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The association between serum 25-hydroxyvitamin D level and subclinical atherosclerosis in healthy population

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Keywords
Vitamin D; Carotid Intima-Media Thickness; Atherosclerosis

Abstract

Background: Subclinical atherosclerosis is the asymptomatic phase of carotid atherosclerosis, and its early diagnosis is important to prevent cerebrovascular diseases. Although the vitamin D plays a role in the structure of vessels, the association between the serum level of vitamin D and subclinical atherosclerosis has not been well-studied. We aimed to investigate the association between serum vitamin D level and carotid artery intima-media thickness (CIMT) in Iranian population.

Methods: One hundred individuals with the age range from 20 to 50 years with no history of cardiovascular risk factors were selected for the analysis. Measurements of serum 25-hydroxyvitamin D3 [25(OH) D3] concentration and CIMT were made. Confounding factors such as diabetes, hypertension (HTN), smoking, alcohol, tobacco, dyslipidemia, cardiovascular disease (CVD), high body mass index (BMI), history of drug intake especially calcium, vitamin D, statins, and anti-hypertensive drugs were considered and then excluded from our study.

Results: The mean serum vitamin D level was 15.55 ± 0.42 ng/ml, whereas in the increased intima-media thickness (IMT), it was 12.50 ± 9.50 ng/ml. 55% of the subjects were diagnosed with subclinical atherosclerosis (IMT ≥ 0.75 mm). Mean IMT was 0.74 ± 0.12 mm; however, it was higher (0.86 ± 0.30) in severe vitamin D deficiency group. The analysis showed an association between serum 25(OH) D3 level and CIMT (P = 0.002). 44% of those participants with subclinical atherosclerosis had also a severe

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vitamin D deficiency, while only 13% of normal people had a severe vitamin D deficiency. Also, a correlation was observed between severe vitamin D deficiency and the presence of plaque or higher IMT.
Conclusion: Serum 25(OH) D3 level was inversely correlated with CIMT in our investigated subjects with no cardiovascular risk factor.

Introduction

Carotid atherosclerosis, as a chronic progressive multifocal vascular disease, is determined as one of the major cerebrovascular risk factors. Accordingly, atherosclerosis has two phases as follows: 1) long asymptomatic phase known as subclinical atherosclerosis and 2) a clinically-established phase that includes manifestations of coronary heart disease (CHD), ischemic heart disease (IHD), or cerebrovascular disease.[1] Although progression to the clinically-established phase occurrs over decades, early diagnosis of subclinical atherosclerosis is required to prevent cerebrovascular disease. The exact prevalence of subclinical atherosclerotic disease is still undetermined. However, in Kuller et al.'s study, among 5000 subjects aged over 65 years old, the prevalence of subclinical atherosclerotic disease was 36.0% in women and 38.7% in men, increasing along with age.[2] Currently, the measurement of the common carotid intima-media thickness (CIMT) using brightness-mode (B-mode) ultrasonography is widely used as a noninvasive, feasible, and accurate tool for early identification of asymptomatic carotid atherosclerosis. The intima-media thickness (IMT) assessment can be individually identified as a risk factor for future cerebrovascular disease.[3,4] The increased CIMT is a useful clinical indicator of subclinical atherosclerosis.[5] On the ultrasound assessment of the IMT, according to Stein et al., the stratification of values should always be adjusted for the patient's age, gender, and race.[6]

The role of metabolic disorders such as impaired fasting glucose (IFG), metabolic syndrome, and diabetes mellitus (DM) has been proved in the subclinical atherosclerosis.[7-10] However, the obtained results were inconsistent regarding the correlation between serum vitamin D level and CIMT.[11,12] In addition to the traditional calcium-related effect, vitamin D plays a key role in vessel structures or endothelial function. Also, there are some studies indicating a possible relationship among the low serum vitamin D level and subclinical atherosclerosis and the increased IMT.[9-11] However, some of their results are conflicting. Hence, we aimed to investigate the association between serum vitamin D level and CIMT in Iranian population.

