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The Relationship of Carotid Intima-Media Thickness with Serum Calcium, Phosphorus, and Vitamin D

Ahmad Enhesari[1], Parya Soltaninejad[2], Ahmad Naghibzadeh-Tahami[3], Zohreh Safi[4], Mohammad Hossein Gozashti[5*]

[1]Physiology Research Center, Institute of Neuropharmacology, Kerman University of Medical Sciences, Kerman, Iran
[2]Gastroenterology and Hepatology Research Center, Institute of Basic and Clinical Physiology Sciences, Kerman University of Medical Sciences, Kerman, Iran
[3]Social Determinants of Health Research Center, Institute for Futures Studies in Health, Kerman University of Medical Sciences, Kerman, Iran
[4]Cardiovascular Research Center, Institute of Basic and Clinical Physiology Sciences, Kerman University of Medical Sciences, Kerman, Iran
[5]Endocrinology and Metabolism Research Center, Institute of Basic and Clinical Physiology Sciences, Kerman University of Medical Sciences, Kerman, Iran

*__Corresponding Author:__ Mohammad Hosseini Gozashti, Email: drgozashti@yahoo.com

Abstract
Background: The potential predictive role of deficiencies in certain elements on the increase in carotid intima-media thickness (CIMT), and consequently on the formation of atherosclerotic plaques, remains an important question. The present study aimed to investigate the relationship between CIMT and serum levels of calcium, phosphorus, and vitamin D.
Methods: The study population consisted of individuals from the Kerman Coronary Artery Disease Risk Factors Study (KERCADRS). Serum samples were collected to measure levels of calcium, phosphorus, and vitamin D. The CIMT was assessed using high-resolution B-mode ultrasound scanning.
Results: A total of 180 cases were evaluated. The mean CIMT was significantly higher in men than in women ($P<0.001$). A significant positive correlation was found between CIMT and both patient age ($P<0.001$) and lower HDL level ($P<0.001$). However, no significant relationships were observed between CIMT and serum calcium, phosphorus, and vitamin D. Using a multivariate linear regression model, significant predictors of mean CIMT were found to be male gender (beta = 0.055, $P<0.001$), patient age (beta 0.006, $P<0.001$), and low serum HDL level (beta = -0.002, $P=0.031$). In this model, vitamin D levels did not predict CIMT (beta = 0.001, $P=0.081$).
Conclusion: The increase in CIMT was significantly associated with male gender, aging, and low serum HDL levels. However, no significant relationships were found between CIMT and changes in serum calcium, phosphorus, and vitamin D.
Keywords: Carotid, Intima-Media thickness, Serum calcium, Serum vitamin D

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Introduction

Atherosclerosis is an important pathological condition that leads to the development of cardiovascular and cerebrovascular diseases. These diseases are major contributors to mortality and morbidity, making their prevention a priority in clinical and research programs (1). The onset of atherosclerosis is the main cause of coronary heart disease and stroke. Various studies have shown that ultrasonography of the carotid artery is more sensitive and accurate than other markers, such as the arterial calcification score, for diagnosing and evaluating subclinical atherosclerosis (2). Therefore, CIMT measured by ultrasonography is a valuable method for assessing and confirming atherosclerosis (3). This index significantly increases in patients with atherosclerotic plaques, serving as a critical predictor of cardiovascular and cerebrovascular disorders (1). Moreover, numerous studies have established a relationship between CIMT and cardiovascular risk factors (4). However, some investigations have not found such associations, leading researchers to explore the relationship between CIMT and other novel risk factors, including inflammatory markers, genetic factors, and even micronutrients such as vitamins (5, 6).

