

The association between the serum level of vitamin D and ischemic heart disease: a study from Jordan

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Background: Decreased levels of vitamin D were associated with increased risk of multiple diseases, including cardiovascular diseases. However, there seem to be some discrepancies among the results obtained from different studies. The aim of the present study was to explore the importance of having sufficient serum levels of vitamin D in reducing the incidence and the progression of coronary artery stenosis and ischemic heart disease (IHD).

Methods: Serum levels of vitamin D were measured using radioimmunoassay in 186 Jordanian patients who underwent investigative coronary catheterization. Of these patients, 133 were suffering from coronary artery stenosis. The association between vitamin D levels, coronary stenosis and many risk factors was determined using SPSS software.

Results and conclusions: Interestingly, the current results did not show an association between vitamin D abnormalities and the incidence or the reoccurrence of coronary artery stenosis. Moreover, significant differences were detected in the prevalence of vitamin D abnormalities based on the patient's gender, and there was a significant association between vitamin D abnormalities and both body mass index and dyslipidemia. However, current results did not show any significant association with other risk factors for IHD. For instance, no association was found with smoking, hypertension, diabetes mellitus, stable and unstable angina or with acute recent myocardial infarction.

Keywords: vitamin D, ischemic heart disease, IHD, coronary artery stenosis, cardiovascular system

Introduction

Vitamin D (25 hydroxyvitamin D (25[OH]D)) abnormality "either deficiency or insufficiency" is a common global epidemic condition, irrespective of geographical distribution, age, or ethnicity and despite the worldwide efforts against rickets.¹ Vitamin D can affect the general population and can be detected in patients suffering from chronic diseases.^{2,3}

The specific clinical manifestations of vitamin D deficiency/insufficiency might be seen as rickets in children, or alternatively, it can precipitate or exacerbate osteopenia, osteoporosis and bone fractures in adults.⁴ The etiology and pathogenesis may vary and are not always clearly understood. However, major causes of deficiency/insufficiency are related to inadequate food intake or inadequate exposure to sunlight.^{4,5}

The steroidal structure of this vitamin and its ability to penetrate cellular barriers can predict for its critical role in regulating cellular function, proliferation and differentiation.³ Thereafter, the causal association between vitamin D abnormalities and the risk of developing or modulating many other diseases can be appreciated. For instance,

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vitamin D abnormalities were linked to the development of multiple arms of the metabolic syndrome.⁶ In agreement with that, increased levels of vitamin D were associated with better glycemic control in patients with type 2 diabetes mellitus (DM).⁷ As well, recent meta-analysis reviews suggested an indirect role of vitamin D in controlling blood pressure.^{8,9} Moreover, many studies suggested an integral role for the active form of vitamin D (calcitriol) in modulating inflammatory response. However, the clinical value of vitamin D in modulating inflammatory diseases is still controversial.¹⁰ Of worthy to mention, the causal association between vitamin D abnormalities and different aspects of dyslipidemia, one of the major components of metabolic syndrome, still needs more investigation and validation.¹¹

Previous studies have shown accumulating evidence on the association between vitamin D deficiency and increased incidence of cardiovascular diseases, such as, hypertension,⁹ left ventricular hypertrophy,¹² heart failure,¹³ peripheral arterial disease¹⁴ and myocardial infarction.¹⁵ These associations were further strengthened based on the significant association between vitamin D abnormalities and the presence of pathophysiological processes underlying atherosclerosis, for instance, inflammation, abnormal vascular function including increased arterial stiffness, abnormal vascular endothelial reactivity, decreased coronary blood flow and vascular calcification including uremic calcification.^{16–18} In addition, the causal association between vitamin D abnormalities and the previously mentioned metabolic diseases can further strengthen this notion. However, controversies do exist between studies conducted in different countries and under different clinical conditions.

The present study aimed at assessing the association between the serum levels of vitamin D and the incidence or reoccurrence of coronary artery restenosis following catheterization and stent implantation in Jordanian adult patients with ischemic heart disease (IHD). Current results could help defining a clinical paradigm for the prevention of atherosclerotic stenosis in patients with coronary artery disease.

