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FGF-21 as a potential biomarker for coronary artery calcification: a non-invasive approach

Oğuzhan Zengin[1], Oğuz Öztürk[2], Hüseyin Çamlı[1], Beste Öztürk[1], Berk Güvercin[1], Ali Can Kurtipek[1], Esma Andaç Uzdoğan[3], Sadettin Emre Eroğlu[2], Emra Asfuroğlu Kalkan[1], İhsan Ateş[1]

[1]*Department of Internal Medicine, Ankara Bilkent City Hospital, Ankara, Turkiye*
[2]*Department of Gastroenterology, Ankara Bilkent City Hospital, Ankara, Turkiye*
[3]*Department of Medical Biochemistry, Ankara Bilkent City Hospital, Ankara, Turkiye*

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Corresponding Author: Oğuzhan Zengin, oguzhanzengin91@gmail.com

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ABSTRACT

Aims: The aim of this study was to investigate the relationship between fibroblast growth factor 21 (FGF-21) levels and coronary artery calcium (CAC) scores calculated using the Agatston method, and to evaluate the potential of FGF-21 as a non-invasive biomarker for the assessment of coronary artery calcification.

Methods: A total of 54 adult individuals who had undergone coronary CT angiography within the past three months solely for cardiovascular risk assessment were prospectively included in the study. Serum FGF-21 levels were measured using the ELISA method, and CAC scores were determined via the Agatston scoring system. The relationship between FGF-21 levels and CAC scores was analyzed using Spearman's correlation test.

Results: A significant and strong positive correlation was observed between FGF-21 levels and CAC scores ($r=0.725$, $p<0.001$). Diabetes mellitus and hyperlipidemia were significantly associated with higher CAC scores ($p=0.006$ and $p=0.024$, respectively), whereas their associations with FGF-21 levels were not statistically significant ($p=0.065$ and $p=0.104$). No significant correlations were found between FGF-21 levels and other variables such as age, gender, hypertension, or biochemical parameters.

Conclusion: The findings suggest that serum FGF-21 levels may be associated with coronary artery calcification and could serve as a non-invasive and easily applicable biomarker in individuals for coronary artery disease. FGF-21 may be particularly useful in clinical settings where access to advanced imaging modalities is limited.

Keywords: FGF-21, coronary calcium score, atherosclerosis, biomarker, non-invasive evaluation

INTRODUCTION

Fibroblast growth factor 21 (FGF-21) is a hormone secreted by hepatocytes and has a regulatory effect on different tissues, including cardiomyocytes, immune cells, and fibroblasts. By acting on energy metabolism, oxidative stress, fibrosis, and inflammation; FGF-21 has been shown to be a possible cardioprotective molecule.[1]

FGF-21 has been shown in studies to play a protective role in several cardiovascular diseases, including MI, diabetic cardiomyopathy, and atherosclerosis.[2-4] In addition, FGF-21 levels help to predict the prognosis of many heart diseases, such as MI, hypertension, and cardiomyopathy.[5,6]

Vascular calcification is an advanced stage of atherosclerotic plaque formation and serves as a marker that indicates an increased risk of cardiovascular events.[7]

FGF-21 plays a key role in energy balance and lipid and glucose metabolism. Its levels rise in conditions like obesity, type 2 diabetes, and metabolic syndrome—major risk factors for cardiovascular disease—linking elevated FGF-21 to increased cardiovascular risk.[8]

FGF-21 is thought to protect against atherosclerosis by regulating several cellular events. It may attenuate endothelial dysfunction through multiple pathways. For example, co-culture of human umbilical cord vascular endothelial cells

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(HUVECs) with FGF-21 delayed endothelial senescence by increasing silent information regulator 1 (SIRT1).[9]

An in vitro study explored the impact of FGF-21 on HUVEC pyroptosis triggered by oxidized low-density lipoprotein. The results revealed that FGF-21 could suppress HUVEC pyroptosis through the involvement of reactive oxygen species and specific protein pathways.[10] In apolipoprotein E-/- (apoE-/-) mice, FGF-21 was found to reduce endothelial apoptosis by inhibiting the Fas signaling pathway.[11] Moreover, FGF-21 exerts its effects by inhibiting the NLRP3 inflammasome pathway.[12] Additionally, an in vivo study demonstrated that FGF-21 alleviates atherosclerosis by inhibiting the NF-κB pathway in endothelial cells.[13]

