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The Association between Serum Interleukin-38 Levels and the Severity of Coronary Artery Calcification: A Cross-Sectional Study

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ABSTRACT

Background: Atherosclerosis is a chronic inflammatory, immune-mediated disease which is a leading cause of global mortality and disability. Coronary artery calcification (CAC) is a key predictor of coronary artery disease (CAD) severity. Interleukin-38 (IL-38), a newly identified anti-inflammatory cytokine, may play a role in modulating inflammation and preventing atherosclerosis progression.

Objective: This study aimed to evaluate the relationship between serum IL-38 levels and CAC severity in patients referred for CT angiography unit of Razieh Firooz Hospital of Kerman city.

Methods: In this cross-sectional study, 151 patients aged 50–70 years were evaluated. The mean age of the participants was 60.1±6.9 years. CAC severity was determined using the Agatston scoring method and multi-detector CT scanners. Serum IL-38 levels were measured via enzyme-linked immunosorbent assay (ELISA). Statistical analyses were performed using an independent T-test and multivariable logistic regression.

Results: Comparing serum IL-38 levels across CAC severity categories showed a statistically significant difference (P=0.039). Mean serum IL-38 in patients with non-severe and severe calcification were 16.8±5.5 pg/mL and 19.4±4.9 pg/mL, respectively. However, in the multivariable regression analysis adjusted for major risk factors including sex, age, diabetes, hypertension, and smoking the association between serum IL-38 levels and CAC severity was not significant (P>0.05). In subgroup analyses, the significant association between IL-38 and CAC severity was observed only in older participants and in patients with established cardiovascular risk factors.

Conclusion: Although serum IL-38 levels were higher in patients with severe CAC, this association did not remain significant after adjustment for major cardiovascular risk factors. Therefore, the observed elevation may reflect age- or risk-related inflammatory changes rather than a direct role of IL-38 in calcification. So, this relationship remains unclear. Further investigation is needed to clarify the potential context-dependent function of IL-38 in atherosclerosis progression.

Keywords: Atherosclerosis, Coronary Artery Calcification, Interleukin-38, Inflammation, Biomarker

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INTRODUCTION

Atherosclerosis is a chronic inflammatory disease involving the arterial wall, and it is a leading cause of global morbidity and mortality (1). The pathology begins with endothelial dysfunction and the retention of low-density lipoproteins (LDL) in the arterial intima. Subsequent oxidative modification of LDL triggers an immune response, recruiting monocytes and T-cells, and promoting the release of pro-inflammatory cytokines, which drive plaque progression and eventual calcification (2-5). Although the atherogenic process can begin early in life, atherosclerotic plaques become clinically significant in a substantial portion of the adult population by middle age (6, 7).

Although genetic factors contribute to susceptibility, modifiable environmental factors-including lifestyle and diet-are significant drivers of atherosclerosis progression. Despite advances in preventive and therapeutic strategies, the disease often continues to progress in individuals classified as low-risk by traditional scoring systems, underscoring the ongoing need for improved diagnostic and prognostic tools (8-11).

Aging, a non-modifiable risk factor, contributes to vascular stiffening and promotes the progression of arterial calcification (12, 13). Coronary artery calcification (CAC), a hallmark of advanced atherosclerosis, is characterized by the deposition of hydroxyapatite crystals within the arterial intima and media (14).

The CAC score, derived from non-contrast CT imaging, serves as a robust biomarker for predicting major adverse cardiovascular events (MACE). It aids in risk stratification and guiding personalized interventions, particularly in asymptomatic individuals and those with diabetes. High CAC scores are independently associated with future cardiovascular events, whereas a score of zero has a high negative predictive value, identifying patients who may safely forgo aggressive lipid-lowering or other intensive therapies (15-18).

Interleukin-38 (IL-38), a a relatively recently characterized anti-inflammatory cytokine of the IL-1 family, has emerged as a potential regulator of inflammation and atherogenesis, including processes associated with vascular calcification (19, 20). Current evidence suggests that IL-38 modulates immune responses partly through suppression of NLRP3 inflammasome activation and downstream caspase-1 signaling, thereby attenuating inflammatory responses that contribute to vascular calcification and systemic inflammation (19, 20).

