

# Association of Major Cardiovascular Risk Factors and the Severity of Coronary Artery Disease with Vitamin D Level

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**Abstract:** Objectives: We aimed to investigate the association of major cardiovascular risk factors and the severity of coronary artery disease (CAD) with vitamin D level. Background: Numerous efforts have been made to reduce cardiovascular morbidity and mortality, especially in acute coronary syndrome (ACS). However, results are still not optimal. Much consideration is set on the revelation of new, conceivably modifiable cardiovascular risk factors. Vitamin D deficiency is proposed to be one such factor, and it might be related to an increased risk of cardiovascular diseases. Methods: We conducted a cross-section study on 475 patients undergoing elective coronary angiography, the participants were subjected to assessment of vitamin D level and major cardiovascular risk factors. The severity of CAD was assessed using the gensini score. Results: There were 352 (74.11%) patients, had a significant CAD. We found that vitamin D level had a significant negative correlation with the gensini score while diabetes and dyslipidemia had a significant positive correlation. The multivariate regression analysis showed that, vitamin D deficiency, diabetes, dyslipidemia, higher BMI, and ACS (p-value <0.05), were statistically significant predictors of a significant CAD. There were 184 (38.74%) patients, had vitamin D deficiency. Also, we found that diabetes and dyslipidemia had a significant negative correlation with vitamin D level. The multivariate regression analysis showed that diabetes and dyslipidemia were statistically significantly associated with low vitamin D levels (p-value 0.005 and 0.024 respectively). Conclusions: Vitamin D deficiency, diabetes, dyslipidemia, higher BMI, and ACS were statistically significant associated with severe CAD. Also, diabetes and dyslipidemia were statistically significant associated with vitamin D deficiency.

**Keywords:** CAD, Cardiovascular Risk Factors, Gensini Score, Vitamin D Level

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## 1. Introduction

CAD is one of the leading causes of death worldwide. Numerous efforts have been made to reduce cardiovascular morbidity and mortality, especially in ACS. However, results are still not optimal [1-4]. Much consideration is set on the revelation of new, conceivably modifiable cardiovascular risk factors. Vitamin D deficiency is proposed to be one such factor, and it might be related to an increased risk of cardiovascular diseases [5-7]. Vitamin D is a prohormone with numerous consequences on the immune system,

inflammatory response, and coagulative and thrombotic pathways, therefore connecting vitamin D to the pathogenesis of CAD, and with the occurrence of its acute complications [2, 3, 8, 9]. Additionally, it has been shown that a deficient vitamin D level may influence the cardiovascular system through a classic mechanism, to be specific by advancing changes in the calcium-phosphate metabolism, or through impacts on the renin-angiotensin-aldosterone system [10]. The impacts of vitamin D deficiency were seen at all stages of atherosclerotic plaque formation, destabilization, and rupture [11]. Besides, it has previously been shown that lower levels of vitamin D are independently connected with

other cardiovascular risk factors, for example, hypertension, diabetes, obesity, and metabolic syndrome [12-15]. In contrast, in a study conducted on a heterogeneous Polish population of cardiac patients with hypertension, diabetes, and/or dyslipidemia, there was no significant association between the level of the 25 (OH) D and the stage of coronary atherosclerosis [16]. So, we aimed to investigate the association of major cardiovascular risk factors and the severity of CAD with vitamin D level.

## 2. Materials and Methods

### 2.1. Design of the Study

This was a cross-section observational two-center study conducted on 475 patients  $\geq 18$  years, presented with stable CAD or ACS indicated for elective coronary angiography, at Sohag and Beni Suf university hospitals.

All subjects provided written informed consent to participate in the study. The study protocol was approved by the ethics committee at Sohag and Beni Suf Faculty of medicine.

Patients were subjected to:

1 Identification of major cardiovascular risk factors (age, gender, smoking, hypertension, diabetes mellitus, dyslipidemia, body mass index (BMI), and Family history of CAD).

2 Assessment of symptoms suggestive of coronary insufficiency as typical exertional chest pain or history of admission to the coronary care unit with ACS.

3 Laboratory testing includes, vitamin D assay, fasting blood sugar, hemoglobin A1c level, lipid profile, liver function, and renal function tests.