In vitro studies show that FGF-21 inhibits foam cell formation and macrophage apoptosis, offering protection against atherosclerosis. It enhances cholesterol efflux by inducing autophagy, upregulating ATP-binding cassette transporters A1 and G1 pathways.[14-18]

In mice treated with a high-fat diet and low-dose streptozotocin, FGF-21 inhibits the migration and proliferation of vascular smooth muscle cells.[19] Additionally, FGF-21 can promote the secretion of adiponectin, which exerts an atheroprotective effect by reducing endothelial dysfunction. This mechanism prevents the conversion of macrophages into foam cells and inhibits the proliferation of vascular smooth muscle cells.[20] Administration of recombinant human FGF-21 (rhFGF21) has been shown to protect against atherosclerotic plaque formation.[21]

In mice, treatment with an FGF-21 analog resulted in a reduction of atheromatous plaques and a decrease in lipid levels.[22] Additionally, the application of rhFGF21 in mice has been shown to reduce the severity of atherosclerotic lesions and increase the stability index.[23]

CAC score is a valuable tool for cardiovascular risk assessment but requires imaging methods like CT angiography, which involve radiation, cost, and limited accessibility. Since FGF-21 is linked to metabolic activity and vascular remodeling, this study investigated whether serum FGF-21 levels are associated with CAC scores (Agatston method) to explore its potential as a biomarker for coronary calcification.

METHODS

All procedures were approved by the Ethics Committee of Ankara Bilkent City Hospital (Date: 29.05.2024, Decision No: TABED 2/209/2024) and were carried out in accordance with the principles of the Declaration of Helsinki. This prospective study was conducted at Ankara Bilkent City Hospital between May 29, 2024 and November 29, 2024. A total of 103 patients who had undergone coronary computed tomography angiography (CTA) within the previous three months and presented to the internal medicine outpatient clinic were evaluated. Of these, 54 adult patients who met the inclusion criteria were enrolled in the study (**Figure 1**). Patients included in the study had no active coronary symptoms, electrocardiographic changes, or clinical signs of acute myocardial infarction. Coronary CTA had been performed within the prior three months solely for cardiovascular risk assessment purposes. No patient underwent invasive coronary angiography. Demographic characteristics, medical history, and biochemical data were recorded for all participants. Individuals with chronic kidney disease, alcohol addiction, a history of coronary artery stenting or revascularization, coronary artery bypass surgery, or malignancy were excluded from the study. Coronary CT images were retrieved from the hospital imaging system and evaluated by a single radiologist. Coronary artery calcium (CAC) scores were calculated using the Agatston method, which is commonly applied in both clinical and research settings to quantify coronary calcification and stratify cardiovascular risk.[24] Venous blood samples were collected in the morning after overnight fasting. Serum levels of FGF-21 were measured using a sandwich enzyme-linked immunosorbent assay kit (SEC918Hu96, species: *Homo sapiens*), intended for research use only. The assays were performed at the Central Biochemistry Laboratory of Ankara Bilkent City Hospital in accordance with the manufacturer's instructions.

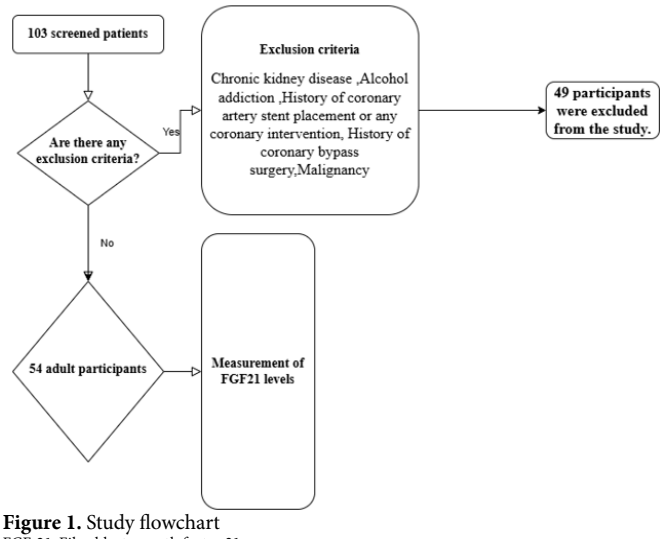

Figure 1. Study flowchart
FGF-21: Fibroblast growth factor 21

Statistical Analysis

Categorical data were presented as counts (with percentages within the group) and compared between groups using the Chi-squared test. The distribution of continuous data was assessed with histograms and Shapiro-Wilk's test in each group. Normally distributed data were expressed as mean±standard deviation, while non-normally distributed continuous data and ordinal data were reported as median (25^{th} percentile-75^{th} percentile). Spearman's correlation test was used to assess the relationships between Agatston calcium scores and FGF-21 values with all continuous data. Statistical analyses were performed with SPSS software (version 26.0, Chicago, IL, USA). A power analysis was conducted for the study, and it was determined that a minimum of 40 patients was required, with a statistical power of 80% and an alpha level of 0.05.

