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The association between the serum 25-hydroxyvitamin D level and cardiovascular events in individuals with and without metabolic syndrome

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Original Article

Abstract

BACKGROUND: Previous studies revealed that the level of 25-hydroxyvitamin D [25(OH)D] could be consider as one the risk factors for the occurrence of cardiovascular diseases (CVDs). This study aimed to evaluate the relationship between serum 25(OH)D level and CVD events in individuals with and without metabolic syndrome (MetS) in an Iranian population.

METHODS: In this nested case-control study conducted as a part of the Isfahan Cohort Study (ISC), 55 patients with CVD events were selected as case group, and 55 sex- and age-matched individuals without CVD events as control group. These participants were divided into the two main groups based on the presence of MetS at baseline.

RESULTS: The level of 25(OH)D in individuals with and without MetS was significantly lower among patients with CVD compared to those without CVD events at the baseline of study and after the follow-up (P = 0.036 and P = 0.039, respectively). The level of 25(OH)D significantly decreased risk of incidence of CVD events in individuals without MetS after adjusting for age, sex, nutrition, and exposure to sunlight [0.19 (0.05-0.73); P = 0.016]. There was not any significant relationship between the amount of 25(OH)D at the baseline and CVD events in individuals with MetS.

CONCLUSION: In individuals with MetS, the level of 25(OH)D is not related to CVD events; as MetS directly influence the pathophysiology of mechanisms which are responsible for CVD events, and maybe this effect obscure the effect of 25(OH)D.

Keywords: Cardiovascular Diseases, Metabolic Syndrome, 25-Hydroxyvitamin D

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Introduction

Cardiovascular disease (CVD) is considered as the main cause of mortality and morbidity around the world,[1] and diabetes mellitus, hypercholesterolemia, smoking, hypertension, obesity, metabolic syndrome (MetS), and physical inactivity are primary risk factors for CVD.[2] The prevalence of CVD and its primary risk factors is increasing more rapidly in Asia than in Western countries.[3] Although, pharmacological therapy and lifestyle modification are critical steps in the management of patients with MetS, but several meta-analyses show several factors are involved in the pathogenesis of MetS.[4]

Epidemiological studies confirm a high prevalence of CVD and metabolic syndrome (MetS) among the Iranian population.[5] Results of previous studies show that the level of vitamin D [25-hydroxyvitamin D or 25(OH)D] can be consider as one of the risk factors for CVD occurrence.[6-8] Previous studies show that

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the level of 25(OH)D is lower than recommended amount among Iranian population.[9] But, still it is unclear that how the level of 25(OH)D can affect the incidence of CVD among Iranian subjects with MetS.

This study aimed to evaluate the relationship between serum level and CVD in individuals with and without metabolic syndrome in an Iranian population. The selected population was free of CVD at baseline, so could be consider as one of the most reliable databases for prediction of CVD and related risk factors.

Materials and Methods

This research was based on a large longitudinal cohort study, begun in 2001. Isfahan Cohort Study (ICS), as one of the biggest longitudinal studies in the Middle East, followed a large population. ICS is a population-based, ongoing longitudinal study on adults aged 35 years or more, living in urban and rural areas of three counties in central Iran namely Isfahan, Najafabad, and Arak.[10] The participants were recruited from January 2 to September 28, 2001 to date.[11] A total of 6323 participants were studied in 2001, 925 were lost to the follow-ups, and the remaining 5398 were followed during 12 years. A large sample was selected from urban and rural population of 35-year-old people and more from Isfahan, Najafabad, and Arak with the use of a random multistage cluster sampling method, and was followed for 12 years. The exhaustive methods, sampling and quantities, and population characteristics of the ICS were previously published.[10,11] Patients with metabolic and inflammatory diseases, and those advised by any agents such as lipid and carbohydrate lowering agents, and consumed 25(OH)D or calcium supplements were excluded from this sub-study.

At first, each participant offered his/her written informed consent. The research committee at Isfahan Cardiovascular Research Institute, as a collaborating center of World Health Organization (WHO), approved the protocol. By the use of a validated questionnaire such as demographic data, socioeconomic information, history of drugs, and risk factors for CVDs, the skilled medical personnel collected the baseline statistics. Besides, dimensions of body weight and height were done on a calibrated beam scale and stadiometer barefoot to the nearest 0.1 kg and 0.1 cm, one-to-one. Then, body weight (kg) was divided by height (m^2) to get body mass index (BMI). Moreover, questions concerning nutrition, physical activity and smoking habits, stress, and exposing in the sunlight were gathered by validated questionnaire which filed out by trained nurses.