4 Assessment of vitamin D level: Vitamin D (25-OH D3) assay was done by using MINI VIDAS®, bioMérieux which is a compact automated immunoassay system based on the Enzyme-Linked Fluorescent Assay (ELFA) principles. ELFA combine the methodology of ELISA testing with the utilization of a fluorescent label in the final detection process, Due to the use of combined labels, the results yield a high level of sensitivity and specificity with rapid turnaround times. The normal value for 25-OH D3 levels in our laboratory is  $\geq 30$  ng/ml, vitamin D insufficiency was from 20 to 30 ng/ml, vitamin D deficiency was considered for values  $< 20$  ng/ml, and severe vitamin D deficiency was considered for values  $< 10$  ng/ml. [17]

5 Coronary angiography was performed by an experienced interventional cardiologist who was blinded for the patient characteristics. Assessment of the severity of CAD had been done by using Gensini score, Gensini score grades narrowing of the lumen of the coronary artery and scores it with numerical values as the following: 1 for 1-25% narrowing, 2 for 26-50% narrowing, 4 for 51-75%, and 8 for 76-90%, 16 for 91-99%, and 32 for a totally occluded artery. This score is then multiplied by a factor, according to the site of lesion: The multiplication factor is 5 for a left main stem lesion, 2.5 for proximal left anterior descending artery (LAD) and

proximal circumflex artery (CX) lesions, 1.5 for a mid-LAD lesion, 1 for distal LAD, mid/distal CX and right coronary artery lesions and 0.5 for any other branch. They were further divided into mild CAD group with Gensini score  $< 26$ , moderate CAD group with Gensini score being 26-54 and severe CAD group with Gensini score  $> 54$  (the patient was considered to have a significant CAD if the gensini score was  $\geq 26$ ). [18]

Exclusion criteria:

Patients receiving vitamin D or calcium supplementation, advanced liver disease, chronic kidney disease (stage III-V), patients had cancer and patients with fever or elevated inflammatory markers.

Definitions:

In this study, the participant was considered diagnosed diabetic if (1) other than during pregnancy he had a physician previously told him that he has diabetes, or (2) taking anti-diabetic treatment. Also, participants were considered as newly diagnosed diabetics if they had one of the following: 1- Fasting plasma glucose  $\geq 126$  mg/dl 2- Symptoms of hyperglycemia and random plasma glucose  $\geq 200$  mg/dl 3- HbA1c  $\geq 6.5\%$  [19].

Systemic hypertension was defined, as a blood pressure  $\geq 140/ \geq 90$  mmHg and/or on current antihypertensive therapy [20].

Elevated triglyceride was defined as triglyceride of  $\geq 150$  mg/dl. Low HDL cholesterol was defined as  $< 40$  mg/dl in males and  $< 50$  mg/dl in females. Elevated LDL was defined as 100 mg/dl or greater [21].

The following formula was used to calculate the minimum size of the required sample:

$$n=(z)^2 p (1 - p) / d^2$$

where n indicates the sample size, z indicates the level of confidence according to the standard normal distribution (for a level of confidence of 95%,  $z=1.96$ ), p indicates the estimated proportion of the population that presents the characteristic, d indicates the tolerated margin of error (for example, we want to know the real proportion within 5%).

Using the previous formula for the sample size calculation  $(n)=(1.96)^2 \times 0.5 (1-0.5) / (0.05)^2=384.16$ . So, the minimum sample size is 385 participants.

### 2.2. Analysis of Data

Data were analyzed using SPSS version 19. Quantitative data were analyzed using the analysis of variance (ANOVA) to compare the means of three or more groups. Qualitative data were compared using the Chi-square test. Fisher's exact correction was used when the expected cell count is less than five. Pearson correlation was used to study the correlation between the Gensini score and other variables and the correlation between vitamin D level and major cardiovascular risk factors. Univariate and multivariate regression analyses were done. Odds ratio (OR) at 95% confidence interval (CI) and p values were computed. P-value was considered significant at or below 0.05.

### 3. Results

The study was conducted on 475 patients  $\geq 18$  years old, a candidate for elective coronary angiography. Table 1 shows the assessment of the severity of CAD using the gensini score and vitamin D level.