RESULTS

The demographics of the entire study population are summarized in **Table 1**. The mean age of the participants was 53.6±8.66 years. Among the population, 29 participants (53.7%) were female. Regarding comorbidities, 18 (33.3%) had diabetes mellitus, 23 (42.6%) had hyperlipidemia, and 17 (31.5%) had hypertension. These characteristics provide important context for understanding the health status and potential risk factors within the study population.

Table 1. Demographics and comorbidities of all population

Age, mean±SD	53.6±8.66
Female gender, n (%)	29 (53.7)
Diabetes mellitus, n (%)	18 (33.3)
Hyperlipidemia, n (%)	23 (42.6)
Hypertension, n (%)	17 (31.5)

SD: Standard deviation

In the overall study population, the median Agatston calcium score was 6 (IQR: 0–41) (Table 2). A statistically significant positive correlation was observed between FGF-21 levels and the Agatston calcium score (median FGF-21: 43.26 pg/ml, IQR: 35.29–59.02; p<0.05), suggesting a potential link between FGF-21 and subclinical coronary atherosclerosis. Additionally, the systemic immune-inflammatory index (SII) was found to be moderately elevated in the population (median: 534, IQR: 403–642), although no statistically significant correlation with calcium score was detected. Other hematological and biochemical parameters, including neutrophil, lymphocyte, and leukocyte counts; hemoglobin; platelet count; urea; creatinine; uric acid; and lipid profile, were within expected reference ranges for a general population with cardiovascular risk factors. These variables did not show statistically significant associations with coronary calcium score in the current analysis.

Table 2. Agatson calcium score and laboratory parameters of all population

Parameters	Median (IQR)
Agatson calcium score	6 (0-41)
FGF 21 (pg/ml)	43.26 (35.29-59.02)
Neutrophil (/µL)	4550 (3850-5190)
Lymphocyte (/µL)	2180 (1860-2720)
Leucocyte (/µL)	7245 (6270-9110)
Hemoglobin (g/dl)	14.2 (13.3-15.6)
Platelet (/µL)	270500 (222000-320000)
Systemic immune inflamatory index	534 (403-642)
Urea (mg/dl)	30 (26-34)
Uric acid (mg/dl)	5.1 (4.5-5.6)
Creatinine (mg/dl)	0.78 (0.66-0.91)
Total cholestrole (mg/dl)	204 (188-237)
Triglyceride (mg/dl)	171 (112-223)
HDL cholestrole (mg/dl)	42 (35-51)
LDL cholestrole (mg/dl)	124 (106-145)
VLDL cholestrole (mg/dl)	34 (22-45)
Non-HDL cholestrole (mg/dl)	161 (134-193)

IQR: Interquartile range, FGF-21: Fibroblast growth factor 21, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, VLDL: Very low-density lipoprotein

As shown in Table 3, in the analysis of Agatston calcium scores and FGF-21 levels across various subgroups, no significant correlation was found between age and Agatston score (p=0.233), although a weak positive correlation was observed between age and FGF-21 levels (p=0.17). Similarly, no significant correlation was observed between gender and either Agatston score (p=0.339) or FGF-21 levels (p=0.931). A significant positive correlation was found between diabetes and Agatston score (p=0.006), with higher calcium scores observed in diabetic patients, while no significant correlation was found for FGF-21 levels (p=0.065). Additionally, a significant correlation was found between hyperlipidemia and Agatston score (p=0.024), with higher calcium scores in patients with hyperlipidemia, although no significant correlation was observed for FGF-21 levels (p=0.104). Finally, no significant correlations were found between hypertension and either Agatston score (p=0.437) or FGF-21 levels (p=0.202). These findings suggest that diabetes and hyperlipidemia are significantly associated with Agatston calcium scores, whereas FGF-21 levels show less significant associations with these factors.