Research findings regarding the relationship between CIMT and vitamin D or calcium levels have remained highly controversial, particularly concerning the relationship between vitamin D and cardiovascular disease risk (7). Recent studies have indicated that lower serum levels of 25-hydroxyvitamin D, or the active form of vitamin D, in childhood correlate with increased CIMT in adulthood (8). In this regard, patients with vitamin D levels below 20 ng/ml exhibit increased CIMT levels. However, a combination of statin therapy and vitamin D supplementation over three years significantly reduces CIMT (9). Therefore, simultaneous treatment with lipid-lowering drugs and vitamin D supplementation may reduce the risk of atherosclerosis by decreasing CIMT. In contrast, some studies have reported no significant association between serum vitamin D and traditional cardiovascular risk factors (8) or even CIMT (10). Additionally, CIMT evaluation by itself is a significant risk factor for atherosclerosis, particularly in smokers (11). Overall, the relationship between serum vitamin D levels, CIMT, and the severity of atherosclerosis remains unclear and warrants further investigation.

Methods

Study Population

Participants in this cross-sectional analytical study were selected from the population-based KERCADRS, which assessed cardiovascular risk factors in Kerman.

Inclusion and Exclusion Criteria

Inclusion Criteria

The requirement for inclusion was informed consent to take part in the research.

Exclusion Criteria

The exclusion criteria were heart or lung diseases, previous history of myocardial infarction or renal failure, history of calcium and vitamin D intake in the past six months, hypertension, hyperparathyroidism, hypoparathyroidism, and chronic renal failure.

Measurement

Age, sex, height, and weight were among the demographics gathered from the KERCADRS data registry and recorded in a designated questionnaire. Serum samples were obtained after a fasting period of at least 12 hours to measure serum calcium, phosphorus, and vitamin D. The samples were stored under appropriate laboratory conditions until analysis. Serum calcium was measured using atomic absorption spectroscopy, while serum phosphate was assessed using a kinetic centrifugal analyzer. Serum vitamin D was also measured by enzyme-linked immunosorbent assay (ELISA). In addition, lipid profiles, FBS, and Cr values were evaluated. Then, participants underwent carotid Doppler ultrasonography to determine CIMT using the Philips iU22 xMATRIX Ultrasound system. High-resolution B-mode ultrasound scanning was used to measure CIMT. The common carotid artery, carotid bulb, and internal carotid artery on both sides of the neck were evaluated to determine the thickest part of the CIMT accurately.

The distance between the leading edges of the lumen-intima and media-adventitia interfaces was referred to as CIMT.

Statistical Analysis

The data were summarized using descriptive statistics, which showed frequency (percentage) for categorical variables and mean ± standard deviation (SD) for quantitative variables. Variables were compared using the Mann-Whitney U test, independent t-test, and chi-square test. Spearman's correlation test was used to evaluate the correlation between quantitative measures. A multivariable linear regression model was also used to evaluate the association between CIMT and baseline indices. Statistical analyses were conducted using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Released 2013, Armonk, New York). A p-value of < 0.05 was considered statistically significant.

Ethical Considerations

The Declaration of Helsinki and the Ministry of Health's medical ethics guidelines, as well as the rules set forth by the Kerman University of Medical Sciences' medical ethics council, were all followed in this study. The study protocols were approved by the Ethics Committee of Kerman University of Medical Sciences. The study was financially supported through research funding. The patients' course of therapy was unaffected by this inquiry, and they were only informed of the findings later (Ethical code: IR.KMU.AH.REC.1397.039).

Results

A total of 180 individuals were enrolled in the study. In terms of age, participants were 17 to 79 years old, with a mean age of 40.99 ± 12.76 years. Regarding gender distribution, 86 individuals (47.8%) were male and 94 (52.2%) were female. The mean Body Mass Index *(BMI)* of patients was 26.20 ± 5.5 kg/m^2. Based on BMI, 74 individuals (41.1%) were classified as individuals with normal weight, 66 (36.7%) as overweight, and 40 (22.2%) as obese. Concerning laboratory indices, the mean serum calcium level was 8.47 ± 0.88 mg/dl, the mean serum phosphorus level was 3.85 ± 0.88 mg/dl, and the mean serum vitamin D concentration was 14.31 ± 7.94 ng/ml. Notably, 151 patients (83.8%) had vitamin D levels below 20 ng/ml, indicating vitamin D deficiency. The mean values were calculated as 85.44 ± 11.01 mg/dl for FBS, 182.92 ± 35.19 mg/dl for total cholesterol, 47.00 ± 10.82 mg/dl for serum HDL, 110.74 ± 30.37 mg/dl for serum LDL, 131.05 ± 30.37 mg/dl for serum triglyceride, and 0.91 ± 0.17 mg/dl for serum creatinine.