Experimental studies further support a protective role for IL-38, showing that IL-38 deficiency is associated with increased arterial calcification, whereas exogenous IL-38 administration suppresses inflammatory and osteogenic signaling pathways implicated in vascular calcification (20). These findings suggest that IL-38 may attenuate disease progression. In addition to its effects on calcification, IL-38 has been linked to modulation of pathological angiogenesis, metabolic dysfunction, and insulin resistance, further highlighting its potential relevance in cardiovascular and metabolic disease (19).

Despite these findings supporting a potential modulatory role for IL-38 in atherosclerosis, the relationship between circulating IL-38 levels the severity of coronary artery calcification in human remains incompletely understood. Accordingly, this study aims to investigate the association between serum IL-38 levels and the severity of coronary artery calcification in patients undergoing coronary CT angiography.

METHODS

Study Design

This cross-sectional observational study was conducted in the CT angiography department of Razieh Firouz Hospital in 2024.

Inclusion and Exclusion Criteria

Eligible participants were 50 to 70 years of age and were referred for evaluation of CAD. This age range was selected to ensure an adequate prevalence of coronary calcification for statistical analysis while minimizing the influence of the multiple comorbidities commonly encountered in older geriatric populations.

Exclusion criteria included hypersensitivity to contrast agents, estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m^2, rheumatic diseases, malignancy, and active infectious or immune-mediated disorders. Additionally, patients using corticosteroids and non-steroidal anti-inflammatory drugs (NSAIDs) were excluded to reduce the potential confounding effect of exogenous anti-inflammatory medications on serum cytokine levels. (NSAIDs) were excluded to reduce the potential confounding effects of exogenous anti-inflammatory medications on serum cytokine levels.

Participants

This cross-sectional study included 151 participants. Based on prior studies evaluating cytokines in atherosclerosis, a target sample size of approximately 150 participants was considered adequate. Initially 170 patients were screened for inclusion; however, 19 were excluded because they did not meet the eligibility criteria or declined to participate, resulting in a final study population of 151 participants. All participants underwent coronary CT angiography and were categorized according to CAC severity into two groups: non-severe calcification (Agatston score <400) and severe calcification (Agatston score ≥400). Baseline demographic and clinical characteristics of the study population are presented in Table 1.

Assessment of Coronary Artery Calcification Severity

CAC scans were performed using a Siemens Somatom Drive Dual Source-Dual Energy 256-slice multidetector CT scanner with a collimation of 128×0.6 mm and a tube voltage of 120 kV. Imaging was conducted according to standard CAC acquisition protocols, obtaining 30 to 40 axial slices with a slice thickness of 3 mm, extending from the level of the aortic root to the cardiac apex.

Before CT angiography, patients underwent standard pre-procedural evaluation, including optimization of heart rate control, confirmation of adherence to fasting instructions, and

Table 1. Demographic and Clinical Characteristics of the Study Population.

Variables	Levels	Frequency	Percent
Sex	Female	68	45.0
	Male	83	55.0
Age (years)	50-60	77	51.0
	61-70	74	49.0
Severity of calcification	Non-severe	128	84.8
	Severe	23	15.2
Diabetics	No	99	65.5
	Yes	52	34.5
Hypertension	No	62	41
	Yes	89	59
Hyper lipidemia	No	72	47.7
	Yes	79	52.3
Opioid Addiction	No	137	90.7
	Yes	14	9.3
Smoker	No	135	89.4
	Yes	16	10.6
Taking statins	No	71	47.1
	Yes	80	52.9

assessment for any history of hypersensitivity to iodinated contrast agents.

In this study, coronary regions with attenuation values >130 Hounsfield units (HU) were considered calcified. Coronary artery calcification was quantified using the Agatston scoring method, and participants were classified into the following categories according to calcification severity: Non-severe calcification: Agatston score <400

Severe calcification: Agatston score ≥400 All CT angiographic images were independently reviewed by an experienced radiologist, and the following variables were recorded:

Coronary Calcium (Agatston) Score
Severity of Coronary Artery Stenosis

All imaging and clinical findings were documented using standardized data collection forms.

