Fibroblast Growth Factor-23 is associated with High-density lipoprotein in Systemic sclerosis Female patients

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ABSTRACT

Introduction: Fibroblast growth factor-23 (FGF23) is a circulating regulator of phosphate and vitamin D metabolism and has been implicated as a putative pathogenic factor in cardiovascular disease. The objectives of this study were: to compare serum FGF23 levels between systemic sclerosis (SSc) patients and healthy controls and to investigate possible associations between FGF23 and serum lipid profile in SSc patients.

Methods: This cross-sectional study was performed in San Cecilio Hospital, Granada (Spain) from November 2017 to May 2019. We enrolled 62 consecutive female patients affected by SSc and 62 healthy women who served as controls. Cardiovascular risk factors and related biochemical parameters were collected. Serum FGF23 was analyzed using enzyme-linked immunosorbent assay (ELISA). Linear regression was used to examine the cross-sectional associations of serum FGF23 concentrations with high density lipoprotein-cholesterol (HDL-c).

Results: There was no significant differences in FGF23 levels between the patients and controls (78.2 ± 60.5 vs. 80.3 ± 56.3 pg/mL, p = 0.662), but we found a statistically significant inverse relationship between FGF23 and HDL-c measurements (r= -0.27; p= 0.03) in women with SSc. In addition, in the linear regression model, higher FGF23 concentrations were associated with lower HDL-c [β = -1.45 95% CI (-2.81, -0.08); p < 0.05].

Conclusions: We report an association between circulating FGF23 and HDL-c in SSc female patients, representing a novel pathway linking high FGF23 to an increased cardiovascular risk.

Keywords: Fibroblast growth factor-23, High-density lipoprotein, Systemic sclerosis.

INTRODUCTION

Systemic sclerosis (SSc) is a generalized connective tissue disorder characterized by fibrosis of the skin and internal organs and widespread vascular lesions. SSc is also characterized by calcification, vasculopathy, and endothelial wall damage, all of which can increase the risk for atherosclerosis and cardiovascular disease.[1] The association between autoimmune diseases and atherosclerosis is well described in many connective tissue diseases such as systemic lupus erythematosus and rheumatoid arthritis, and lead to increased cardiovascular morbidity and mortality.[2,3] Mechanisms by which atherosclerosis is promoted in connective tissue diseases remain unknown, but is believed to be secondary to chronic inflammation,[4,5] altered lipid profiles and function,[6,7] autoantibodies,[8] and endothelial dysfunction.[9]

Fibroblast growth factor-23 (FGF23) is a bone-derived circulating hormone that directly controls serum levels of phosphate, 1,25-dihydroxy vitamin D3, and parathyroid hormone (PTH) and has been implicated as a putative pathogenic factor in cardiovascular disease.[10-14] FGF23 could exert hormonal control on fat mass and glucose metabolism, since it shares structural similarities with the other FGF subfamily members (FGF15/19 and FGF21) that are involved in carbohydrate and lipid metabolism.[15,16-20] A previous study has linked FGF23 to traditional cardiovascular risk factors, including dyslipidemia in patients with rheumatoid arthritis.[21]

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Table I. Characteristics of women with Systemic Sclerosis and healthy controls.

Parameter	SSc (Mean + SD)	HC (Mean + SD)	*p* value
Age, years	53.2 ± 10.1	52.7 ± 9.7	0.71
Height, cm	159.5 ± 5.6	160.9 ± 7.1	0.23
Body weight, kg	66.8 ± 12	67.2 ± 12	0.90
Body mass index, kg/m^2	26.3 ± 4.9	25.9 ± 4.3	0.90
Waist circumference, cm	83.5 ± 11	83.1 ± 13.4	0.64
Smoking, n (%)	11 (17.7)	15 (24.2)	0.04
Hypertension, n (%)	8 (12.9)	11 (17.7)	0.87
Diabetes mellitus, n (%)	2 (3.2)	2 (3.2)	0.62
Dyslipidemia, n (%)	21 (33.8)	14 (22.5)	0.17
Disease duration, years	8.8 ± 6.9	-	-
lcSSc, n (%)	44 (70.9)	-	-
dcSSc, n (%)	18 (29.1)	-	-

Abbreviations: dcSSc: diffuse cutaneous SSc, HC: healthy control, lcSSc: limited cutaneous SSc, SD: standard deviation, SSc: systemic sclerosis.

