the relationship between vitamin D deficiency and IMT of carotid artery in patients with hypertension

Abstract

Patients with hypertension are at increased risk for atherogenesis due to some background conditions. Recognition of related factors would help to better preventive programming and reduction of mortality and morbidity. Vitamin D level is a contributing factor in this era.

This study determined the relationship between vitamin D deficiency and the intima-media thickness of carotid artery in patients with hypertension. In this cross-sectional comparative-descriptive study, 100 cases of hypertension attended training hospitals affiliated with Shahid Beheshti University of Medical Sciences in Tehran-Iran in 2018, and 2019 were enrolled. The relationship between vitamin D level (RIA method) and intima-media thickness of carotid artery (by real-time B mode ultrasonography) with 3-14 MHz linear probe in them was determined.

Vitamin D was deficient in 26%, insufficient in 41%, and sufficient in 33%. The mean IMT was 0.71 ± 0.27. The mean IMT was 1.05, 0.65, and 0.50 in those with deficiency, insufficiency, and sufficiency of vitamin D showing significant differences between groups (P=0.0001).

According to our study, vitamin D is deficient in 26% of cases with hypertension. The IMT was related to vitamin D levels and was higher in those with lower vitamin D serum levels.

Keywords: *Hypovitaminosis D, Hypertension, Carotid IMT*

Dr. Shabnam Karami

Department of Radiology, Taleghani Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Gmail: karamishabnam337@gmail.com

Introduction

Cardiovascular diseases (CVD) are among the leading causes of death worldwide, with approximately 18 million mortalities annually accounting for 32% of worldwide deaths. Various risk factors include behavioral risk factors, increased lipid levels, hypertension, obesity, and diabetes mellitus. Thus, the hypertensive population is at greater risk for CVD (1, 2). Atherosclerosis is characterized by the accumulation of lipids and fibrous caps in the arteries and is the pathophysiologic basis leading to cardiovascular disease. Due to CVDs' chronic nature, atherosclerotic changes appear many decades before CVD development (3-5).

Intima media thickness (IMT) is the distance between the artery wall's intimal-luminal and medial adventitial interfaces and is a subclinical atherosclerosis indicator. An IMT z-score over 1.96 People with increased intima-media thickness alongside atherosclerotic plaques are at increased risk for cardiovascular incidents (6). Thus, intima-media thickness is an independent age-related risk factor that can be used as a screening tool to detect high-risk patients in the early stages (7-9).

IMT is evaluated in the common carotid artery among different arteries, using B mode sonography due to the early formation of atherosclerotic plaques there. Despite the common carotid artery being the preferred inspection location, the abdominal aorta is the first artery to be impacted by atherosclerosis because of its non-invasive, straightforward, and more accessible access. (5, 10).

Vitamin D is associated with many physiologic processes; most investigated the calcium and phosphor metabolism, while the role of low vitamin D in diabetes mellitus, hypertension, and cardiovascular diseases has been proposed. Recent studies suggest an inverse association between intima-media thickness as the surrogate subtle atherosclerosis indicator and vitamin D serum levels (11, 12). The presence of vitamin D receptors in endothelial and vascular smooth muscle cells modulates age-related vascular changes, including inflammation, oxidative stress, and endothelial progenitor cell dysfunction, by modulating insulin growth like factor 1 (IGF-1) synthesis or activity. Studies suggest the impact of vitamin D as far as fetal period and downregulation of inflammatory cytokines such as tumor necrosis factor-alpha (TNF-a) and interleukin(IL) 6 (5, 9).

This study aims at determining the relationship between vitamin D deficiency and intima-media thickness of carotid artery in patients with primary hypertension.

Methods

This study is a cross-sectional comparable-descriptive study including 100 patients with hypertension among Shahid Beheshti medical university educational hospitals throughout Tehran during 2018 and 2019. Patients' data, including demographic and laboratory, and sonography reports, were collected from patients' records using a questionnaire. Patients with primary hypertension with a negative history of supplementary vitamins intake were enrolled in this study, and patients with vitamin D supplement intakes, secondary hypertension, hypokalemia, diuretic therapy, bone metabolic diseases other than osteoporosis, history of previous coronary disease, cerebrovascular disease, ischemic attacks, peripheral vascular disease, liver diseases, and collagen vascular diseases were excluded.

All patients were initially evaluated for cardiac diseases using electrocardiography (ECG), and the patient's body mass index (BMI) was recorded initially and during the study.