Measurement of Serum IL-38 Levels
Sample Collection and Preparation

Following enrollment and prior to the administration of contrast agents or performance of imaging procedures, 5–10 mL of peripheral venous blood was collected from each participant. Blood samples were placed in EDTA-containing tubes and transported to the laboratory at the Afzalipour Medical School. Plasma samples were processed and stored at -70°C until laboratory analysis.

Measurement Method

Serum levels of IL-38 were measured using a commercially available enzyme-linked immunosorbent assay (ELISA) kit. (ZellBio GmbH, Germany), according to the manufacturer's instructions. IL-38 levels were reported in picograms per milliliter (pg/mL).

Statistical Analysis

Data analysis was performed using SPSS software. The normality of data distribution was assessed using the Shapiro-Wilk test. Continuous variables were expressed as mean±standard deviation (SD). Differences in serum IL-38 levels between groups were assessed using the independent t-test was employed. To adjust for potential confounding factors, multivariable logistic regression analysis was performed, with coronary artery calcification severity as the dependent variable and age, sex, diabetes, hypertension, and smoking status included as covariates. A P-value <0.05 was considered statistically significant.

RESULTS

Demographic and Clinical Characteristics

A total of 151 patients were included in the study, with a mean age of 60.1±6.9 years; 55.0% were male and 45.0% were female. Regarding cardiovascular risk factors, 34.5% of participants had diabetes mellitus, 59% had hypertension, 52.3% had hyperlipidemia, and 10.6% were current smokers. Statin therapy was reported in 52.9% of participants. Based on Agatston scores, 128 patients (84.8%) were categorized as having non-severe calcification, whereas 23 patients (15.2%) were classified as having severe calcification (Table 1).

Association between IL-38 and CAC Severity

Comparing serum IL-38 levels between CAC severity groups demonstrated a statistically significant difference (P=0.039). Mean serum IL-38 levels were 16.8±5.5 pg/mL in patients with non-severe calcification and 19.4±4.9 pg/mL in those with severe calcification (Table 2).

Multivariable Analysis

To evaluate whether serum IL-38 levels were independently associated with severe CAC, a multivariable logistic regression analysis was performed adjusting for sex, age, diabetes, hypertension, and smoking status. Although higher serum IL-38 concentrations were associated with increased odds of severe CAC, this association did not reach statistical significance (OR=1.039, 95% CI: [0.944, 1.139], P=0.424).

Table 2. Association between Serum IL-38 Levels and Coronary Artery Calcification Severity.

Variables	Subgroups	Mean±SD	T	P-value
Severity of calcification	Non-severe	16.8±5.5	-2.08	0.039*
	Severe	19.4±4.9		

IL-38 Levels expressed as mean±SD, Test: independent T-test, *significant at the 0.05 level

Table 3. Multivariable Logistic Regression Analysis of the Association between Serum IL-38 Levels and Coronary Artery Calcification Severity

Variables	Adjusted OR	P-value	95% Confidence Interval	
Serum IL-38	1.039	0.424	0.944	1.139
Sex	4.868	0.009*	1.542	16.901
Age	1.159	<0.001*	1.068	1.267
Diabetes	0.590	0.389	0.181	2.021
Hypertension	0.474	0.197	0.156	1.548
Hyper lipidemia	2.477	0.117	0.652	31.823
Smoker	2.123	0.320	0.486	9.500

*Significant at the 0.05 level

Table 4. Association between Serum IL-38 Levels and Coronary Artery Calcification Severity in Different Subgroups.