There were 352 (74.11%) out of 475 patients, had a significant CAD. We found that, vitamin D level had a significant negative correlation with gensini score (correlation coefficient 'r'=- 0.430, p value < 0.001), while diabetes and dyslipidemia had a significant positive correlation ('r'=0.299 and 220 respectively, p value < 0.001) (Table 2).

The multivariate regression analysis showed that, vitamin D deficiency, diabetes, dyslipidemia, higher BMI, and patients presented with ACS were statistically significant

associated with severe CAD (OR: 2.134, 95% CI: 1.637-2.781; p-value <0.001), (OR: 2.890, 95% CI: 1.789-4.670; p-value <0.001), (OR: 3.639, 95% CI: 2.083-6.358; p-value <0.001), (OR: 1.089, 95% CI: 1.013-1.172; p-value 0.021) and (OR: 1.641, 95% CI: 1.138-2.367; p-value 0.008) respectively. (Tables 3, 4)

There were 184 (38.74%) patients had vitamin D deficiency. We found that, diabetes and dyslipidemia had a significant negative correlation with vitamin D level ('r'=- 0.169, p-value < 0.001 and 'r'=- 0.141, p-value 0.002 respectively). (Table 5)

The multivariate regression analysis showed that diabetes and dyslipidemia were statistically significant associated with vitamin D deficiency (OR: 1.757, 95% CI: 1.180 - 2.614, p-value 0.005 and OR: 1.665, 95% CI: 1.069 - 2.594, p-value 0.024 respectively) (Tables 6, 7).

**Table 1.** Distribution of patient characteristics in relation to gensini score.

| Characteristic           | Gensini Score          |                        |                        | P value |
|--------------------------|------------------------|------------------------|------------------------|---------|
|                          | < 26<br>N=123 (25.89%) | - 54<br>N=188 (39.58%) | > 54<br>N=164 (34.53%) |         |
| Age (years)              |                        |                        |                        |         |
| Mean $\pm$ SD            | 50.52 $\pm$ 9.35       | 52.74 $\pm$ 10.54      | 51.49 $\pm$ 11.27      | 0.18    |
| Gender                   |                        |                        |                        |         |
| Male                     | 85 (69.11%)            | 132 (70.21%)           | 104 (63.41%)           | 0.363   |
| Female                   | 38 (30.89%)            | 56 (29.79%)            | 60 (36.59%)            |         |
| Hypertension             |                        |                        |                        |         |
| Yes                      | 57 (46.34%)            | 99 (52.66%)            | 92 (56.10%)            | 0.258   |
| Diabetes                 |                        |                        |                        |         |
| Yes                      | 45 (36.59%)            | 108 (57.45%)           | 123 (75%)              | < 0.001 |
| Dyslipidemia             |                        |                        |                        |         |
| Yes                      | 36 (29.27%)            | 107 (56.91%)           | 97 (59.15%)            | < 0.001 |
| Smoking                  |                        |                        |                        |         |
| Yes                      | 63 (51.22%)            | 100 (53.19%)           | 98 (59.76%)            | 0.293   |
| BMI (kg/m <sup>2</sup> ) |                        |                        |                        |         |
| Mean $\pm$ SD            | 26.20 $\pm$ 3.34       | 27.07 $\pm$ 3.64       | 26.88 $\pm$ 3.33       | 0.082   |
| Family history           |                        |                        |                        |         |
| Yes                      | 22 (17.89%)            | 31 (16.49%)            | 27 (16.46%)            | 0.937   |
| Clinical presentation    |                        |                        |                        |         |
| Stable CAD               | 23 (18.70%)            | 23 (12.23%)            | 18 (10.98%)            | 0.350   |
| ACS                      | 100 (81.30%)           | 165 (87.77%)           | 146 (89.02%)           |         |
| Vitamin D level          |                        |                        |                        |         |
| < 10                     | 4 (3.25%)              | 15 (7.98%)             | 30 (18.29%)            |         |
| $\geq 10$ - < 20         | 11 (8.94%)             | 52 (27.66%)            | 72 (43.90%)            | < 0.001 |
| $\geq 20$ - < 30         | 35 (28.46%)            | 54 (28.72%)            | 32 (19.51%)            |         |
| $\geq 30$                | 73 (59.35%)            | 67 (35.64%)            | 30 (18.29%)            |         |

Abbreviations: ACS, acute coronary syndrome: BMI, body mass index: CAD, coronary artery disease: N, number: SD, standard deviation.