Clinical and para clinical tests: Fasting (12 hours) blood samples (10 ml) were collected from all contributors, and were tested at the Isfahan central laboratory of Cardiovascular Research Center. Serum total cholesterol (TC), triglycerides, and fasting blood sugar (FBS) were calculated enzymatically, using an autoanalyzer (Eppendorf, Hamburg, Germany), and serum high-density lipoprotein-cholesterol (HDL-C) was measured after precipitation of low-density lipoproteins with dextran sulfate-magnesium. By using the Friedewald equation, we calculated serum low-density lipoprotein-cholesterol (LDL-C) in subjects who had triglycerides less than 400 mg/dl, otherwise we used standard kits to measure. Blood samples were centrifuged immediately in each county, total samples were transported to the central laboratory in 1 hour, and FBS and 2-hour post-prandial [0] (2hpp) glucose tests were measured immediately in the reference area. Serum frozen at -20 °C transported to the central laboratory by a 3-hour transportation with cold chain (-20 °C), and kept frozen there until measured within 72 hours.[11]

25(OH)D was measured using the enzyme-linked immunosorbent assay (ELISA) kit (Cal biotech, USA). A serum level of less than 25 ng/ml was considered as vitamin D deficiency.[6]

Subjects selected based on the Adult Treatment Panel (ATP III) criteria. When a subject had three of the five listed criteria, a diagnosis of the MetS could be made. The primary clinical outcome of MetS was identified as CVD. ATPIII defined the MetS essentially as a clustering of metabolic complications of obesity. The listed criteria included abdominal obesity, determined by increased waist circumference (WC), raised triglycerides, reduced HDL, elevated blood pressure, and raised plasma glucose.[12]

CVD events defined as acute myocardial infarction (AMI), unstable angina pectoris (UAP), sudden cardiac death (SCD), and stroke.[13]

The methodology used to obtain measurements of clinical and biochemical variables have been previously published.[14] All the cohorts participants followed through telephone call, and all the events were recorded. The cohort follow-up procedure is explained in detail elsewhere.[11]

Discrete variables were presented as frequency (percentage). Continuous variables were expressed as mean ± standard deviation (SD). Comparison of categorical variables between two groups was done

using chi-square test, and across quantitative variables by one-way ANOVA test. Cox proportional hazards model was chosen as the best approach for analyzing survival time data to investigate the association of 25(OH)D level and occurrence of CVD events in MetS and non-MetS groups separately. We fitted three adjusted models further than crude model to remove the effects of covariates including, adjusted for age and sex, adjusted for age, sex, and dietary score, and adjusted for age, sex, dietary score, and exposure to sunlight for the last one, which quantity was reported as hazards ratio (HR) [95% of confidence interval (95% CI)]. For all analyses, statistical significance was considered at a level of 0.050. All data were analyzed by using Statistical Package for the Social Sciences (SPSS) software (version 19.0, SPSS Inc., Chicago, IL, USA).

Results

In this sub-study, 52 patients with MetS and 58 age- and sex-adjusted individuals without MetS participated, all of them free of CVD events at baseline.

Comparisons of baseline characteristics between the groups are presented in table 1. The mean of age was higher among subjects with CVD events without considering MetS. There were no significant differences between education, marital status, residency in rural or urban area, physical activity, smoking, nutritional habits, and level of stress in subjects with and without MetS, No significant differences existed in the time spent on exposure to the sunlight in the study groups as well.

Table 2 shows clinical and biochemical characteristics of the study groups. The level of 25(OH)D in subjects with and without MetS was significantly lower among patients with CVD compared with those without CVD events at the baseline of study and after follow-up (P = 0.036 and P = 0.039, respectively).

No significant difference existed between the study groups in terms of triglycerides, HDL-C, FBS, TC, LDL-C, WC, BMI, and diastolic blood pressure. In subjects without MetS, significant changes was seen in systolic blood pressure between those with or without CVD events [129.39 ± 22.65 and 117.58 ± 19.31 mmHg, respectively, P = 0.030].