Laboratory tests including Serum triglyceride, thyroid-stimulating hormone (TSH), parathyroid hormone (PTH), low-density lipoprotein (LDL), high-density lipoprotein (HDL), creatinine, potassium, calcium, phosphorus, HbA1c and Alkaline phosphatase (ALKP) were assessed using photometric methods. PTH and TSH levels were also recorded. 25(OH) vitamin D levels were assessed using the radioimmunoassay(RIA) technique. The same experienced radiologist blinded to patients' laboratory data conducted Common carotid intima-media thickness (IMT) using non-invasive real-time B mode ultrasonography (Hitachi Arietta V70, Japan) by a 4-13MHz linear probe, 2 cm below carotid bifurcation bilaterally, and readings are reported as the mean of 4 measurements of both sides. In this study, atherosclerotic plaques were defined as carotid intima-media thickness exceeding 1 millimeter.

Serum vitamin D levels exceeding 30ng/ml were considered sufficient, while serum levels between 21-29ng/ml were considered insufficient, and serum vitamin D levels less than 20ng/ml were considered deficient.

The study protocol was approved by the Shahid Beheshti University of Medical Sciences ethics committee (Ethics code) and written informed consent was acquired, and data were extracted following ethical standards.

Statistics

Statistical Package for the social sciences (SPSS) version 26 was used for statistical analysis. Qualitative variables were expressed as frequency. Associations among quantitative variables were analyzed using the Independent t-test, Pearson, and ANOVA tests.

Results

This study consisted of 75 males (75%) and 25 females (25%) with a mean age of 55.60±13.825 (mean ±SD). Vitamin D serum levels were deficient in 26% and insufficient and sufficient in 41% and 33%, respectively. Patients' mean BMI was 29.67±5.570, with a BMI of 35.28 ±4.291 in deficient patients, and hypertension duration was on average 10.12±7.38 years with 11.34±4.84 in vitamin D deficient patients. Patient's laboratory evaluations are summarized in Table 1 and Table 2.

Vitamin D		Age	BMI	Hypertension Duration(Yrs)	HbA1C	Alkaline Phosphatase	Ca	K
Deficient	Mean	62.00	35.28	11.3462	5.231	206.50	8.985	4.18
	Std. Deviation	11.207	4.291	4.84101	0.8970	127.983	0.8938	0.767
Insufficient	Mean	53.41	28.97	10.8049	5.151	148.88	9.102	4.24
	Std. Deviation	13.664	5.099	8.16462	0.9287	111.683	1.4885	0.791
Sufficient	Mean	53.27	26.13	8.3030	22.991	105.51	8.806	4.25
	Std. Deviation	14.657	3.163	7.86799	74.1883	84.368	1.7170	0.674
Total	Mean	55.60	29.67	10.1200	11.059	149.55	8.974	4.23
	Std. Deviation	13.825	5.570	7.38587	43.0166	113.908	1.4374	0.741

Table 1. Patients demographic and laboratory data based on serum vitamin D levels (HbA1c?)

Vitamin D		TG	TSH	PTH	P	Cr	LDL	HDL
Deficient	Mean	178.69	2.32	40.81	4.777	0.958	117.38	42.73
	Std. Deviation	28.530	1.399	17.868	0.5406	0.1677	21.321	8.107
Insufficient	Mean	173.32	3.02	43.00	4.766	0.907	115.54	41.88
	Std. Deviation	28.987	1.350	16.368	0.3877	0.1506	20.985	6.161
Sufficient	Mean	169.76	2.87	42.30	4.761	0.879	113.97	40.94
	Std. Deviation	27.356	1.226	16.663	0.5798	0.1219	21.059	5.567
Total	Mean	173.54	2.79	42.20	4.767	0.911	115.50	41.79
	Std. Deviation	28.262	1.341	16.715	0.4932	0.1483	20.923	6.514

Table 2. Patients' demographic and laboratory data based on serum vitamin D levels

Serum vitamin D was significantly higher in male patients (p=0.0001). In this study, serum vitamin D deficiency was significantly associated with older age (p value=0.022), higher BMI (p-value=0.0001), and elevated ALKP (p-value=0.003).

The mean IMT value was 0.706±0.27 mm. Mean IMT values were significantly different among groups with 1.05 mm, 0.65 mm, and 0.50 mm in vitamin D deficient, insufficient, and sufficient, respectively (p-value=0.0001).

IMT was significantly higher in male patients (0.74mm) compared to female patients (0.57mm) (p value=0.001)

No association was found between IMT and smoking. Our study demonstrated increased IMT to be associated with older age (p-value=0.0001), higher BMI (p-value=0.0001), elevated ALKP (p-value=0.001), elevated LDL(p-value=0.049), and lower TSH (p-value=0.049). Pearson's correlation test for IMT is presented in Table 3.