**Table 2.** Correlation between gensini score and other variables.

| Variables                            | Correlation coefficient (r) | P value |
|--------------------------------------|-----------------------------|---------|
| Age                                  | 0.028                       | 0.539   |
| Gender (male/ female)                | 0.051                       | 0.27    |
| Hypertension                         | 0.074                       | 0.106   |
| Diabetes                             | 0.299                       | < 0.001 |
| Dyslipidemia                         | 0.220                       | < 0.001 |
| Smoking                              | 0.068                       | 0.137   |
| BMI                                  | 0.070                       | 0.128   |
| Family history                       | 0.014                       | 0.763   |
| Clinical presentation Stable CAD ACS | 0.082                       | 0.075   |
| Vitamin D level                      | -0.430                      | < 0.001 |

Abbreviations: ACS, acute coronary syndrome: BMI, body mass index: CAD, coronary artery disease: r, correlation coefficient.

**Table 3.** Univariate analysis of variables as regards to severity of CAD.

| Variable                 | Gensini score < 26 | Gensini score ≥ 26 | P value |
|--------------------------|--------------------|--------------------|---------|
|                          | N=123 (25.89%)     | N=352 (74.11%)     |         |
| Age (years)              |                    |                    |         |
| Mean±SD                  | 50.52±9.35         | 52.16±10.89        | 0.138   |
| Gender                   |                    |                    |         |
| Male                     | 85 (69.11%)        | 236 (67.05%)       | 0.674   |
| Female                   | 38 (30.89%)        | 116 (32.95%)       |         |
| Hypertension             |                    |                    |         |
| Yes                      | 57 (46.34%)        | 191 (54.26%)       | 0.130   |
| Diabetes                 |                    |                    |         |
| Yes                      | 45 (36.59%)        | 231 (65.63%)       | < 0.001 |
| Dyslipidemia             |                    |                    |         |
| Yes                      | 36 (29.27%)        | 204 (57.95%)       | < 0.001 |
| Smoking                  |                    |                    |         |
| Yes                      | 63 (51.22%)        | 198 (56.25%)       | 0.334   |
| BMI (kg/m <sup>2</sup> ) |                    |                    |         |
| Mean±SD                  | 26.20±3.34         | 26.99±3.49         | 0.029   |
| Family history           |                    |                    |         |
| Yes                      | 22 (17.89%)        | 58 (16.49%)        | 0.719   |
| Clinical presentation    |                    |                    |         |
| Stable CAD               | 23 (18.70%)        | 41 (11.65%)        | 0.125   |
| ACS                      | 100 (81.30%)       | 311 (88.35%)       |         |
| Vitamin D level          |                    |                    |         |
| < 10                     | 4 (3.25%)          | 45 (12.78%)        |         |
| ≥ 10 – < 20              | 11 (8.94%)         | 124 (35.23%)       | < 0.001 |
| ≥ 20 – < 30              | 35 (28.46%)        | 86 (24.43%)        |         |
| ≥ 30                     | 73 (59.35%)        | 97 (27.56%)        |         |

Abbreviations: ACS, acute coronary syndrome: BMI, body mass index: CAD, coronary artery disease: N, number: SD, standard deviation.

**Table 4.** Multivariate regression analysis for predictors of severe CAD.

| Variables                             | OR (95% CI)                | P value |
|---------------------------------------|----------------------------|---------|
| Age                                   | 0.984 (0.961-1.008)        | 0.193   |
| Gender (male/ female)                 | 1.053 (0.631-1.757)        | 0.844   |
| Hypertension                          | 1.377 (0.847-2.237)        | 0.197   |
| Diabetes                              | 2.890 (1.789-4.670)        | < 0.001 |
| Dyslipidemia                          | 3.639 (2.083-6.358)        | < 0.001 |
| Smoking                               | 0.679 (0.392-1.174)        | 0.166   |
| BMI                                   | 1.089 (1.013-1.172)        | 0.021   |
| Family history                        | 1.123 (0.593-2.125)        | 0.721   |
| Clinical presentation ACS /Stable CAD | 1.641 (1.138-2.367)        | 0.008   |
| Vitamin D level                       | - 2.134 (-1.637 - - 2.781) | < 0.001 |

Abbreviations: ACS, acute coronary syndrome: BMI, body mass index: CAD, coronary artery disease: CI, confidence interval: OR, odds ratio.