Table II. Serum FGF23 and biochemistry of the patients and healthy controls.

Parameter	SSc, Mean ± SD	HC, Mean ± SD	p value
FGF23, pg/ml	78.2 ± 60.5	80.3 ± 56.3	0.66
Serum phosphate, mg/dl	3.6 ± 0.5	3.4 ± 0.5	0.04
Serum calcium, mg/dl	9.5 ± 0.3	9.4 ± 0.4	0.05
Glucose, mg/dl	88.4 ± 9.4	92.1 ± 13.0	0.07
Cholesterol, mg/dl	199.8 ± 34.9	211.8 ± 37.3	0.06
LDL-c, mg/dl	122.1 ± 32.0	129.7 ± 30.7	0.17
HDL-c, mg/dl	57.8 ± 15.5	63.3 ± 13.1	0.03
Triglycerides, mg/dl	105.2 ± 54.1	107.7 ± 53.9	0.79
Uric acid, mg/dl	4.6 ± 1.1	4.6 ± 1.3	0.91
BNP, pg/ml	41.2 ± 27.5	28.3 ± 19.9	0.003
Serum creatinine, mg/dl	0.7 ± 0.8	0.7 ± 0.2	0.12
eGFR, ml/min	93 ± 17.2	97 ± 13.2	0.19
CRP, mg/dl	0.4 ± 0.4	0.2 ± 0.1	0.007
ESR, mm/h	21.1 ± 16	11.3 ± 10.2	0.001
ANAs, n (%)	53 (85.4)	-	-
Anti-centromere, n (%)	32 (51.6)	-	-
Anti-Scl70, n (%)	15 (24.1)	-	-

Abbreviations: ANA: antinuclear antibodies, BNP: brain natriuretic peptide, CRP: C-reactive protein, eGFR: estimated glomerular filtration rate, ESR: erythrocyte sedimentation rate, FGF23: fibroblast growth factor-23, HC: healthy control, HDL: high density lipoprotein, LDL: low density lipoprotein, SD: standard deviation, SSc: systemic sclerosis.

The objectives of this study were: to compare serum FGF23 levels between SSc patients and healthy controls and to investigate possible associations between FGF23 and serum lipid profile in SSc patients.

METHODS

Study subjects. This cross-sectional study was performed in San Cecilio Hospital, Granada (Spain) from November 2017 to May 2019. We prospectively enrolled 62 consecutive female patients affected by SSc ≥ 18 years old and 62 healthy women age-matched who served as controls. All patients included in this study had normal serum creatinine (Cr) levels, and met the 2013 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) criteria for SSc.[22] Individuals with prevalent cardiovascular disease (acute myocardial infarction, angina pectoris, stroke, or peripheral arterial disease) were excluded.

At the clinic visit, participants completed questionnaires about their lifestyle characteristics, medical history, and current medication used. Informed consent was obtained for all subjects, and the study was approved by the Research Ethics Committee of Hospital Clinico Universitario San Cecilio in Granada, Spain, and conducted in accordance with the guidelines in the Declaration of Helsinki.

Cardiovascular assessment. Current smokers were defined as those who reported having smoked ≥1 cigarette per day regularly during the year preceding the examination. Waist circumference, weight, and height were measured; and body mass index (BMI) was calculated as weight (kg)/height (m^2). Two recordings of blood pressure were obtained from the right arm of the seated subjects; measurements were taken in 5-min intervals, then mean values were calculated. Hypertension was defined as the mean of 3 independent measures of blood pressure ≥ 140/90 mmHg or current use of antihypertensive drugs. Type 2 diabetes mellitus (T2DM) was defined by self-reported use of insulin, or oral hypoglycaemic medications, or a fasting glucose level ≥126 mg/dl. Kidney function was assessed using the estimated glomerular filtration rate (eGFR) calculated by the CKD-Epi study equation.[23]

Laboratory measurements. In all the cases, a fasting blood sample was taken in the morning, and was stored at -70°C until the assays were performed.