Materials and Methods

Study design and population: This cross-sectional study was conducted from April 2017 to March 2018. 100 individuals were randomly selected using convenience sampling techniques from 158 healthy outpatients who were referred to Vali-e Asr Hospital, Zanjan, Iran, and then signed the written informed consent. Complete information including demographic characteristics, drug history, risk factors, and related diseases were obtained by a reliable questionnaire. Inclusion criteria consisted of 20-50-year-old healthy outpatients with no history of chronic medical diseases, drug consumption, or a risk factor that could affect carotid media thickness. The exclusion criteria comprised a history of any known or suspected chronic disease such as history of hematologic diseases, chronic kidney diseases (CKD), liver diseases, malignancies, cardiovascular disease (CVD) or cerebrovascular accident (CVA), and immunologic disorders.

Those with the history of DM, high blood pressure (BP), hyperlipidemia, smoking, and history of alcohol consumption by any extent, subjects who were on anti-hyperglycemic medications, statins, antihypertensive drugs, the participates with confounding factors such as consumption of medications that alter vitamin D metabolism (vitamin/mineral supplements) or affect IMT (e.g., statins), and overweight and obese participants [high body mass index (BMI)] were excluded from this study.

Laboratory and para-clinical investigations: 5 cc of venous blood was taken from each participant to measure blood glucose and lipid profiles [total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglyceride (TG)]. The measurement of the blood serum 25-hydroxyvitamin D3 [25(OH) D3] concentration was made via electrochemiluminescence Immunoassay (ECLIA), which is a highly successful detection system with high versatility, wide dynamic detection range, low background noise, and a good reproducibility that achieves clinical quality data in various sample types.[13] To avoid seasonal variations, all vitamin D samples were obtained during the winter season (November 2018-March 2018, when sunlight exposure is poor).

Vitamin D deficiency is often defined as < 20 ng/ml (50 nmol/l), its insufficiency is defined as 20-32 ng/ml (50-80 nmol/l), and its optimal levels are > 40 ng/ml (100 nmol/l).[14]

The thickness of carotid intima-media with B-mode ultrasound was performed by a single trained physician. CIMT is a double-line pattern defined as the distance between the lumen-intima and the media-adventitia interface. Most commonly, measurements were bilaterally made in the common carotid artery (CCA) on the far wall within a region free from plaque, at least 5 mm below its end from a longitudinal view. The IMT values were obtained by the use of ultrasound system (Esaote, MYLab40 system, Italy) with the frequencies ranged between 7-10 MHz linear transducers. The ultrasound measurements were done with the patient lying in the supine position with rotated neck to the opposite side of investigation. Moreover, there are several IMT measurement systems including the followings: manual, semi-manual, and automated or edge detection based according to Mannheim CIMT Consensus (2004–2006) (Figure 1).[15]

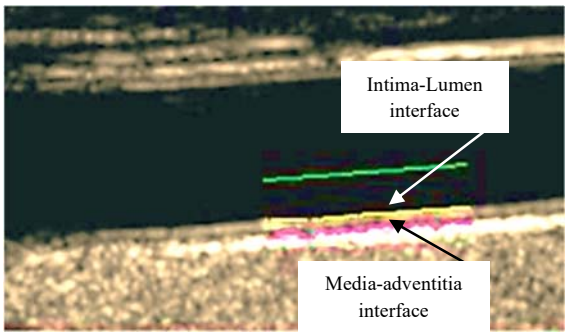

Figure 1. Longitudinal view selected for assessment of carotid wall segment and semi-automated intima-media thickness (IMT) measurement (≥ of 10 mm length) using an edge detection technique

As the manual measurements are more operator-dependent, the automated system was used for IMT measurement. Carotid plaques are commonly determined as a focal structure that intrude on arterial lumen of at least 50% of the surrounding IMT or display a thickness of ≥ 1.5 mm as measured by the media-adventitia interface to the intima-lumen interface.