Additionally, the mean CIMT for the right side of the ultrasonography assessment was 0.44 ± 0.92 mm, the mean CIMT for the left side was 0.45 ± 0.13 mm, and the mean CIMT for both sides was 0.44 ± 0.13 mm.

Regarding the relationship between underlying indices and right CIMT (Table 1), the mean CIMT was significantly higher in men than in women ($P < 0.001$).

Serum HDL levels showed a substantial negative correlation ($P < 0.001$) with the right CIMT, while patient age showed a statistically significant positive correlation ($P < 0.001$), indicating that higher CIMT values were predicted in older patients and those with lower HDL levels. However, CIMT and laboratory indicators such as serum levels of calcium, phosphorus, and vitamin D did not significantly correlate. Similar findings were noted for left CIMT (Table 1).

According to the multivariate linear regression model, the predictors of mean CIMT included male gender (beta = 0.055, $P < 0.001$), patient age (beta = 0.006, $P < 0.001$), and low serum HDL level (beta = -0.002, $P = 0.031$). In this model, vitamin D level was not a significant predictor of CIMT (beta = 0.001, $P = 0.081$) (Table 2).

Discussion

Recent studies have explored the relationship of various elements and micronutrients with CIMT, yielding contradictory results. A central question remains whether deficiencies in elements such as calcium, phosphorus, or vitamin D predict the increase in CIMT, and consequently, the formation of atherosclerotic plaques (12). This study aimed to address this question. To this end, CIMT values from both sides were evaluated using ultrasonography, and the values of each of the above elements were assessed using special laboratory kits (Pars azmoon Inc kits for Calcium using Selectra Pro S Automatic Biochemistry Analyzer & Monobind Inc kits for phosphorus evaluation using ELISA reader) and in a reference laboratory.

The findings from this study revealed that higher CIMT levels were observed in men than in women, among older individuals, and in those with low HDL levels. The higher CIMT levels in men compared to women can be attributed to hormonal differences, physiological characteristics of the vascular wall in men, and genetic variations between the two genders. Furthermore, the effect of androgenic and estrogenic hormones on vascular wall proliferation has been documented, and it is evident that CIMT changes significantly with the onset of menopause (7).

Regarding age-related effects on CIMT, studies have shown that aging contributes to arterial wall stiffness and intima wall thickness. Besides, aging is associated with physiological changes in blood pressure that influence the structural nature of the vascular wall (3). This study also found a negative relationship between CIMT and HDL and a significant relationship between CIMT and cardiovascular risk factors. It is confirmed that fat accumulation and deposition in the arterial wall can increase the thickness of the intima layer, revealing atherosclerotic changes in the arteries (6, 13).

Nevertheless, this study observed no correlation between CIMT and calcium, phosphorus, and vitamin D levels. In other words, deficiencies in these elements do not appear to be associated with an increased risk of CIMT. Taskiran et al (6) found no significant relationship at all. In the study by Monteiro et al (14), a significant negative relationship was noted between CIMT and serum vitamin D and blood glucose levels, yet the relationship between CIMT and vitamin D remained insignificant (14). Wang's study (5) indicated a negative correlation between vitamin D levels and CIMT. Hao et al (15) also found a significant negative relationship between serum vitamin D levels and CIMT. According to Kamycheva et al (4), there is no discernible correlation between CIMT and the serum vitamin D and calcium indices in either gender.