Variables		IL-38 Mean±SD (pg/mL)	IL-38 Mean±SD (pg/mL)	P-value
Severity of calcification		Non-severe	severe	
Age	50-60 years	16.7±5.9	17.0±4.9	0.942
	61-70 years	16.8±5.1	19.9±5.0	0.025*
Sex	Female	16.5±5.4	21.1±3.9	0.114
	Male	17.1±5.6	19.1±5.1	0.183
Hypertension	No	15.5±6.4	17.6±5.1	0.281
	Yes	17.6±4.7	21.3±4.1	0.017*
Diabetic	No	16.1±5.5	18.7±5.3	0.088
	Yes	18.1±5.3	21.4±2.8	0.039*
Smoker	No	16.8±5.6	19.3±4.1	0.024*
	Yes	17.1±4.4	19.9±8.9	0.406
Opioid addiction	No	16.7±5.7	19.1±4.4	0.056
	Yes	18.1±3.2	21.8±8.1	0.227
Hyperlipidemia	No	16.2±5.6	18.2±2.7	0.333
	Yes	17.3±5.4	20.1±5.7	0.096
Statin Use	No	16.4±5.7	18.6±2.9	0.258
	Yes	17.1±5.3	19.9±5.9	0.095

IL-38 Levels expressed as mean±SD, Test: independent T-test, *significant at the 0.05 level

In contrast increasing age was independently associated with a higher likelihood of severe calcification (OR=1.159, 95% CI: 1.068, 1.267, P=<0.001). Male sex was also significantly associated with severe CAC, with men demonstrating approximately a fivefold higher likelihood of severe calcification compared with women (OR=4.868, 95% CI: 1.542, 16.901, P=0.009) (Table 3).

Subgroup Analyses

Subgroup analysis demonstrated that the association between higher serum IL-38 and greater CAC severity was most

pronounced among older participants aged 61-70 years (P=0.025). Significant differences in IL-38 levels between CAC severity groups were also observed among patients with hypertension (P=0.017), diabetes (P=0.039), and non-smokers (P=0.024). In contrast, no statistically significant differences in IL-38 levels according to CAC severity were identified based on sex, hyperlipidemia, or statin use (Table 4).

DISCUSSION

This study aimed to investigate the association between serum IL-38 levels and the severity of CAC. The results demonstrated a significant positive association between serum IL-38 levels and CAC severity, particularly among patients with cardiovascular risk factors such as hypertension and diabetes. However, multivariate analysis showed that this association was no longer statistically significant after adjustment for potential confounding variables, including age, smoking, and hypertension.

This progressive increase in IL-38 levels may reflect its regulatory role in inflammatory and vascular calcification processes. Zhang et al. (2019) similarly highlighted the inhibitory and regulatory role of IL-38, a member of the IL-1 cytokine family, in atherosclerosis (19), Chronic inflammation is a hallmark of atherosclerosis, and IL-38 has been shown to exert anti-inflammatory and anti-atherosclerotic effects through inhibition of key signaling pathways such as MAPK and NF-κB (25). Despite these reported mechanisms, our study demonstrated a significant positive association between serum IL-38 levels and CAC severity, with IL-38 levels progressively increasing alongside greater degrees of calcification. A potential mechanism underlying these findings is the established concept that heavily calcified coronary plaques are more stable than lipid-rich plaques and are less prone to rupture. Plaques associated with acute thrombotic events, including plaque rupture and plaque erosion, which are among the most common causes of acute coronary syndromes, typically demonstrate less calcification than stable coronary plaques. Therefore, the increased levels of IL-38 observed in association with calcified plaques may represent a compensatory or protective response aimed at promoting plaque stabilization.

Supporting this protective hypothesis, Ismailzadeh et al. (2019) demonstrated that IL-38 expression increases in response to vascular injury and may play a regulatory role in inflammatory processes (26). Chen et al. (2023) also reported that IL-38 is involved in metabolic regulation during vascular calcification, suggesting that its elevation may represent a compensatory immune response to limit this process (27). The observed increase in IL-38 levels with CAC severity across most subgroups further supports its potential role as a regulatory cytokine in chronic inflammation and vascular calcification. IL-38 may therefore represent a compensatory mechanism aimed at attenuating inflammation and slowing the progression of atherosclerosis, as suggested by Barreiro et al. (2022) (31).