Table 3 shows the HR of the level of 25(OH)D and risk of incidence of CVD among the participants with and without MetS at the baseline. The level of 25(OH)D non-significantly decreased the risk of incidence of CVD events in the subjects without MetS at the baseline [0.39 (0.14-1.03), P = 0.060]. But after adjusting for age, sex, nutrition, and exposure to sunlight, we found that the level of 25(OH)D decreased the risk of CVD events [0.19 (0.05-0.73), P = 0.016]. These findings did not show any significant relationship between amount of 25(OH)D at the baseline and CVD events in participants with MetS.

Table 1. The demographic characteristics of study groups

Variable	Group					
	With metabolic syndrome			Without metabolic syndrome		
	With CVD event (n = 26)	Without CVD event (n = 26)	P	With CVD event (n = 29)	Without CVD event (n = 29)	P
	Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD	
Age (year)	56.50 ± 8.90	51.30 ± 7.20	0.024	58.50 ± 8.40	51.30 ± 7.90	0.001
Physical activity (Mets/week)	786.51 ± 365.69	957.20 ± 658.53	0.250	661.28 ± 401.06	1165.51 ± 1102.69	0.026
Global dietary index	0.92 ± 0.32	0.95 ± 0.22	0.770	0.98 ± 0.24	1.11 ± 0.17	0.020
	n (%)	n (%)		n (%)	n (%)	
Men	5 (19.2)	5 (19.2)	> 0.999	25 (86.2)	14 (48.3)	0.004
Women	21 (80.8)	21 (80.8)		4 (13.8)	15 (51.7)	
Illiterate	11 (42.3)	8 (30.8)	0.660	5 (17.2)	8 (27.6)	0.640
Primary school	11 (42.3)	14 (53.8)		17 (58.6)	15 (51.7)	
More than primary school	4 (15.4)	4 (15.4)		7 (24.1)	6 (20.7)	
Urban	18 (69.2)	12 (46.2)	0.160	27 (93.1)	19 (65.5)	0.021
Rural	8 (53.8)	14 (53.8)		2 (6.9)	10 (34.5)	
Married	21 (80.8)	22(88.0)	0.370	28(96.6)	27(93.1)	0.500
Low stress	9(34.6)	8(30.8)	> 0.999	13(44.8)	9(31.0)	0.410
High stress	17(65.4)	18(69.2)		16(55.2)	20(69.0)	
Smoking	1(3.8)	1(3.8)	> 0.999	9(31.0)	3(10.3)	0.100
	Median (IQR)	Median (IQR)		Median (IQR)	Median (IQR)	
Exposure to sunlight (minute)	120 (60-240)	60 (30-120)	0.110	120 (45-240)	60 (30-150)	0.730*

CVD: Cardiovascular disease; SD: Standard deviation; IQR: Interquartile range
* Mann-Whitney test

Table 2. The clinical characteristics of study groups

Variable	Group					
	With metabolic syndrome			Without metabolic syndrome		
	With CVD event (n = 26)	Without CVD event (n = 26)	P	With CVD event (n = 29)	Without CVD event (n = 29)	P
	Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD	
Serum vitamin D (ng/ml)	22.14 ± 14.49	32.99 ± 21.15	0.036	16.84 ± 12.61	24.24 ± 14.01	0.039
Fasting blood glucose (mg/dl)	122.96 ± 52.64	119.63 ± 42.34	0.800	90.00 ± 9.82	92.46 ± 23.36	0.600
Triglyceride (mg/dl)	239.80 ± 141.29	228.66 ± 143.86	0.770	152.44 ± 108.29	164.08 ± 110.73	0.680
Total cholesterol (mg/dl)	226.40 ± 46.83	219.16 ± 27.29	0.500	213.31 ± 41.81	209.55 ± 48.04	0.750
High-density lipoprotein (mg/dl)	43.82 ± 9.05	40.93 ± 8.28	0.230	46.65 ± 12.01	50.49 ± 9.84	0.180
Low-density lipoprotein (mg/dl)	135.23 ± 23.43	131.60 ± 21.46	0.490	127.65 ± 33.32	128.06 ± 29.36	0.960
Waist circumference (cm)	104.07 ± 7.78	103.23 ± 6.92	0.680	87.48 ± 9.57	88.72 ± 10.12	0.630
BMI (kg/m^2)	31.88 ± 4.32	30.91 ± 3.30	0.370	24.55 ± 3.04	25.47 ± 4.40	0.360
Systolic blood pressure (mmHg)	134.90 ± 21.61	132.50 ± 20.27	0.680	129.39 ± 22.65	117.58 ± 19.31	0.030
Diastolic blood pressure (mmHg)	82.11 ± 13.27	82.59 ± 10.68	0.880	77.84 ± 12.56	78.10 ± 11.15	0.940
	n (%)	n (%)		n (%)	n (%)	
Vitamin D ≥ 25 ng/ml	11 (42.3)	15 (57.7)	0.270	6 (20.7)	11 (37.9)	0.140