Table 3. Comparison of Agatson calcium score and FGF21 levels between subgroups with Spearman's correlation test

	Agatson		FGF-21	
	Median (IQR)	p	Median (IQR)	p
Age		0.17		0.233
50 or younger (n=17)	1 (0-12)		37.5 (35.3-50)	
51 or older (n=37)	8 (0-78)		45.3 (36.9-60.9)	
Gender		0.339		0.931
Male (n=25)	10 (0-46)		41.5 (35.6-57.8)	
Female (n=29)	3 (0-25)		45 (35.3-59)	
Diabetes mellitus		0.006		0.065
No (n=36)	1 (0-12)		40 (34.7-51.2)	
Yes (n=18)	23 (3-86)		48.1 (39.7-68.7)	
Hyperlipemia		0.024		0.104
No (n=31)	1 (0-12)		37.5 (34.4-53.4)	
Yes (n=23)	23 (0-86)		46.2 (38.7-68.7)	
Hypertension		0.437		0.202
No (n=37)	5 (0-22)		40 (34.4-53.4)	
Yes (n=17)	7 (0-85)		46,9 (38.7-63.4)	

IQR: Interquartile range, FGF-21: Fibroblast growth factor 21

As shown in Table 4, Spearman's correlation test was performed to examine the relationships between Agatston calcium scores and FGF-21 levels with various clinical parameters. A significant positive correlation was observed between the Agatston calcium score and FGF-21 levels (r=0.725, p<0.001), indicating a strong association between these two variables. Additionally, age showed weak positive correlations with both Agatston calcium score (r=0.242, p=0.079) and FGF-21 levels (r=0.26, p=0.058), although neither of these correlations reached statistical significance.

Regarding other parameters, no significant correlations were found between Agatston calcium scores or FGF-21 levels and the following variables: neutrophils, lymphocytes, leucocytes, hemoglobin, platelets, SII, urea, uric acid, creatinine, total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, VLDL cholesterol, or non-HDL cholesterol (all p-values >0.05). This suggests that these clinical markers do not have a substantial relationship with Agatston calcium scores or FGF-21 levels in this study population.

A strong positive correlation was observed between FGF-21 levels and Agatston-based CAC scores (r=0.725, p<0.001). This relationship is visually illustrated in Figure 2, which presents the Spearman's correlation between the two parameters, highlighting their significant association.

Table 4. Spearman's correlation test of Agatston calcium score and FGF21 levels

	Agatson calcium score		FGF21	
	Correlation coefficient	p	Correlation coefficient	p
Age	0.242	0.079	0.26	0.058
Agatson calcium score	1	.	0.725	<0.001
FGF 21 (pg/ml)	0.725	<0.001	1	.
Neutrophil (/µL)	0.145	0.295	-0.061	0.66
Lymphocyte (/µL)	0.246	0.073	0.181	0.189
Leucocyte (/µL)	0.171	0.217	-0.021	0.88
Hemoglobin(g/dl)	0.173	0.21	0.001	0.992
Platelet (/µL)	-0.158	0.254	0.027	0.845
Systemic immune inflamatory index	-0.204	0.14	-0.251	0.068
Urea (mg/dl)	0.025	0.858	-0.004	0.98
Uric acid (mg/dl)	-0.052	0.706	0.064	0.648
Serum Creatin (mg/dl)	0.197	0.152	0.084	0.544
Total cholestrole (mg/dl)	0.011	0.939	0.097	0.483
Triglyceride (mg/dl)	0.197	0.153	0.227	0.098
HDL cholestrole (mg/dl)	-0.216	0.117	-0.207	0.133
LDL cholestrole (mg/dl)	-0.018	0.9	0.019	0.893
VLDL cholestrole (mg/dl)	0.197	0.153	0.232	0.092
Non-HDL cholestrole (mg/dl)	0.036	0.797	0.093	0.502

FGF-21: Fibroblast growth factor 21, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, VLDL: Very low-density lipoprotein

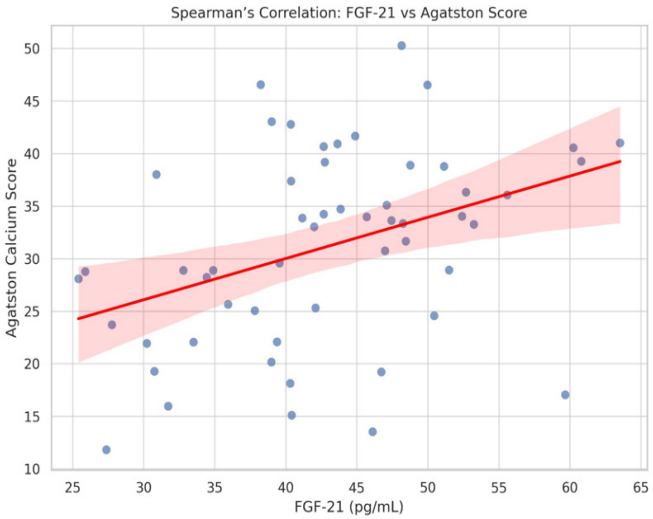

Figure 2. Spearman's correlation between FGF-21 and Agatston score
FGF-21: Fibroblast growth factor 21

