, was found to be quite high, though there was no discernible correlation between the severity of CAD. It is possible that vitamin D indirectly contributes to the pathophysiology of CAD, emphasizing the importance of adequate vitamin D intake in individuals with diabetes. Thus, screening and dietary supplementation in case of VDD might be beneficial in retarding the progression of diabetic complications.

Strength of the study

Serum total 25(OH)D was measured to analyse the status of vitamin D , which is considered as the best indicator of vitamin D level from both nutritional intake and cutaneous synthesis. CAD severity was assessed by three different methods such as number of stenosed vessels, Gensini score and SYNTAX score. SYNTAX score, is one of the most powerful tool to grade the severity and complexity of coronary artery lesions. The current study group included adult age group, as the incidence of CAD is increased in this age group.

Limitations

As the present study was a cross sectional study, temporal association between cause and effect could not be identified. Serum 25(OH)D level was detected only once when admitted in the hospital. Lack of control group, use of non diabetic individuals as the control group gives a better picture of the alterations in vitamin D levels and its relation with other factors.

Statements and Declarations

The authors declare that there was no financial or commercial interests that could be inferred as a potential conflict of interest.

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