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Serum FGF-23 and klotho levels in patients with systemic sclerosis and its relationship with carotid intima media thickness

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Abstract
Aim: Systemic sclerosis (SSc) is an uncommon connective tissue disease characterized by skin fibrosis. Fibrosis of internal organs such as the lungs and heart is also involved in SSc via complex pathophysiological mechanisms. Increased serum fibroblast growth factor (FGF-23) is related to cardiac hypertrophy and fibrosis in chronic kidney disease. We investigated the likely role of FGF-23 and Klotho in SSc and their link with carotid intima-media thickness (CIMT) in these patients.
Material and Methods: A total of 86 participants (43 SSc patients between 18 and 65 years old and 43 healthy volunteers) were included in the study. We recorded patients' demographic data, clinical features, and biochemical and hormonal parameters. A radiologist performed the ultrasonographic examination of CIMT. The chi-square test and Fisher's exact test were utilized for comparisons of categorical variables.
Results: In SSc patients, the FGF-23 level was significantly higher. According to our subgroup analysis, the patients with interstitial lung disease (ILD) had significantly higher FGF-23 levels than patients without ILD (p=0.031). However, the levels of alpha-klotho were similar between the two groups. The mean CIMT in SSc patients was significantly higher than in the control group (0.62 ± 0.11 vs. 0.49 ± 0.10, mm; p<0.001). There were no correlations between FGF-23 (p=0.086, r=0.265), α-klotho (p=0.820, r=0.036), FGF23/α-klotho (p=0.90, r=0.019), and CIMT in SSc patients.
Discussion: FGF-23 can play a culprit role in the pathogenesis of SSc. It was not related to CIMT as a predictor of atherosclerosis. It can predict lung involvement and disease prognosis.

Keywords
Systemic Sclerosis, FGF-23, Klotho, Carotid Intima-Media, Endothelial Dysfunction

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Introduction

Systemic sclerosis (SSc) is an uncommon autoimmune disease. Underlying complex pathogenetic mechanisms include endothelial dysfunction, microvascular damage, and increased tissue fibrosis. Microvascular disease is a significant feature of SSc. Besides, cardiovascular disease (CVD) is also commonly seen in SSc patients, and it is thought to occur as a result of endothelial dysfunction [1].

Nevertheless, there are conflicting data regarding the presence of atherosclerosis in SSc patients. It is unclear whether the increased incidence of CVD originates from only atherosclerosis or disease-related processes. However, it's well known that, the most significant changes include endothelial dysfunction and increased carotid intima-media thickness (CIMT) in the atherosclerosis process [2]. A comparative large cohort study has revealed that SSc patients have comparable subclinical atherosclerosis as RA patients. In this study, clinicians evaluated atherosclerosis by using two parameters, including CIMT and pulse wave velocity (PWV) [3].

Fibroblast growth factor (FGF-23) functions as a hormone-like FGF in the endocrine FGF family. It works physiologically through co-factors such as α-klotho via FGF receptors. FGF-23 expression is minimal in the gastrointestinal system, immune system, reproductive system, and cardiovascular system of healthy adults. In patients with end-stage chronic kidney disease (CKD), elevated serum FGF23 levels are associated with endothelial dysfunction, small vessel disease, and cardiac fibrosis [4]. A recent study investigated FGF-23 and CIMT in maintenance hemodialysis (HD) patients. A multiple regression analysis revealed a positive relation between high FGF-23 concentration and increased CIMT as a predictor of atherosclerosis [5]. However, CIMT and FGF-23 were also investigated in peritoneal dialysis (PD) patients. Although higher CIMT was related to increased cardiovascular mortality, with FGF-23 having no correlations [6]. In addition, the ratio of urinary phosphate (U-P) excretion (mg/day) to FGF-23 (known as nephron index) has been studied in diabetic predialysis CKD patients. The ratio was negatively correlated with CIMT for atherosclerosis in predialysis CKD [7].

Patients with SSc can experience asymptomatic endothelial dysfunction. The clinical applicability of the CIMT has been shown in SSc patients with endothelial dysfunction that can be caused by chronic inflammation and ischemia-reperfusion injury [8]. A recent study showed a positive relation between serum predictive biomarkers of vasculopathy and inflammation such as CRP, IL-6, intercellular adhesion molecule, and the presence of carotid plaque in SSc patients [9. However, the literature needs studies demonstrating the relationships between FGF-23, klotho, and CIMT in patients with SSc. We aimed to investigate CIMT as a predictor of endothelial dysfunction and its relationship with FGF-23 and klotho.