Patients and methods

Study population and design

The study was a single-center, crossover, observational study that was conducted in tertiary health care level settings after receiving the proper approval from the institutional review board at King Abdullah University Hospital in Jordan. All participants in this study provided written informed consent. A total of 186 patients were subjected to the study between September 2014 and December 2015. Those patients were

identified by having investigative/diagnostic catheterization for the exclusion of significant coronary artery disease (CAD) before non-coronary cardiac surgeries as a result of having an indication of developing IHD after thrombolysis in myocardial infarction (TIMI) score evaluation. This was done even if they had asymptomatic condition, suspected to have acute coronary syndrome, positive exercise stress test or contraindications to obtain exercise stress test, uninterpretable stress test results, suspected coronary anomalies or congenital heart disease. Concomitantly, those patients were further categorized under two different subgroups; the first group comprised 133 patients who were found to have significant artery stenosis and accordingly received a stent implantation (DESyne® Novolimumst-*eluting* coronary stent system, cobalt chromium platform, Elixir Medical Corporation, Milpitas, CA, USA). The second group comprised 53 age- and gender-matched subjects with normal (apparently healthy) coronary arteries, which was considered as the control group for the study. The exclusion criteria, for this study, included: severe valve disease, liver or kidney failure, diseases related to bone metabolism, primary or secondary hyperparathyroidism, use of drugs affecting calcium metabolism, history of malignancy or osteoporosis. Demographic and clinical properties were recorded, and blood samples were obtained for biochemical and vitamin D (25[OH] D) analyses.

Laboratory and biochemical measurements

Blood samples were collected at the morning of the catheterization procedure and after overnight fasting. Levels of total cholesterol, high-density lipoprotein cholesterol and triglycerides in serum were measured using an Abbott Aeroset autoanalyzer with original kits (Abbott Laboratories, Abbott Park, IL, USA). Low-density lipoprotein cholesterol levels were calculated using Friedewald equation.

A radioimmunoassay procedure was used to measure vitamin D (25[OH] D) levels (DiaSorin, Stillwater, MN, USA). The intra- and inter-assay coefficients of variations (CVs) were 3% and 3.3%, respectively. According to the serum levels of vitamin D, patients were categorized into three subgroups; patients with vitamin D deficiency (vitamin D level of <20 ng/mL), patients with vitamin D insufficiency (vitamin D level of 20–30 ng/mL) and patients with normal levels of vitamin D (vitamin D level of >30 ng/mL). High-sensitivity C-reactive protein level was determined by immuno-turbidimetric method (Abbott Aeroset 1600, Abbott reagents; Abbott Laboratories). Serum uric acid levels were measured using an enzymatic colorimetric test on a Roche Hitachi 911 Chemistry Analyzer (Hoffman-La Roche Ltd., Basel, Switzerland).

Statistical analysis

Statistical analysis was performed using SPSS software (version 16.0; SPSS, Chicago, IL, USA). The associations between the categorical variables and vitamin D subcategories were tested using the chi-square test. Independent *t*-test was performed to compare the mean of vitamin D concentration between the categorical variables. Bivariate Pearson correlation was used to study the association of some continuous variables (age and body mass index [BMI]) with the concentration level of vitamin D. The associations or the differences were considered significant when *p*-value <0.5.

Results

The present study included 186 participants who were initially suspected to have IHD. Their sociodemographic and clinical characteristics were obtained. Alarming, most of our patients were not having normal/sufficient levels of vitamin D (94.1%). Of the 94.1% of patients, 69.9% were suffering from vitamin D deficiency, whereas 24.2% were suffering from vitamin D insufficiency.

Association between vitamin D levels and risk factors for IHD

As expected, the number of male patients (*n*=144) was higher than the number of female patients (*n*=42), with 3:1 ratio. As well, the ratios for the number of patients who were suffering from vitamin D deficiency compared to the other groups (normal or insufficiency) were 2:1 and 4:1 for males and females, respectively. The percentage of patients with normal vitamin D levels was comparable between both genders (6.3% of male patients and 4.8% of female patients). Yet, the percentage of the patients who were suffering from vitamin D deficiency (compared to the percentage of patients who were suffering from insufficiency) was lower in male patients (66% vs 27.8%, respectively) when compared to female patients (83.3% vs 11.9%, respectively). In general, vitamin D levels were significantly lower in female patients when compared to males (*P* = 0.036) (Table 1).

The association between many atherosclerotic risk factors and vitamin D deficiency or insufficiency was obtained with focus on factors associated with metabolic syndrome (hypertension, DM and dyslipidemia) and smoking. Current findings showed that vitamin D levels were reversely associated with the coincidence of dyslipidemia, where patients who were not complaining of dyslipidemia appeared to suffer from high levels of vitamin D abnormality (*P* = 0.035). No correlation was found between the coincidence of smoking, hypertension or DM and

vitamin D deficiency or insufficiency (*P* = 0.213, 0.258 and 0.73, respectively).