DISCUSSION

In our study, the relationship between FGF-21 levels and the coronary calcium score based on the Agatston method was examined, and the potential of FGF-21 as a non-invasive biomarker for coronary calcium score was investigated. Our study revealed a strong positive correlation between FGF-21 levels and the Agatston-based coronary calcium score ($r=0.725$, $p<0.001$). This finding supports the hypothesis that FGF-21 could serve as a non-invasive biomarker indicative of subclinical atherosclerosis. While the coronary calcium score remains a valuable imaging-based risk stratification tool, the non-radiative and accessible nature of FGF-21 offers practical advantages, especially in settings where CT imaging is not feasible. FGF-21 plays a significant role in metabolic processes and may influence vascular calcification.[2]

Previous research has demonstrated the significant role of the Agatston-based coronary calcium score in identifying individuals at high risk of atherosclerosis.[25] Additionally, many cardiovascular disease guidelines emphasize the use of the Agatston-based coronary calcium score as a primary tool for predicting coronary artery disease risk.[26,27] However, the necessity of imaging methods for calculating the Agatston score limits its applicability in all healthcare centers. Imaging requirements, particularly CT scans, can lead to radiation exposure, which could be avoided by using non-invasive biomarkers like FGF-21.

Numerous studies in the literature have investigated the relationship between FGF-21 levels and cardiovascular disease prognosis. Early clinical studies have shown that elevated FGF-21 levels are associated with cardiovascular events and higher mortality.[28,29] However, the relationship between the Agatston-based coronary calcium score and FGF-21 has not been previously explored in the literature, and our study is the first to evaluate this relationship. Several in vitro studies have shown that FGF-21 can reduce endothelial dysfunction and atherosclerosis through various mechanisms.[30] In our study, a significant correlation was observed between the Agatston-based coronary calcium score, which is an indicator of endothelial dysfunction, and FGF-21 levels, due to the exclusion of participants with known coronary artery disease and coronary bypass surgery. This suggests that FGF-21 may play a role in the early stages of atherosclerosis development.[25] Many studies in the literature have explored how FGF-21 achieves this.

FGF-21 modulates key mechanisms of atherosclerosis by reducing foam cell formation, inhibiting endothelial apoptosis and pyroptosis, and suppressing vascular smooth muscle cell proliferation through multiple signaling pathways, including SIRT1, Fas, NLRP3 and NF-κB. It reduces the formation of foam cells derived from macrophages, decreases endothelial apoptosis by inhibiting the Fas signaling pathway, and reduces endothelial pyroptosis by inhibiting certain inflammatory pathways.[12-14] Furthermore, FGF-21 inhibits the migration and proliferation of vascular smooth muscle cells via the FGFR1-BALAK tyrosine kinase-NLRP3 inflammatory pathway.[19] FGF-21 also inhibits the transformation of macrophages into foam cells and the proliferation of vascular smooth muscle cells by stimulating adiponectin secretion.[20]

In addition to these effects, FGF-21 may influence atherosclerosis and coronary artery disease through metabolic pathways. Some studies have shown that FGF-21 increases insulin-independent glucose uptake and reduces serum triglyceride levels.[31] However, in our study, no correlation was found between FGF-21 levels and triglyceride levels. This discrepancy may be attributed to the fact that the triglyceride levels of participants in our study were within the normal range. This suggests that the effects of FGF-21 on metabolism may vary depending on individual characteristics and clinical conditions.

Recent studies have shown that certain diabetes medications, such as sodium/glucose cotransporter-2 inhibitors (SGLT2i), can increase serum FGF-21 levels.[32] Future studies should investigate the relationship between the Agatston-based

coronary calcium score and FGF-21 in patients treated with SGLT2 inhibitors. This may be particularly important for diabetic patients, as these drugs can affect both metabolic pathways and FGF-21 levels, potentially influencing the development of coronary artery disease.