Material and Methods

Patients

A total of 86 participants were included in the study. Forty-three individuals diagnosed with SSc, between 18 and 65 years old, presented at the Rheumatology Outpatient Clinic of Pamukkale University Faculty of Medicine Hospital (patient group) and 43 healthy volunteers (control group). All patients have fulfilled the classification criteria [10]. The study was conducted per the Helsinki Declaration, and each participant obtained a patient consent form. Exclusion criteria were defined as having overlap syndromes, liver or kidney dysfunction, various malignancies, thyroid/parathyroid disorders, severe cardiac valve pathologies, NYHA class III and IV heart failure, acute coronary syndrome or acute cerebrovascular events in the recent six weeks, pregnancy, acute infectious diseases, diabetes mellitus, hypertension, hyperlipidemia, habits as smoking or alcohol, being on treatment with vitamin D therapy within the last six months.

Clinical and Laboratory Evaluations

The duration of the disease, ongoing treatment modalities, type of systemic involvement, autoantibody profiles, and biochemical results of the patients were recorded using their outpatient clinic records.

Procedures for FGF-23 (catalog number CUSABIO-E10113h) and Klotho (catalog number CUSABIO-E13235h) were conducted following the manufacturer's recommendations. We used a C-terminal ELISA kit to determine the serum FGF-23 concentration (the concentration ranged from 3.12 pg/ml to 200 pg/ml; the sensitivity was 0.78 pg/ml). We also used a human Klotho ELISA kit to determine the plasma alpha form of Klotho level (with a measurement range of 0.156 ng/ml to 10 ng/ml and a sensitivity of 0.039 ng/ml).

Ultrasonographic Measurement of Carotid Intima Media Thickness

One radiologist with five years of experience conducted all ultrasonography assessments and was blinded to the patients on the same day following a 12-hour fasting period. The CIMT was assessed during neutral respiration in the supine position. Intima-media thickness measurements were taken from three different points, 1 cm proximal to the carotid bifurcation, in non-plaque areas of the right and left common carotid arteries. The average of these measurements was accepted as intima-media thickness [11]. Measurements were conducted using a Canon Aplio i800 ultrasound device (Canon Medical Systems, Otawara, Tochigi, Japan) with a Multi-Frequency Ultrawideband iDMS Linear (i18LX5) probe.

Statistical analysis

The G*Power 3.1 program was utilized for sample calculations in the present study. Considering studies conducted between SSc patients and healthy controls, an effect size (d=0.7) for the difference in FGF-23 and Klotho levels was assumed. With a Type 1 error rate (α) of 0.05 and a power level (1-β) of 0.95, a minimum of 42 individuals were calculated from each group for the study. Analyses were performed using SPSS 22.0. The normality of the distribution of continuous variables was evaluated using the Shapiro–Wilk and Kolmogorov–Smirnov normality tests. Student's t-test was used to compare normally distributed parameters between two groups, while the Mann–Whitney U test was used for non-normally distributed parameters. The chi-square test and Fisher's exact test were utilized to compare categorical variables. The results are presented as the mean ± SD, median (min–max), and n (%). A significance level of $p<0.05$ was used to indicate statistical significance.

Ethical Approval

This study was approved by the Ethics Committee of Pamukkale University, Faculty of Medicine (Date: 2021-01-28, No: 1).

Results

The demographic data, clinical characteristics, and comparisons of biochemical and hormonal parameters between our SSc patients and healthy controls are presented in Table 1. Both groups were similar in age, gender distribution, and body mass index. The mean age distribution is 50.3 ± 12.6 years in the patient group, while 50.2 ± 9.8 years in the control group. Each study subgroups consist of 39 females and 4 males. FGF-23 levels were significantly higher in SSc patients than in control patients. However, the two groups had no significant difference in Klotho levels. The mean CIMT in SSc patients was significantly higher than in the control group (0.62 ± 0.11 vs. 0.49 ± 0.10, mm; p<0.001). Plaque detection in the carotid arteries was observed in 20.9% of the SSc patients (9 patients), while in the control group, it was 2.3% (1 patient), revealing a significant difference between the two groups (p=0.007). Subgroup analyses were conducted based on the duration of illness in the patient group; the patients were classified as early-stage (with a disease duration of 5 years or less) or late-stage disease (with a disease duration exceeding five years). All late-stage patients (n =28) were ANA positive, while 86.7% of early-stage patients (n =13) were ANA positive, with a statistical difference (p=0.048). In early- and late- stage disease groups, there were no significant differences respectively; in serum Klotho (median values 394; 427, p=0929) and FGF-23 levels (median 21.1; 20.9, p=0.211) and carotid intima-media thickness (median 0.61; 0.63, p=0.156). In our study, carotid plaques, digital ulcers, pulmonary arterial hypertension, and interstitial lung disease were more significant in the late-stage disease group than in the early-stage disease group.