In contrast to the stable calcification observed in our cohort, Lu et al. (2023) investigated IL-38 levels in patients with ST-elevation myocardial infarction (STEMI). Their study demonstrated that lower plasma IL-38 levels were associated with an increased risk of major adverse cardiovascular events (MACE), with patients in the low IL-38 group showing a significantly higher incidence of MACE compared with those in the high IL-38 group (28). These findings suggest a dual role for IL-38: in stable, calcified atherosclerosis, IL-38 may be upregulated as a protective or compensatory response; whereas insufficient IL-38 expression may contribute to plaque instability and acute coronary events such as STEMI.

A significant association between IL-38 levels and CAC severity was observed in the age group 61–70 years. Notably, IL-38 levels

were higher across all CAC severity categories in the 61–70 years group compared with the 50–60 year group. This age-related increase may be attributable to chronic inflammation and oxidative stress, which increase with aging and contribute to elevated production of both pro-inflammatory and anti-inflammatory cytokines, as described by Tyrell et al. (29). Additionally, Esmailzadeh et al. suggested that IL-38 may function as a compensatory response to vascular injury, which is more prevalent in older individuals (26).

This study found no significant association between IL-38 levels and CAC severity based on sex, although IL-38 levels increased with CAC severity in both males and females. These findings are consistent with those of Kou et al., who reported that IL-38 levels were associated with cardiovascular events following percutaneous coronary intervention (PCI) in both sexes (30). Interestingly, in the non-severe calcification group, females exhibited higher IL-38 levels than males, whereas in the severe calcification group, males had higher levels. This sex-related difference may be influenced by hormonal effects on inflammatory responses, as well as known differences in the progression of atherosclerosis between males and females.

Finally, the increase in IL-38 levels with higher CAC score may reflect compensatory responses to oxidative stress and inflammation in these patients. Similar patterns were observed in patients with diabetes mellitus and hyperlipidemia, suggesting that IL-38 may have potential as a biomarker of CAC severity independent of metabolic or behavioral risk factors.

Limitations

Several limitations of this study should be acknowledged. First, the cross-sectional design precludes determination of a causal relationship between IL-38 levels and CAC severity. Second, the relatively small sample size may limit the generalizability of the findings to larger populations. Third, other potential confounding factors, including dietary habits, physical activity, and genetic predispositions, were not evaluated. Finally, the absence of complementary molecular analyses and advanced imaging modalities limits a more comprehensive understanding of the mechanisms underlying elevated IL-38 levels.

CONCLUSION

Although serum IL-38 levels were higher in patients with severe CAC, this association did not remain statistically significant after adjustment for major cardiovascular risk factors, including age, sex, diabetes, hypertension, and smoking. Notably, increasing age and male sex were independently associated with a higher likelihood of calcification, with men demonstrating approximately a fivefold higher odds compared with women. Therefore, the observed elevation in IL-38 levels may reflect age- or sex-related inflammatory and cardiovascular risk processes rather than a direct causal role of IL-38 in coronary calcification. Consequently, the precise relationship between IL-38 and CAC remains incompletely understood. Further longitudinal studies with larger sample sizes are warranted to clarify the potential context-dependent role of IL-38 in atherosclerosis progression and to determine whether it functions primarily as a biomarker or mediator of calcification.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Kerman University of Medical Sciences (IR.KMU.AH.REC.1403.098). Written informed consent was obtained from all participants in accordance with ethical guidelines and established research standards.

CONFLICT OF INTEREST

The authors declare that they have no competing interests, competing financial or non-financial interests that have influenced the outcomes of this research.

CONSENT FOR PUBLICATION

Not applicable.

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DATA AVAILABILITY

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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AUTHORS' CONTRIBUTION

MR: Conceptualization, Data curation, Writing – original draft. MM, AJ, AS, NZ: Methodology, Supervision, Validation, Project administration. PJA: Methodology, Data curation. MR, NZ, HR: Data curation, Investigation, Writing – review & editing. NZ, PJA, HR: Writing – review & editing, Supervision.

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