Discussion

Vitamin D is an essential factor in many organs' metabolism, and its roles have been recognized in distinct and various functions. Recent research have postulated additional roles for it in conditions ranging from diabetes mellitus, autoimmune illnesses, cardiovascular disease, and cerebrovascular disease. Its significance in bone metabolism and calcium and phosphorus balance has been recognised for many years.. A newly proposed function for vitamin D is its role in maintaining vascular tissue function, thus acting as a protective factor against cardiovascular diseases (7, 8). It is suggested that vitamin D exerts such action by imposing anti-inflammatory and anti-proliferative effects on cardiac and vascular tissues using its receptors on endothelial cells, smooth muscle cells, cardiomyocytes, macrophages, and lymphocytes.

It is suggested that vitamin D achieves its protective and anti-inflammatory effects by stimulating prostacyclin production in smooth muscle cells, preventing cell adhesion, and up-regulating anti-inflammatory cytokines. Vitamin D also promotes regulatory T-cell development (10, 11). Moreover, vitamin D deficiency attenuates its ability to suppress the renin-angiotensin system, leading to hypertension and contributing more to cardiovascular disease development (8).

Since cardiovascular diseases have chronic pathophysiology, studies suggest that atherosclerosis, the inflammatory processes underlying these diseases, dates back even to infancy(5, 7, 8). Thus, assessing cardiovascular risk and mitigating related risk factors can be achieved to reduce CVD probabilities. Carotid intima-media thickness is a surrogate factor that can present subclinical atherosclerosis formation status. Evaluating cIMT can be performed using different imaging modalities, but ultrasonography is gaining popularity due to its cheap, non-invasive nature and easy accessibility (7). It is suggested that every 0.1 mm and 0.163 mm increase in carotid IMT increases cardiovascular risk by 24% and 43%, respectively, establishing its importance in clinical settings (7, 13).

In our study, 26% and 41% of the patients had vitamin D deficiency and insufficiency, respectively, with a mean IMT value was 0.706±0.27 mm. Our study determined a significant difference in IMT and patients' vitamin D levels, with increased intima-media thickness among vitamin D-deficient patients. However, there are conflicting results regarding the vitamin D and IMT association. Satilmis et al. suggested a direct association between 25(OH) vitamin D deficiency and the development and progression of atherosclerosis in different populations, while Arman et al. reported no significant association between carotid IMT and 25(OH) vitamin D deficiency (5, 8). In a meta-analysis study conducted by Elamin et al., vitamin D was supplemented as an intervention, yet no significant association was found regarding cardiovascular diseases and mortality (14). On the contrary, Luopli et al. suggested an increased IMT and carotid plaque formation in vitamin D-deficient patients (13). In another study, Choi et al. suggested high vitamin D serum levels be inversely associated with maximal carotid plaque thickness but not associated with the prevalence of carotid plaques or the formation of new plaques (10).

These differences were attributed to some extent to ethnicity. Bacha et al. reported a higher IMT among African American adolescents than white American peers of similar BMI, body fat percentage, and CVD risk profile (15). In another study conducted by Gjødesen et al., vitamin D was reported as a minor risk factor in the development of atherosclerosis in the Inuit Arctic population (16). In a study conducted on a Korean population, there was no association between vitamin D serum level and cIMT, while a study conducted on the Dutch population showed a slight increase in cIMT in 25 (OH) vitamin D over 20 ng/dl (17).

A Study conducted by Mantha et al. proposed smoking as an atherosclerosis risk factor, while we did not find a significant association between smoking and IMT (18). Also, Satilmis et al. proposed a direct association between vitamin D serum level and total cholesterol to HDL ratio. In our study, Increased cIMT was associated with increased LDL level, but no association was found between cIMT and HDL level (8).

The current study is one of the first studies conducted that evaluates Serum Vitamin D levels and cIMT association in the Iranian population. This study was also conducted in a multicenter setting and enrolled patients from different geographical distributions; however, there are several limitations. A small sample size (n=100) affects the generalizability of this study; thus, it is recommended for future studies to use a greater sample size. Vitamin D levels were calculated based on a single measurement, thus limiting their ability to accurately estimate the patient's serum vitamin D status since vitamin D levels tend to change seasonally and even during the day. Moreover, the duration of vitamin D deficiency was also unclear. Also, due to the cross-sectional nature of this study, we could determine association and not

causality, so conducting a longitudinal study could resolve the issues mentioned above. Furthermore, we did not collect data regarding lifestyle patterns in this study, including dietary patterns and activity.