Subgroup analysis was also performed among the patients with and without interstitial lung disease. FGF-23 levels were higher in the SSc-ILD group with a statistical significance (21.6; 16.8 respectively, p= 0.031), whereas the Klotho levels and carotid intima-media thickness were similar between the subgroups. The DLCO mean values were significantly lower in the SSc-ILD group (58.2 ± 18.1 vs. 70.3 ± 20.0, p= 0.043). Cyclophosphamide, mycophenolate mofetil, and rituximab were significantly more commonly preferred for medical treatment in the SSc-ILD group (p= 0.001, p= 0.029, and p= 0.033, respectively). However, Methotrexate was a more frequently used drug in patients without ILD (p= 0.006).

We evaluated the association of FGF-23, Klotho, and FGF23/Klotho ratio with age, BMI, disease duration, carotid intima-media thickness, and biochemical and hormonal parameters in the patients (Tables 2 and 3). We found a negative correlation between FGF-23 levels and the serum albumin concentration (p=0.001, r=-0.489) and a positive correlation with the serum C-reactive protein (CRP) level (p=0.025, r=0.342) and sedimentation rate (p=0.017, r= 0.362).

Table 1. Comparison of demographic data, clinical characteristics, biochemical parameters, and hormonal parameters between SSc patients and healthy controls

Parameters	SSc Patients (n=43)	Healthy Group (n=43)	P value
BMI (kg/m^2) median (min–max)	25.2 (17.1-34.0)	25.2 (17.9-31.2)	0.839
ALT median (min–max)	15.0 (2.0-32.2)	14.0 (7.0-40.0)	0.739
CRP median (min–max)	1.69 (0.09 - 29.7)	1.36 (0.23 -10.74)	0.132
ESR median (min–max)	21.0 (2.0-120.0)	10.0 (2.0-41.0)	0.051
PTH median (min–max)	60.8 (20.7-168.1)	50.9 (32.4-105.0)	0.302
FGF-23 median (min–max)	21.1 (8.3-57.5)	14.3 (8.3-35.8)	<0.001*
Klotho median (min–max)	409.0 (96.0-5551.0)	336.0 (140.0-1172.0)	0.262
CIMT mean ± SD	0.62 ± 0.11	0.49 ± 0.10	<0.001*
Carotid plaque n(%)	9 (20.9)	1 (2.3)	0.007*

BMI is body mass index, ALT is alanine aminotransferase, CRP is c-reactive protein, ESR is erythrocyte sedimentation rate, PTH is parathormone, FGF-23 is fibroblast growth factor-23, and CIMT is carotid intima-media thickness

Table 2. The Relationship of FGF-23, Klotho, and FGF23/Klotho ratio with age, BMI, disease duration, and carotid intima-media thickness

	Age	BMI	Disease Duration	CIMT
FGF-23	r=0.193 (p= 0.215)	r=-0.249 (p=0.486)	r=0.223 (p=0.150)	r=0.265 (p=0.086)
Klotho	r=0.104 (p=0.507)	r=0.058 (p=0.711)	r=-0.171 (p=0.273)	r=-0.036 (p=0.820)
FGF23/Klotho Index	r=-0.214 (p=0.168)	r=0.049 (p=0.753)	r=0.025 (p=0.872)	r=-0.019 (p=0.903)

BMI: body mass index, FGF-23: fibroblast growth factor-23, CIMT: carotid intima-media thickness

Table 3. The Relationship of FGF-23, Klotho, and FGF23/Klotho ratio with laboratory values

Parameters	FGF-23	Klotho	FGF23/Klotho ratio
ALT	r=0.095, p=0.544	r=0.134, p=0.392	r=0.025, p=0.874
Creatinin	r=-0.186, p=0.232	r=0.071, p=0.650	r=-0.189, p=0.226
Calcium	r=0.218, p=0.160	r=0.165, p=0.292	r=0.024, p=0.877
Albumin	r=-0.489, p=0.001*	r=-0.085, p=0.586	r=-0.243, p=0.117
Phosphor	r=0.216, p=0.164	r=0.096, p=0.539	r=0.004, p=0.982
Vitamine D	r=0.063, p=0.688	r=0.068, p=0.664	r=0.061, p=0.696
CRP	r=0.342, p=0.025*	r=0.004, p=0.982	r=0.248, p=0.109
ESR	r=0.362, p=0.017	r=0.174, p=0.265	r=0.079, p=0.615
PTH	r=0.227, p=0.143	r=0.039, p=0.804	r=0.192, p=0.218