There are dissimilarities in IMT values in different countries' healthy population.[16-18]

Cut-off values for 97.5th percentile for four different age classes by gender were estimated according to population-based estimates from the VITA project.[19]

The written consent, questionnaire, and the whole study were approved by the local ethics committee. The written consent forms were given and complete information was provided about the investigations. The obtained data were analyzed by SPSS software (version 11, SPSS Inc., Chicago, IL, USA). Descriptive results were presented as number, percent, mean, and standard deviation (SD). Chi-square test was performed to assess the relationship between IMT (as grouped) and age groups; independent sample t-test was performed to compare the quantitative results by sex and IMT groups, and analysis of variance (ANOVA) was used for comparing IMT in vitamin D groups. Pearson correlation coefficient was calculated to assess the relationship between age and IMT with vitamin D. Logistic regression analysis was performed to evaluate the effect of vitamin D level on IMT (as categorized) by removing the potential confounders. Values less than 0.05 were considered as statistically significant.

Results

The population studied had a mean age of 37 ± 13 years, and 69 (69%) of the individuals were women. The baseline characteristics of enrolled subjects grouped according to gender status are shown in table 1. The results of our study showed that 55% of the subjects had subclinical atherosclerosis (IMT ≥ 0.75 mm) [30 men (80%) and 25 women (40%)]. Also, most of these people (45.5%) were aged between 30-40 years followed by those with 40-50 years old (38.2%) and 20-30 years old (16.4%). In the group with normal IMT (IMT < 0.75 mm), most of the cases (42.2%) were aged between 20-30 years old.

Table 1. Baseline characteristics of investigated subjects

Variable	Men (n = 39) (mean ± SD)	Women (n = 61) (mean ± SD)	P
BMI (kg/m^2)	23.00 ± 3.50	23.00 ± 3.25	0.879
FBS (mg/dl)	93.00 ± 9.00	91.00 ± 14.00	0.250
Serum total cholesterol (mg/dl)	161.00 ± 45.00	157.00 ± 32.50	0.407
Serum TG (mg/dl)	110.00 ± 56.00	105.00 ± 46.00	0.313
Serum HDL (mg/dl)	48.00 ± 13.00	47.00 ± 6.00	0.950
BUN (mg/dl)	12.00 ± 4.00	12.00 ± 3.00	0.801
Creatinine (mg/dl)	0.80 ± 0.20	0.80 ± 0.20	0.911
Vitamin D (mg/dl)	12.30 ± 9.60	19.70 ± 16.95	0.018
IMT (mm)	0.07 ± 0.11	0.72 ± 0.11	0.003
Age (year)	37.00 ± 10.00	36.00 ± 15.00	0.486
Calcium (mg/dl)	9.30 ± 0.80	9.20 ± 0.65	0.797

BMI: Body mass index; FBS: Fasting blood sugar; TG: Triglyceride; HDL: High-density lipoprotein; BUN: Blood urine nitrogen; IMT: Intima-media thickness; SD: Standard deviation

The association between age and IMT was found to be statistically significant that was evaluated by chi-square test (P = 0.002). A study on vitamin D levels in the subjects showed that about 83% (Figure 2) of the subjects had insufficient vitamin D levels [serum level of vitamin D = 20-30 ng/ml, 37 women (60.7%) and 17 men (41.0%)] or severe vitamin D deficiencies [vitamin D < 20 ng/ml, 12 women (19.7%) and 15 men (46.0%)].

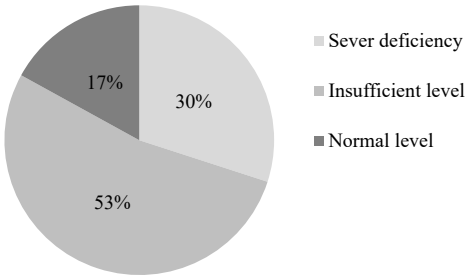

Figure 2. Distribution of vitamin D deficiency in investigated subjects

Accordingly, nearly 44% of people with subclinical atherosclerosis had a severe vitamin D deficiency, while only 13% of normal people had a severe vitamin D deficiency (Figure 3).