**Table 5.** Correlation between patient characteristics and vitamin D level.

| Variables                             | Correlation coefficient (r) | P value |
|---------------------------------------|-----------------------------|---------|
| Age                                   | -0.050                      | 0.280   |
| Gender (male/ female)                 | 0.078                       | 0.091   |
| Hypertension                          | -0.079                      | 0.085   |
| Diabetes                              | -0.169                      | < 0.001 |
| Dyslipidemia                          | -0.141                      | 0.002   |
| Smoking                               | -0.022                      | 0.632   |
| BMI                                   | -0.057                      | 0.219   |
| Family history                        | -0.007                      | 0.847   |
| Clinical presentation Stable CAD» ACS | - 0.006                     | 0.900   |

Abbreviations: ACS, acute coronary syndrome: BMI, body mass index: CAD, coronary artery disease: r, correlation coefficient.

**Table 6.** Distribution of patient characteristics in relation to vitamin D level.

| Characteristic                      | Vitamin D level       |                               |                               |                        | P value |
|-------------------------------------|-----------------------|-------------------------------|-------------------------------|------------------------|---------|
|                                     | < 10<br>N=49 (10.32%) | ≥ 10 – < 20<br>N=135 (28.42%) | ≥ 20 – < 30<br>N=121 (25.47%) | ≥ 30<br>N=170 (35.79%) |         |
| Age (years)<br>Mean±SD              | 52.94±11.94           | 51.84±11.56                   | 52.11±10.25                   | 51.03±9.42             | 0.034   |
| Gender                              |                       |                               |                               |                        |         |
| Male                                | 26 (53.06%)           | 91 (67.41%)                   | 86 (71.07%)                   | 118 (69.41%)           | 0.130   |
| Female                              | 23 (46.94%)           | 44 (32.59%)                   | 35 (28.93%)                   | 52 (30.59%)            |         |
| Hypertension                        |                       |                               |                               |                        |         |
| Yes                                 | 30 (61.22%)           | 77 (57.04%)                   | 56 (46.28%)                   | 85 (50%)               | 0.180   |
| Diabetes                            |                       |                               |                               |                        |         |
| Yes                                 | 33 (67.35%)           | 90 (66.66%)                   | 74 (61.16%)                   | 79 (46.47%)            | 0.001   |
| Dyslipidemia                        |                       |                               |                               |                        |         |
| Yes                                 | 28 (57.14%)           | 77 (57.04%)                   | 68 (56.20%)                   | 67 (39.41%)            | 0.004   |
| Smoking                             |                       |                               |                               |                        |         |
| Yes                                 | 30 (61.22%)           | 68 (50.37%)                   | 71 (58.68%)                   | 92 (54.18%)            | 0.449   |
| BMI (kg/m <sup>2</sup> )<br>Mean±SD | 26.49±3.51            | 27.17±3.63                    | 27.05±3.41                    | 26.36±3.34             | 0.309   |
| Family history                      |                       |                               |                               |                        |         |
| Yes                                 | 10 (20.41%)           | 20 (14.81%)                   | 19 (15.70%)                   | 31 (18.24%)            | 0.756   |
| Clinical presentation               |                       |                               |                               |                        |         |
| Stable CAD                          | 5 (18.70%)            | 19 (12.23%)                   | 22 (10.98%)                   | 18 (10.98%)            | 0.094   |
| ACS                                 | 44 (81.30%)           | 116 (87.77%)                  | 99 (89.02%)                   | 152 (89.02%)           |         |

Abbreviations: ACS, acute coronary syndrome; BMI, body mass index; CAD, coronary artery disease; N, number; SD, standard deviation.