ALT stands for alanine aminotransferase, CRP for C-reactive protein, ESR for erythrocyte sedimentation rate, PTH for parathormone, and FGF-23 for fibroblast growth factor-23

Discussion

Endothelial dysfunction has significant clinical implications in many chronic inflammatory connective tissue diseases. This vasculopathy may lead to accelerated atherosclerosis with an increased risk of cardiovascular events and mortality [12]. Recent studies reported that patients with SSc have an increased risk of cardiovascular disease [13]. This is the first study in which we investigated serum FGF-23, serum Klotho, and their relationship with CIMT as a predictor of atherosclerosis. Although macrovascular damage is less frequent in SSc patients, increased stiffness of large arteries, formation of plaque, increased CIMT, and increased myocardial infarction are observed in recent studies [14]. Our study also detected increased CIMT in SSc patients compared with healthy controls. Increased CIMT can be a sign of increased atherosclerosis in these patients.

A recent systematic meta-analysis revealed a positive correlation between FGF-23 and arterial calcification, carotid intima-media thickness (CIMT), and pulse wave velocity (PWV)

[15]. Elevated circulating levels of FGF23 are associated with pathological cardiac remodeling left ventricular hypertrophy, myocardial fibrosis, and increased cardiovascular mortality. It's well known that higher FGF-23 levels are related to increased risk of cardiovascular diseases in chronic kidney disease [16]. Although serum FGF-23 and CIMT were increased in SSc patients than healthy controls in our study, there was no relationship between both of them. In a way that supports our conclusion, a recently published Mendelian randomization study also showed no causal link between nonatherosclerotic and atherosclerotic cardiovascular diseases (carotid and cardiac problems) and predicted FGF-23 levels [17].

In the study by Guerra et al., serum FGF23 levels were more significant in SSc patients than in controls (p = 0.01). However, no relationship between FGF-23 and disease severity was observed [18]. However, FGF-23 was higher in patients with lung involvement in our study. There is also a stated link between inflammation and FGF-23. Inflammation is one of the factors that increases FGF23 production as well as iron deficiency [19]. Especially bone tissue is the main source of FGF-23 in acute inflammation [20]. According to our study, there were also the negative correlation between FGF-23 levels and the serum albumin concentration and a positive correlation with CRP and ESR. This result also led us to think about its possible inflammation-related role in SSc patients except atherosclerosis.

Few studies have evaluated FGF-23 and Klotho levels in SSc patients. The authors investigated their effect on other disease manifestations such as calcinosis or fracture risk of bones. These studies have conflicting results. Ahmadi R et al have detected similar FGF-23 levels in SSc patients in addition to decreased serum Klotho levels compared with healthy controls [21]. Transgenic mice without Klotho expression develop a phenotype characterized by accelerated aging, skin atrophy, lung emphysema, osteoporosis, delayed wound healing, and vascular calcification [22]. Although similar FGF-23 levels between SSc patients and healthy controls (78.2 ± 60.5 vs. 80.3 ± 56.3 pg/mL, p=0.662) were detected, higher values of FGF-23 were related to the presence of calcinosis in SSc patients [23]. Lucia Cantero-Nieto et al. also showed similar FGF-23 levels in SSc patients and healthy controls. In their study, higher FGF-23 levels were associated with higher Fracture Risk Assessment Tool (FRAX) scores in SSc patients [24]. In our study, SSc patients, such as healthy controls, had similar serum Klotho levels.

Limitation

Our study also has a few limitations. The sample size is small, and the patients are from a single health center. SSc patients were not analyzed in subgroups in terms of limited and diffuse involvement due to the lack of patient size. Only one radiologist has evaluated all patients,

Conclusion

The serum levels of FGF-23 and α-klotho are unrelated to increased CIMT in SSc patients. There are still unexplained points in the pathogenesis of the disease. FGF-23 can play a role in patients with lung involvement, and it can be related to the inflammation pathway. Increased CIMT can be related to atherosclerosis.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and Human Rights Statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or compareable ethical standards.

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Conflict of Interest

The authors declare that there is no conflict of interest.

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