Of interest, there was a significant reverse association between vitamin D concentration/ measurements and the value of the patient's BMI (*P* = 0.015). It appeared that patients with lower BMI can have higher levels of vitamin D, regardless of being normal or abnormal levels.

Association between vitamin D levels and previous incidences of IHD

No correlation was found between previous incidences of IHD and the subcategory of vitamin D abnormality. However, the number of patients with previous incidences of IHD was very low in the current study (Table 2).

Association between vitamin D levels and the anatomical location of coronary artery stenosis

According to this study, there was no association between vitamin D levels and the anatomical location of the coronary artery stenosis. Left anterior coronary artery, posterior coronary artery and left circumflex artery were the most affected arteries by coronary stenosis (Table 3).

Association between vitamin D levels and the incidence of coronary stenosis or restenosis despite supplementation

Current results showed no correlation between the levels of vitamin D and the prevalence of coronary stenosis. As well, there was no association between vitamin D levels and the incidence of new coronary stenosis (restenosis) in the same patients after at least 2 years of follow-up, although there was a trend of significant association between vitamin D levels and the incidence of restenosis ($0.1 > P\text{-value} > 0.05$). However, the small number of patients who came back for follow-up and who were found to suffer from coronary restenosis made us careful about this interpretation (Table 4).

Discussion

Vascular endothelial cells, smooth muscle cells and inflammatory cells can play complementary roles in vascular homeostasis and in the formation and stabilization of atherosclerotic lesions.^{19–21} The presence of vitamin D receptors within the nucleus of these cells can advocate for its integral mechanistic role in the development and progression of ischemic diseases,^{15,22–24} especially due to the fact that the activation of these receptors has the ability to affect the

Table 1 The association between vitamin D levels and risk factors for ischemic heart disease

Categorical variables	Association with vitamin D levels according to vitamin D subcategories			Association with vitamin D levels according to vitamin D concentration
	Deficiency, n (% within vitamin D subcategory)	Insufficiency, n (% within vitamin D subcategory)	Normal, n (% within vitamin D subcategory)	
Gender	P-value: 0.086			t-test according to categorical variables P-value: 0.036
Female	35 (26.9)	5 (11.1)	2 (18.2)	
	Percentages within females according to vitamin D subcategory (83.3%, 11.9% and 4.8%)			
Male	95 (73.1)	40 (88.9)	9 (81.8)	
	Percentages within males according to vitamin D subcategory (66%, 27.8% and 6.3%)			
Smoking	P-value: 0.213			t-test according to categorical variables P-value: 0.249
No	54 (42.5)	25 (56.8)	4 (36.4)	
	Percentages within non-smokers according to vitamin D subcategory (65.1%, 30.1% and 4.8%)			
Yes	73 (57.5)	19 (43.2)	7 (63.6)	
	Percentages within smokers according to vitamin D subcategory 173.7%, 19.2% and 7.1%)			
Hypertension	P-value: 0.258			t-test according to categorical variables P-value: 0.013
No	53 (40.8)	22 (48.9)	7 (63.6)	
	Percentages within non-hypertensive patients according to vitamin D subcategory (64.6%, 26.8% and 8.5%)			
Yes	77 (59.2)	23 (51.1)	4 (36.4)	
	Percentages within hypertensive patients according to vitamin D subcategory (74%, 22.1% and 3.8%)			
Diabetes mellitus	P-value: 0.730			t-test according to categorical variables P-value: 0.114
No	81 (62.3)	31 (68.9)	7 (63.6)	
	Percentages within non-diabetic patients according to vitamin D subcategory (68.1%, 26.1% and 5.9%)			
Yes	49 (37.7)	14 (31.1)	4 (36.4)	
	Percentages within diabetic patients according to vitamin D subcategory (73.1%, 20.9% and 6%)			
Dyslipidemia	P-value: 0.035			t-test according to categorical variables P-value: 0.125
No	116 (89.2)	33 (173.3)	9 (81.8)	
	Percentages within non-dyslipidemia patients according to vitamin D subcategory (73.4%, 20.9% and 5.7%)			
Yes	14 (10.8)	12 (26.7)	2 (18.2)	
	Percentages within dyslipidemia patients according to vitamin D subcategory (50%, 42.9% and 7.1%)			
Body mass index (BMI)				Bivariate Pearson correlation P-value: 0.015 (negative association)
Age (years)				Bivariate Pearson correlation P-value: 0.25

expression and function of more than 200 genes.^{15,25} The possible association between vitamin D levels and many ischemic risk factors can strengthen such a notion.^{3,6-8,25,26}

However, similar to other studies,^{15,22,27} results of the current study did not show significant association between these abnormalities and the incidence or prevalence of IHD.