Furthermore, Ramirez-Morros et al (12) showed the calcium/phosphorus product had a significant direct correlation with the number of carotid plaques. However, CIMT and vitamin D levels were significantly

Table 1. The association between baseline factors and CIMT

Factor	Right CIMT		Left CIMT	
	Beta coefficient	*P* value	Beta coefficient	*P* value
Age	0.632	< 0.001	0.649	< 0.001
BMI	0.272	< 0.001	0.266	< 0.001
Calcium	0.070	0.352	0.018	0.812
Phosphorus	-0.123	0.101	-0.060	0.293
Vitamin D	-0.023	0.756	0.042	0.578
FBS	0.375	0.001	0.380	0.001
Cholesterol	0.163	0.030	0.163	0.030
Triglyceride	0.267	0.030	0.254	0.001
LDL	0.171	0.047	0.189	0.040
HDL	-0.303	0.001	-0.256	0.001
Serum creatinine	0.078	0.560	0.061	0.480

Table 2. Multivariate linear regression model for factors associated with CIMT

Factor	Beta	SE	*P* value
Gender	-0.036	0.015	< 0.001
Age	0.006	0.001	< 0.001
BMI	-1.918	0.001	0.890
Calcium	0.016	0.009	0.073
Phosphorus	-0.004	0.009	0.683
Vitamin D	0.001	0.001	0.801
FBS	0.001	0.001	0.085
Cholesterol	-1.379	0.001	0.953
Triglyceride	7.547	0.001	0.496
HDL	-0.002	0.001	0.031
Creatinine	-0.028	0.041	0.495

correlated negatively.

The disparities in the relationships of CIMT with calcium, phosphorus, and vitamin D indices may be related to the underlying health conditions of the participants and the criteria for entering the study. In many cases where a significant relationship was observed between CIMT and these elements, the study populations included patients with hypertension, inflammatory disorders, and diabetes mellitus (14). In other words, when accounting for underlying conditions, the relationship of CIMT with calcium, phosphorus, and vitamin D could be more clearly defined. In addition, this relationship might have been influenced by genetic traits and characteristics of the study populations, such as variations in vascular walls (13, 16).

Conclusion

The increase in CIMT is strongly correlated with low HDL levels, age, and male gender. However, CIMT and variations in serum levels of calcium, phosphorus, and vitamin D did not significantly correlate. Given the contradictory findings regarding the relationship between CIMT and calcium, phosphorus, and vitamin D, and considering the impact of various confounding factors, such as racial characteristics, lifestyle patterns, and genetic variants, repeating this study while accounting for these characteristics is essential.

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Authors' Contribution

Conceptualization: Ahmad Enhesari, Parya Soltaninejad, Mohammad Hossein Gozashti.
Data curation: Parya Soltaninejad, Mohammad Hossein Gozashti.
Formal analysis: Ahmad Naghibzadeh-Tahami.
Funding acquisition: Mohammad Hossein Gozashti.
Investigation: Parya Soltaninejad.
Methodology: Ahmad Enhesari, Ahmad Naghibzadeh-Tahami.
Project administration: Mohammad Hossein Gozashti.
Resources: Ahmad Enhesari, Parya Soltaninejad, Mohammad Hossein Gozashti.
Software: Ahmad Naghibzadeh-Tahami.
Supervision: Ahmad Enhesari, Mohammad Hossein Gozashti.
Validation: Mohammad Hossein Gozashti, Ahmad Enhesari.
Visualization: Zohreh Safi.
Writing–original draft: Ahmad Enhesari, Ahmad Naghibzadeh-Tahami, Parya Soltaninejad, Mohammad Hossein Gozashti, Zohreh Safi.

Competing Interests

The authors declare that they have no conflict of interest.

Ethical Approval

The study was approved by the Ethics Committee of Kerman University of Medical Sciences (KUMS) (Ethical code: IR.KMU.AH.REC.1397.039). Ethical considerations were taken into account during data collection and analysis.

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