**Table 7.** Multivariate regression analysis for predictors of vitamin D level.

| Variables                             | OR (95% CI)         | P value |
|---------------------------------------|---------------------|---------|
| Age                                   | 0.994 (0.977-1.012) | 0.534   |
| Gender (male/ female)                 | 0.761 (0.508-1.141) | 0.187   |
| Hypertension                          | 1.405 (0.953-2.071) | 0.086   |
| Diabetes                              | 1.757 (1.180-2.614) | 0.005   |
| Dyslipidemia                          | 1.665 (1.069-2.594) | 0.024   |
| Smoking                               | 0.677 (0.432-1.060) | 0.088   |
| BMI                                   | 0.964 (0.912-1.018) | 0.189   |
| Family history                        | 0.975 (0.572-1.662) | 0.927   |
| Clinical presentation Stable CAD» ACS | 0.822 (0.613-1.102) | 0.822   |

Abbreviations: ACS, acute coronary syndrome; BMI, body mass index; CAD, coronary artery disease; CI, confidence interval; OR, odds ratio.

## 4. Discussion

Egypt is one of the developing countries, facing a major socio-economic burden regarding the management of the prevalent cardiovascular diseases and their outcomes. So, it is important to detect and manage any well-established preventable and modifiable cardiovascular risk factors and the revelation of new modifiable risk factors to reduce cardiovascular morbidity and mortality.

In our study, we found that 74.11% of patients, had severe CAD and 38.74% of patients had vitamin D deficiency. Also, we identified that vitamin D deficiency, diabetes, dyslipidemia, higher BMI, and ACS were statistically significantly associated with severe CAD. Besides, diabetes and dyslipidemia were statistically significantly associated with vitamin D deficiency. Also, BMI showed a significant positive correlation with the severity of CAD, while vitamin D level showed a significant negative correlation. Considering the major cardiovascular risk factors, both diabetes and dyslipidemia showed a significant negative correlation with vitamin D level.

Our results were in line with the results of two prospective

studies conducted by Dziejcz EA, et al. the first one published in 2017, was conducted on 337 Polish cardiac patients with type 2 diabetes undergoing coronary angiography and showed that, diabetic cardiac patients had significant differences in the vitamin D level between the groups related to the severity of coronary atherosclerosis, and showed that, a group of cardiac patients with diabetes and significant stenosis in three coronary arteries, hospitalized due to ACS, with the history of previous myocardial infarction and hyperlipidemia, had the lowest vitamin D level. Another study published in 2019 was conducted on 410 non-diabetic patients candidate for coronary angiography reported that, 76% of patients had vitamin D deficiency and patients with one to three-vessel atherosclerosis have a significantly lower vitamin D level compared to patients with insignificant CAD, and lower vitamin D level was observed in ACS patients compared to patients diagnosed with stable CAD. We found a lower incidence of vitamin D deficiency (38.74%) which could be explained by our sunny climate [22, 23].

Verdoia M, et al. conducted a cross-sectional study on 1484 patients undergoing elective coronary angiography. They found that hypovitaminosis D was observed in 70.4%

of patients and vitamin D deficiency was significantly associated with the prevalence and extent of CAD and detected a significant association between vitamin D deficiency and major cardiovascular risk factors such as age, female gender, renal failure, hypercholesterolemia, anemia and smoking, that is matched with our results [24].

In the Atherosclerosis Risk in Communities (ARIC), in a chose gathering of participants the value of vitamin D concentration below 17.2 ng/ml was associated with a higher risk of stroke [25] and a higher risk of CAD [26].

Goleniewska et al. conducted a study on 130 patients with ST-elevation myocardial infarction (STEMI), they identified vitamin D level as an independent predictor of multivessel CAD at multiple logistic regression analysis [27]. Another study evaluated 101 Israeli patients undergoing elective coronary arteriography by Shor et al. showed that there was a correlation between low vitamin D level and severe CAD after adjustment for confounders such as sex, age, body mass index, ethnicity and active tobacco smoking [28]. Syal et al. studied 100 Indian patients undergoing coronary angiography and reported that Indian patients with angiographically documented CAD more commonly have vitamin D deficiency. Also, a significantly higher incidence of two- and three-vessel disease was found in patients with vitamin D deficiency compared to patients with a normal vitamin D level [29]. Besides, Gondim et al. inspected 166 patients with type 2 diabetes determined to have STEMI and observed a higher percentage of vitamin D deficiency compared to patients without STEMI. Also, a higher incidence of multivessel disease was observed in diabetic patients with vitamin D deficiency compared to nondiabetic patients [30]. Shanker et al. studied 287 Indian patients with CAD and reported that vitamin D levels were significantly lower than in matched healthy controls, and patients with low vitamin D levels having a greater risk of CAD than those with higher vitamin D levels [31]. Also, Verdoia M, et al. conducted a study on 1811 patients undergoing coronary angiography and demonstrated that lower levels of vitamin D were associated with an increased prevalence and severity of CAD in females. While in male patients, vitamin D levels were independently related to the prevalence of CAD, but not related to the severity of CAD [32].