FGF-21 derivatives have been shown to have positive effects on body weight, lipid profiles, and various metabolic conditions.[33-35] This could be due to the fact that the lipid profiles of participants with a diagnosis of hyperlipidemia in our study were well-controlled. In the future, controlled studies examining FGF-21 levels in patients with lipid profiles within normal reference ranges may help clarify the relationship between FGF-21 and lipid metabolism. In our study, while serum FGF-21 levels were significantly correlated with CAC scores, no significant association was observed between FGF-21 and traditional metabolic risk factors such as diabetes mellitus and hyperlipidemia. This finding suggests that FGF-21 may reflect coronary artery calcification independently of these conventional risk factors. It raises the possibility that FGF-21 is directly involved in or responds to the atherosclerotic process itself, rather than acting solely as a marker of metabolic disturbances. Further studies with larger sample sizes are warranted to better elucidate the underlying mechanisms of this association.

In our study, we also examined the relationship between the Agatston-based coronary calcium score and conditions such as diabetes and hyperlipidemia. The lack of a statistically significant association between FGF-21 levels and diabetes or dyslipidemia may stem from the relatively small sample size. Alternatively, these comorbidities may elevate FGF-21 levels via mechanisms involving endothelial dysfunction, independent of calcification severity. Furthermore, the study population was composed of asymptomatic individuals undergoing coronary CT solely for risk stratification, allowing the evaluation of FGF-21 in a relatively isolated cohort. One of the aims of our study was to prevent unnecessary testing in borderline cases before coronary CT angiography by considering FGF-21 levels. Future studies could focus on patients with coronary artery disease.

The use of FGF-21 as a non-invasive and easily applicable biomarker for coronary artery disease risk. FGF-21 could be used in the clinical setting to guide patient selection for CT imaging. Additionally, in patients with low FGF-21 levels, unnecessary imaging procedures may be avoided. We recommend further research on the relationship between FGF-21 and the Agatston-based coronary calcium score, including prognostic studies.

Limitations

This study has several limitations. Although a power analysis was conducted, the sample size remains relatively limited. This constraint particularly affected our ability to perform subgroup analyses based on comorbid conditions such as diabetes and hyperlipidemia, or across different calcium score ranges. Additionally, the study was conducted at a single center, which may limit the generalizability of the findings to populations with different demographic and clinical characteristics.

Due to its cross-sectional design, the study does not allow for evaluation of whether FGF-21 levels can predict future cardiovascular events. Moreover, the CAC scores were assessed by a single radiologist, introducing the possibility of observer bias. Another limitation concerns the use of medications that may influence FGF-21 levels, such as statins or SGLT2 inhibitors. These agents were not included in the analysis because complete, standardized, and reliable retrospective data on medication use were not available, and adherence to prescribed therapies could not be confirmed. Consequently, potential pharmacological interactions could not be assessed.

Finally, the findings of this study were not validated in an independent external cohort. Therefore, multicenter, prospective studies with larger sample sizes are warranted to confirm the generalizability and validity of these results.

CONCLUSION

This study demonstrated a significant and strong positive correlation between serum FGF-21 levels and Agatston-based CAC scores. These findings suggest that FGF-21 may serve as a practical, non-invasive biomarker capable of reflecting subclinical atherosclerosis. Particularly in clinical settings where coronary CT angiography is not readily available due to limitations such as radiation exposure and cost, the use of FGF-21 as a preliminary screening tool could enhance clinical decision-making.

Notably, no significant associations were observed between FGF-21 levels and conventional metabolic risk factors such as diabetes mellitus and hyperlipidemia. This may indicate that FGF-21 functions as a cardiovascular risk indicator independently of these classical metabolic conditions.

The study population consisted of asymptomatic individuals undergoing coronary CT angiography for risk assessment rather than diagnostic purposes. This provided a unique opportunity to investigate the relationship between FGF-21 levels and early vascular changes. Our findings suggest that FGF-21 may be associated not only with metabolic pathways, but also with direct atherosclerotic mechanisms such as endothelial dysfunction and vascular wall inflammation.

In conclusion, FGF-21 appears to hold potential as a non-invasive screening marker for individuals at risk of coronary artery disease who do not yet present with clinical symptoms. Further large-scale, multicenter, prospective studies are warranted to clarify the diagnostic and prognostic value of this biomarker. Moreover, future research exploring FGF-21 levels across different patient subgroups and in the context of various pharmacological treatments would provide valuable insights for the field.

ETHICAL DECLARATIONS

Ethics Committee Approval

All procedures were approved by the Ethics Committee of Ankara Bilkent City Hospital (Date: 29.05.2024, Decision No: TABED 2/209/2024).

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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