Table 2 The association between vitamin D levels and previous incidences of ischemic heart disease

Categorical variables	Association with vitamin D levels according to vitamin D subcategories		
	Deficiency, n (% within vitamin D subcategory)	Insufficiency, n (% within vitamin D subcategory)	Normal, n (% within vitamin D subcategory)
Stable angina	P-value: 0.415		
No	126 (96.9)	45 (100.0)	11 (100.0)
	Percentages within the variable according to vitamin D subcategory (69.2%, 24.7% and 6%)		
Yes	4 (3.1)	0 (0)	0 (0)
	Percentages according to vitamin D subcategory (100%, 0% and 0%)		
Unstable angina	P-value: 0.812		
No	126 (96.9)	44 (97.8)	11 (100.0)
	Percentages according to vitamin D subcategory (69.6%, 24.3% and 6.1%)		
Yes	4 (3.1)	1 (2.2)	0 (0)
	Percentages according to vitamin D subcategory (80%, 20% and 0%)		
Acute MI	P-value: 0.177		
No	121 (93.1)	45 (100.0)	10 (90.9)
	Percentages according to vitamin D subcategory (68.8%, 25.6% and 5.7%)		
Yes	9 (6.9)	0 (0)	1 (9.1)
	Percentages according to vitamin D subcategory (90%, 0% and 10%)		
Recent MI	P-value: 0.219		
No	125 (96.9)	45 (100.0)	10 (90.9)
	Percentages according to vitamin D subcategory (69.4%, 25% and 5.6%)		
Yes	4 (3.1)	0 (0)	1 (9.1)
	Percentages according to vitamin D subcategory (80%, 0% and 10%)		

Table 3 The association between vitamin D levels and the anatomical location of coronary artery stenosis

Categorical variables	Association with vitamin D levels according to vitamin D subcategories		
	Deficiency, n	Insufficiency, n	Normal, n
Left main coronary artery	P-value: 0.160		
No	120	38	11
Yes	10	7	0
Left anterior descending	P-value: 0.946		
No	52	17	4
Yes	78	28	7
Diagonal	P-value: 0.680		
No	104	32	9
Yes	25	13	2
Ramus intermediate	P-value: 0.408		
No	120	44	10
Yes	10	1	1
Left circumflex	P-value: 0.974		
No	79	30	6
Yes	52	15	5
Marginal branch	P-value: 0.215		
No	103	31	11
Yes	27	14	0
Right coronary	P-value: 0.648		
No	64	19	6
Yes	66	26	5
Right posterior descending	P-value: 0.439		
No	126	42	11
Yes	4	3	0

Vitamin D abnormalities are very common and considered the leading cause of supplemental nutrition deficiencies worldwide, especially in elderly.^{22,28} Reduced exposure to sunlight, gastrointestinal abnormalities, reduced activities

and low skin synthesis in elderly²² can greatly predispose for this condition. In Jordan, the prevalence of vitamin D abnormalities was very high in patients with metabolic syndrome, postpartum women, night shift workers, infants and

Table 4 The association between vitamin D levels and the incidence of coronary stenosis or restenosis despite supplementation

Categorical variables	Association with vitamin D levels according to vitamin D sub-categories		
	Deficiency, n	Insufficiency, n	Normal, n
Coronary stenosis	P-value: 0.334		
No	41	9	3
Yes	89	36	8
Coronary restenosis over 2 years	P-value: 0.079		
No	115	43	8
Yes	15	2	3

patients with certain diseases.^{29–32} In agreement with that, the current study showed that most patients were having abnormal levels of vitamin D.

Correlation between vitamin D abnormalities and patient's gender has been previously reported.^{33–35} In the current study, female gender was associated with more severe cases of vitamin D deficiency. Apart from the hormonal and genetic factors, this can be attributed to cultural issues where females in Arab countries are less exposed to sunlight, possibly because they are excessively covered with clothes “wearing Hijab” and many of them stay at home for longer periods in comparison to men.³⁶

The association between vitamin D levels and the main parameters of the metabolic syndrome

Factors related to the metabolic syndrome,⁶ such as hypertension,^{8,9} DM^{7,26} and dyslipidemia, have been associated with vitamin D abnormalities. In Jordan, previous studies did not show clear associations between vitamin D levels and these factors.^{29,37} Current study showed that vitamin D abnormalities can be associated in a way or another with some of these risk factors.