CVD: Cardiovascular disease; SD: Standard deviation; BMI: Body mass index

Discussion

This nested case-control study compared the impact of 25(OH)D status on CVD events among subjects with or without MetS at baseline prospectively; and demonstrated significant relationship between serum 25(OH)D level at baseline and incidence of CVD events in individuals without MetS in an Iranian population. Although, several studies focused on the relationship between 25(OH)D and CVD events, but this study, for the first time among Iranian population, showed the relationship between CVD events and 25(OH)D in subjects with MetS at the baseline and after follow up for 10 years (during ICS) with focusing on the occurrence of CVD events. In addition, very few researchers have been evaluated the effect of 25(OH)D on risk of CVD events in longitudinal studies.

Our previous results displayed having MetS increased the risk of CVD by 2 times,[14] so it seems that in subjects with MetS, the effect of MetS is obscure the effect of 25(OH)D; as MetS affects the pathophysiology of mechanisms which are responsible for CVD events. It is clear that hypovitaminosis D has extra-skeletal effects that influence the progress of various pathologies including those that make up a large number of morbidity and mortality cases, such as CVD, diabetes mellitus, and MetS.[15] Mechanism for how 25(OH)D may improve CVD events is unclear; though, it has postulated that down regulation of the renin-angiotensin aldosterone system could have effect on the cardiovascular system.[16] A few studies have evaluated the role of 25(OH)D acting directly on cardiac tissue, particularly in response to injury.[17] Proposed mechanisms have effects on the renin-angiotensin system, on glycemic control, and inflammatory cytokines, and direct effects on the vasculature and regulation of parathormone (PTH) levels, and calcium deposition in vascular smooth muscle. Earlier studies support the proposal that low serum 25(OH)D concentrations are associated with increased risk of the development of the MetS.[18] For example, Gagnon et al.[19] studied 4164 adults (mean age of 50 years; 58% women; 92% Euripides) over the following 5 years, and identified 528 incident cases (12.7%) of the MetS.[19]

Table 3. The hazard ratio of vitamin D serum level and risk of cardiovascular disease (CVD) among the study groups

Models	Group			
	With metabolic syndrome		Non metabolic syndrome	
	HR (95% CI)	P	HR (95% CI)	P
Crude	0.70 (0.32-1.53)	0.370	0.39 (0.14-1.03)	0.060
Model 1	0.53 (0.24-1.18)	0.120	0.23 (0.07-0.73)	0.013
Model 2	0.53 (0.24-1.18)	0.120	0.24 (0.07-0.82)	0.023
Model 3	0.54 (0.23-1.24)	0.140	0.19 (0.05-0.73)	0.016

HR: Hazard ratio; CI: Confidence interval

Mode 1: Adjusted for age and sex; Model 2: Adjusted for age, sex, and dietary score ; Model 3: Adjusted for age, sex, dietary score, and exposure to sunlight

We found positive relationship between systolic blood pressure and CVD events among subjects without MetS; interestingly, it seems that exposure to the sunlight is related to the synthesized 25(OH)D and could be playing a vital role in the regulation of blood pressure. The effect of 25(OH)D level on blood pressure could decrease by increasing age.[20]

We used the cutoff point of 25 ng/ml for 25(OH)D; so our results showed subjects in the lowest quartile for 25(OH)D had increased hazard ratios for cardiovascular mortality compared with subjects in the highest quartile for 25(OH)D. Similar findings have been reported in incident hemodialysis patients.[21] Previous and smaller study from India did not find any benefit from having optimal levels of 25(OH)D in subjects with CVD. In contrast, they described that very high levels of 25(OH)D (> 89 ng/ml) were associated with increased risk of ischemic heart disease.[22]

This study was limited to the small sample size; but its strength is related to the long follow-up period. We do not have any information about the use of sunscreen by participants in this study.

Conclusion

Our findings showed significant relationship between serum 25(OH)D level and CVD events in individuals without MetS in an Iranian population which participated in the ICS. It seems that in subjects with MetS, the level of 25(OH)D is not related to the CVD events, as MetS affects the pathophysiology of mechanisms responsible for CVD events.

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Conflict of Interests

Authors have no conflict of interests.

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