Conclusion

In Our study, vitamin D deficiency and insufficiency were seen in 26% and 41% of cases with hypertension, respectively. There was a significant inverse association between carotid IMT and vitamin D serum levels (Table 4). Higher Vitamin D serum levels were seen in older and male patients and patients with higher BMI and elevated ALKP levels. Increased IMT was associated with older age, higher BMI, elevated ALKP and LDL levels, and lower TSH levels. Both IMT and Vitamin D serum levels were significantly higher among male patients, and neither was associated with smoking. (Table 3)

		IMT
Age	Pearson Correlation Sig. (2-tailed)	0.485 0.000
BMI	Pearson Correlation Sig. (2-tailed)	0.808 0.000
Hypertension Duration (Yes)	Pearson Correlation Sig. (2-tailed)	0.175 0.081
HbA1C	Pearson Correlation Sig. (2-tailed)	-0.134 0.184
Alkaline phosphatase	Pearson Correlation Sig. (2-tailed)	0.334 0.001
Calcium	Pearson Correlation Sig. (2-tailed)	0.048 0.636
Potassium	Pearson Correlation Sig. (2-tailed)	-0.66 0.511
Triglyceride	Pearson Correlation Sig. (2-tailed)	0.107 0.291
TSH	Pearson Correlation Sig. (2-tailed)	-0.198 0.049
PTH	Pearson Correlation Sig. (2-tailed)	0.033 0.746
Phosphorus	Pearson Correlation Sig. (2-tailed)	0.123 0.222
Creatinine	Pearson Correlation Sig. (2-tailed)	0.193 0.055
LDL	Pearson Correlation Sig. (2-tailed)	0.197 0.049
HDL	Pearson Correlation Sig. (2-tailed)	-0.033 0.746
IMT	Pearson Correlation Sig. (2-tailed)	1

Table 3. Pearson correlation test for IMT distribution

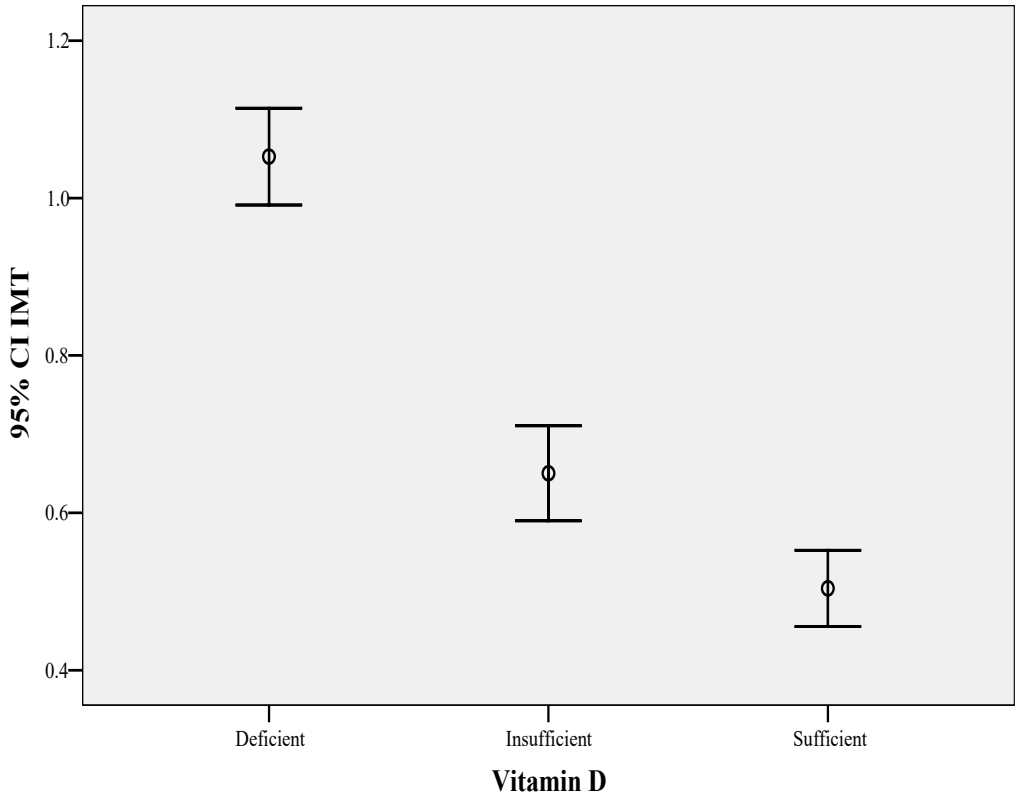

Table 4. IMT box-plot based on patients' serum vitamin D levels

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Conflict of interest
The authors have no conflicts of interest relevant to this article.
Ethical Considerations: Non

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