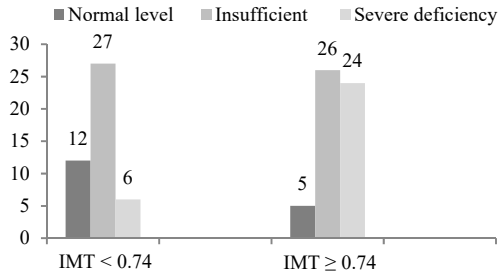

Figure 3. Vitamin D levels in two groups of participants by intima-media thickness (IMT) levels (P = 0.002)

Mean vitamin D level in normal IMT group was 23.40 ± 14.00 ng/ml, whereas in the increased IMT group, it was found as 12.50 ± 9.50 ng/ml (Table 2). This association was found to be statistically significant (P ≤ 0.0001). Mean IMT was higher (0.86 ± 0.30) in severe vitamin D deficiency group compared to the individuals with insufficient (0.78 ± 0.10) and normal (0.71 ± 0.80) vitamin D levels (ANOVA P < 0.001). The age-adjusted prevalence of hypovitaminosis D was higher in men than in women (12.30 ± 9.60 vs. 19.70 ± 16.95, P < 0.001) and they also had higher IMT (0.79 ± 0.11 vs. 0.72 ± 0.11). In addition, there was a negative correlation between IMT and vitamin D (r = -0.539, P < 0.001) and a positive correlation between IMT and age (r = 0.493, P < 0.001). The mean IMT in normal IMT group was 0.70 ± 0.09 mm, whereas it was 0.81 ± 0.10 mm among the individuals with subclinical atherosclerosis. 9 (16.4% out of the individuals with subclinical atherosclerosis) had plaques with no significant hemodynamic change (5 right, 4 left). Carotid bulbs were the most common plaque localization. 2 men and 7 women had plaque in their ultrasound evaluations. In this regard, all of these 9 people had severe vitamin D deficiencies (mean vitamin D level in this group was 12.06 ± 7.80 ng/ml). As shown in tables 2 and 3, we can assume the variable "age" as a potential confounder, so we performed the logistic regression analysis to remove the confounding effect of age and to adjust the potential effects of other variables [such as BMI, fasting blood sugar (FBS), and cholesterol]. The odds ratio (OR) for the effect of vitamin D level and age on IMT (as categorized) were 0.819 (0.742-0.905, P < 0.001) and 1.300 (1.200-1.400, P < 0.001), respectively. The complete results are presented in table 3.

Table 2. Baseline characteristics of investigated subjects according to the intima-media thickness (IMT) values

Variable	IMT < 0.75 mm (mean ± SD)	IMT ≥ 0.75 mm (mean ± SD)	P
BMI (kg/m^2)	23.25 ± 3.25	23.00 ± 3.50	0.629
FBS (mg/dl)	92.00 ± 14.00	91.00 ± 10.00	0.457
Cholesterol (mg/dl)	157.00 ± 50.50	161.00 ± 37.00	0.216
TG (mg/dl)	106.00 ± 54.00	105.00 ± 49.00	0.158
HDL (mg/dl)	48.00 ± 15.50	47.00 ± 16.00	0.862
BUN (mg/dl)	12.00 ± 2.50	12.00 ± 4.00	0.053
Creatinine (mg/dl)	0.80 ± 0.20	0.80 ± 0.20	0.584
Vitamin D (mg/dl)	23.40 ± 14.00	12.50 ± 9.50	< 0.001
Age (year)	33.00 ± 13.50	39.00 ± 11.00	0.001
Calcium (mg/dl)	9.00 ± 0.60	9.30 ± 0.80	0.358

BMI: Body mass index; FBS: Fasting blood sugar; TG: Triglyceride; HDL: High-density lipoprotein; BUN: Blood urine nitrogen; IMT: Intima-media thickness; SD: Standard deviation

Table 3. Multivariate logistic regression results for assessing the relation of study variables and intima-media thickness (IMT) (as categorized to less than 0.75 mm and more)

Variables in the model	OR	95% CI		P
		Lower	Upper	
BMI	1.140	0.859	1.522	0.357
FBS	0.980	0.893	1.063	0.563
Cholesterol	1.030	1.001	1.068	0.042
TG	1.010	0.994	1.030	0.204
HDL	1.000	0.931	1.079	0.957
BUN	1.020	0.816	1.272	0.870
Creatinine	12.151	0.057	2.579	0.361
Vitamin D	0.820	0.742	0.905	< 0.001
Age	1.260	1.116	1.432	< 0.001
Calcium	5.310	1.039	27.162	0.045
Sex (male to female)	4.620	1.239	17.219	0.023