As mentioned earlier, the association between vitamin D abnormalities and hypertension in normal or diabetic patients was previously reported.³⁸ In addition, the supplementation of vitamin D products may have the ability to reduce the arterial blood pressure either in normal or diabetic patients. This modulating effect can be possibly attributed to the inhibition of the renin–angiotensin–aldosterone (RAAS) system.³⁹ Moreover, arterial stiffness and vascular dysfunction are evident in patients with vitamin D abnormalities, which may predispose for elevated blood pressure and atherosclerosis and may benefit, at least theoretically, from vitamin D supplementation.^{40,41} However, all these lines of evidence are challenged by the fact that most of the studies, which used vitamin D supplementation

to ameliorate vascular dysfunction and the associated hypertension, failed to achieve consistent modulation.^{27,42,43} These contradictory results can be supported by current findings where no association between the subcategories of vitamin D abnormality and hypertension was detected. Current study was able to show a significant decrease in vitamin D levels in hypertensive compared to the normal patients.^{44–47}

DM, on the other hand, is another risk factor that can predispose for IHD. Vitamin D abnormalities are thought to be associated with DM by affecting the RAAS system, the calcium cellular concentration and the inflammatory repertoire surrounding the pancreatic cells.^{48,49} However, in patients with DM, meta-analysis reviews failed to provide consistent evidence on the ability of vitamin D supplementation to modulate the course or progression of prediabetic or diabetic conditions.^{49–51} Therefore, it was not surprising that we could not detect any association between vitamin D levels and the prevalence of DM in our study.

Interestingly, current findings showed that vitamin D levels were reversely associated with the coincidence of dyslipidemia, where patients with dyslipidemia appeared to have better vitamin D subcategorical levels (deficiency vs insufficiency). However, these patients did not have proper and sufficient levels of vitamin D. On the other hand, there was no significant difference between patients with or without dyslipidemia based on vitamin D concentration. These contradictory results can be attributed to the nature of the measured parameters and the statistical analyses that were used, even within the same study. The integral role of cholesterol as a precursor for vitamin D synthesis and the cholesterol integral role in vitamin D proper absorption⁵² may explain why vitamin D levels may be reduced but cannot be totally deficient in patients with high cholesterol levels (dyslipidemia). Actually, this relationship may explain, in part, why vitamin D deficiency may be of epiphenomenal nature and may not be associated with increased risk of IHD, as more

cholesterol, which is a risk for IHD, can be accompanied with better vitamin D levels.

Finally, there was a significant reverse association between vitamin D concentration and the value of the patient's BMI. It appeared that patients with lower BMI can have higher levels of vitamin D, regardless of being normal, insufficient or deficient in vitamin D levels. Part of this reduction may be related to the excessive destruction/deposition of vitamin D in adipose tissue (in patients with high BMI), rather than the BMI increase that was caused by vitamin D abnormalities.^{53,54} On the other hand, the established association between BMI measurement and different parameters of metabolic syndrome can explain the contradictory results regarding the association between vitamin D levels and these parameters. Hence, reduction in vitamin D levels with increased BMI may give false-positive association between vitamin D abnormalities (reduced levels) and the risk for developing hypertension, DM or IHD.

Vitamin D and the prevalence/incidence of IHD

In the current study, the anatomical location of atherosclerotic lesions, which were affecting coronary vessels, was not significantly associated or corresponding with vitamin D subcategorical levels. Previous reports have indications on the ability of vitamin D deficiency to differentially affect the stiffness and functions of the arteries based on their diameter and structure.⁵⁵⁻⁵⁷ However, in the current study, lesions at either large or small (bifurcations) coronary vessels were not significantly associated with the changes in vitamin D levels.

On the other hand, we could not find correlation between the prevalence of IHD and the subcategorical level of vitamin D neither retrospectively by obtaining history for patients at the time of the study nor prospectively by patients' follow-up to identify any case of recurrent IHD. Recent and, especially, interventional studies support the current findings.^{15,22,27,45} It is possible that many factors can affect the development or recurrence of IHD, such as vitamin D levels, which can act as a confounder, and it appears that it has less influence than other factors. Current studies and randomized large clinical studies that are conducted continue to reveal and clarify the association between vitamin D and cardiovascular diseases.⁵⁸

Conclusion

We could not find a significant indication on the feasibility of using vitamin D levels or the presence of vitamin D deficiency or insufficiency as predictors for the possibility of developing or reoccurring of coronary artery diseases.

However, vitamin D abnormalities could be related to IHD or other conditions, which may directly or indirectly affect the progression or prognosis of these diseases; hence, detecting its level and keeping within the normal range is encouraged.

Disclosure

The authors report no conflicts of interest in this work.

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