We identified a significant association between vitamin D deficiency and diabetes and dyslipidemia that matches with the results of a cross-sectional study in 3788 Chinese subjects conducted by Jiang X, et al. who concluded that Vitamin D deficiency was significantly associated with dyslipidemia and serum vitamin D was inversely correlated with LDL cholesterol and triglycerides levels, and positively correlated with HDL cholesterol level [33]. Also, Jorde R, et al. showed that there was a significant increase in serum TC, HDL-C, and LDL-C, and a significant decrease in serum LDL-C/HDL-C ratio and TAG across increasing serum 25 (OH) D quartiles [34]. Another study conducted on 150 Indian patients by Chaudhuri JR, et al. showed that vitamin D deficiency was found in 39.3% of patients and significantly associated with dyslipidemia and mean serum glucose [35].

Ge H, et al., conducted a study with 1191 participants and reported that serum 25 (OH) D3 deficiency was associated with dyslipidemia [36]. Alhewishel M A, et al. 2020 investigated the association between diabetes and vitamin D level in Saudi Arabia and showed that 89.53% of the patients had a vitamin D level below the normal range and vitamin D level was inversely proportional to the level of fasting glucose and HbA1c [37]. Dalgård C, et al. also, concluded that vitamin D sufficiency may protect against type 2 diabetes in elderly subjects [38].

Despite all this evidence supporting the association between vitamin D level and diabetes, dyslipidemia, and severity of coronary artery disease, the results of vitamin D supplementation are still controversial as regard this issue. Sugden et al. showed that vitamin D supplementation improved endothelial function in diabetics with low vitamin D levels [39]. A randomized trial conducted by Witham et al. agreed with Sugden et al. in that a single high dose of vitamin D2 improves endothelial function [39, 40]. A systematic review and meta-analysis created by Wu et al. concluded that vitamin D supplementation could be successful at improving glycemic control, in a chose gathering of diabetic patients, that is, with vitamin D deficiency at baseline or nonobese [41]. Other studies suggested a beneficial effect of vitamin D supplementation only in patients at risk of diabetes [42-44]. In contrast, Sokol et al. showed no change in proinflammatory cytokine levels and endothelial function in patients with CAD after repletion of cholecalciferol [45]. Similar results of a systematic review and a meta-analysis created by Elamin MB, et al. who failed to detect a statistically significant reduction in mortality and cardiovascular risks, such as stroke and myocardial infarction, after vitamin D supplementation [46].

We need more trials focusing on patients at major risk for cardiovascular diseases, and those with well-established cardiovascular diseases and severe atherosclerosis to study the actual benefit of vitamin D supplementation in those patients.

## 5. Limitations of Our Study

First, it was a cross-section observational study that only suggests a statistical association but cannot prove it. Secondly, we did not consider some confounders that may affect the results such as medications used by the participants especially, statins that may affect the severity of atherosclerosis or diet and some drugs that may affect vitamin D level. Finally, we assessed the severity of CAD depending on coronary angiography and gensini score that does not consider coronary calcifications.

## 6. Conclusion

In our study, vitamin D deficiency, diabetes, dyslipidemia, higher BMI, and ACS were statistically significant associated with severe coronary atherosclerosis. Also, diabetes and dyslipidemia were statistically significant associated with

vitamin D deficiency. Therefore, it might be concluded that vitamin D deficiency is a significant predictor of diabetes, dyslipidemia, and severe CAD. Large randomized controlled trials are required to study the effect of vitamin D supplementation on the reduction of cardiovascular risk and severity of CAD.

## List of Abbreviations

ACS=acute coronary syndrome  
 BMI=body mass index  
 CAD=coronary artery disease  
 CI=confidence interval  
 CX=circumflex artery  
 LAD=left anterior descending artery  
 OR=odds ratio  
 SD=standard deviation  
 STEMI=ST elevation myocardial infarction.

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