BMI: Body mass index; FBS: Fasting blood sugar; TG: Triglyceride; HDL: High-density lipoprotein; BUN: Blood urine nitrogen; OR: Odds ratio; CI: Confidence interval

Discussion

This study found a significant negative correlation between serum level of vitamin D and CIMT in healthy subjects with no history of any risk factor that could affect carotid media thickness such as DM, high BP, hyperlipidemia, and smoking. Also, we found severe vitamin D deficiencies related to the presence of plaque or higher IMT. The mean serum vitamin D level was 15.55 ± 0.42 ng/ml, whereas in the increased IMT group, it was 12.50 ± 9.50 ng/ml. Mean IMT was 0.74 ± 0.12 mm; however, in severe vitamin D deficiency group, it was higher (0.86 ± 0.30). Our study results are consistent with a study by Carrelli et al.[20] who investigated 203 community-dwelling adults in 2011 with no prior cardiovascular risk factor by the measurement of 25(OH) D and IMT. Accordingly, their results supported an association between vitamin D deficiencies and carotid subclinical atherosclerosis or the presence of plaques; however, in their study, CIMT was similar in men and women, while, our data support that hypovitaminosis is more prevalent in men than women and they also have higher IMT; therefore, they are at the increased risk for atherosclerosis. A resembling study by Deleskog et al. evaluated 3430 middle-aged patients with cardiovascular risk factor in 2013 and showed that IMT was higher in men than women,[12] which was similar to our study results. We found a relatively high prevalence (~85%) of hypovitaminosis D [defined as a serum 25(OH) D concentration ≤ 30 nmol/l], such that, nearly half of the individuals with subclinical atherosclerosis had severe deficiencies. Most of these people (25 people, 45.5%) who had higher IMT values were aged between 30-40 years followed by those with the age between 40-50 years (38.2%). Therefore, the age-related increase of the IMT was proven according to Taskiran et al.[21] study who investigated the association between serum level of vitamin D and IMT in patients with hypertension (HTN) and showed the age-dependent increase of IMT. Although they found no inverse correlation between vitamin D and IMT, maybe the difference was because of HTN history in their investigated subjects. In another study, Giri et al. found higher mean IMT among the patients with ischemic stroke, which had a negative association with vitamin D,[22] which was inconsistent with our study. Findings of a study by Hao et al. also was in agreement with our results.[23] Accordingly, they investigated 926 Chinese postmenopausal women and reported an inverse association between CIMT and serum level of vitamin D in this group.

In current survey, most of these people (45.5%) were aged between 30-40 years old, and in the group with normal IMT (IMT < 0.7 mm), most of the cases (42.2%) were aged between 20-30 years old. It was better to note that more elderly patients had been included; however, it should also be mentioned that young adult stroke is more common in Iran. A higher proportion of stroke occurs in young adults and children (17% of all stroke cases occurred in those younger than 45 years old), though these rates are comparable to those reported in the nearby countries such as Qatar (18.0%) and Libya (19.1%) and certainly are higher than the western hemisphere.[24]

Notably, we considered other confounding variables such as DM, HTN, smoking, alcohol, tobacco, dyslipidemia, BMI, C-reactive protein (CRP), and drug history especially the medications that alter vitamin D metabolism or affect IMT, fracture, and serum calcium. Age was different between the groups and could have confounding effect and we also considered it in analysis. In this study, some confounding factors such as a history of exercise and duration of sunlight exposure were not evaluated. These results demonstrate the need for performing future studies on the possible protective effect of vitamin D supplementation on the progression of atherosclerosis.

Limitations

Small sample size, young and middle-aged

participants, and lack of long-term follow-up were the limitations of our study.

Conclusion

From this study, it can be concluded that serum vitamin D level is inversely correlated with CIMT in the patients in general population. Moreover, a correlation between severe vitamin D deficiency and the presence of plaque or higher IMT was also observed. In addition, we found that the average IMT was higher in men compared to women. According to a negative association between serum vitamin D level and CIMT, vitamin D supplementation may prevent or postpone the clinical phase of atherosclerosis in general population and of course in men.

Conflict of Interests

The authors declare no conflict of interest in this study.

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