The sera were tested for creatinine, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), brain natriuretic peptide (BNP) and FGF23. Creatinine was determined by Jaffe method (Siemens Healthcare Diagnostic Inc. NY, USA). CRP was measured by turbidimetric immunoassay (Siemens Healthcare Diagnostic Inc. NY, USA). ESR was measured by Westergren method. BNP was quantified in heparinised plasma using a solid-phase two-site chemiluminescent immunometric assay (*Biomérieux,* France). Serum FGF23 (*Elabscience*, USA) was measured by enzyme-linked immunosorbent assay (ELISA) according to the manufacturer's recommendations. Antinuclear

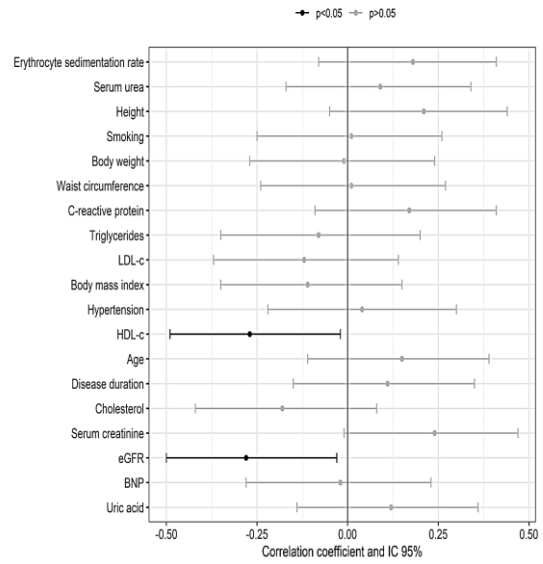

Figure 1. Correlations between fibroblast growth factor-23 and Study Parameters in Systemic Sclerosis patients. BNP: brain natriuretic peptide, eGFR: estimated glomerular filtration rate, HDL: high density lipoprotein, LDL: low density lipoprotein.

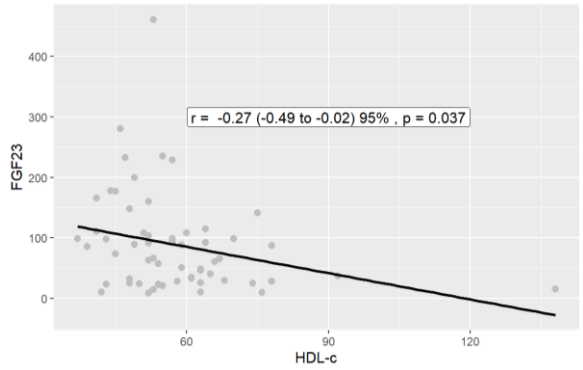

Figure 2. Correlation between fibroblast growth factor-23 [FGF23 (pg/ml)] and high density lipoprotein [HDL-c (mg/dl)].

antibodies were assessed using ELISA kits produced by *Generic Assay Dahlewitz* Germany. Calcium and phosphorus were determined colorimetrically using commercial reagents in an automated chemical analyzer (Siemmens Healthcare Diagnostic Inc. NY, USA). Serum uric acid was measured by oxidisation with the specific enzyme uricase to form allantoin and hydrogen peroxide. Fasting plasma glucose was measured in fresh specimens with a hexokinase reagent kit (Siemens Healthcare Diagnostic Inc. NY, USA). Total cholesterol and triglyceride levels were determined by fully enzymatic techniques. High-density lipoprotein (HDL) was determined after precipitation of apolipoprotein B (apoB)–containing lipoproteins with magnesium sulphate and dextran sulphate. Low-density lipoprotein (LDL) was calculated using the Friedewald formula. All other routine serum biochemical parameters were measured at the Department of Clinical Chemistry, San Cecilio Hospital.

Statistical analysis. Data were analysed by statistical software SPSS 21 (Chicago, IL, USA), using independent samples *t*-test, Mann-Whitney U test, and Chi-square test where appropriate. Spearman's coefficient and Pearson's correlation were calculated as suitable to determine the correlation between the bio-chemical parameters. *P*-values of less than 0.05 were considered statistically significant. Assuming an alpha risk of 0.05%, a sample size of 62 patients was calculated. The quantitative data were shown as mean ± standard deviation (SD) and median (Q1–Q3) as suitable. To test if we can admit that the distribution is normal, we use the Shapiro-Wilk test. Linear regression was used to examine the cross-sectional associations of serum FGF23 concentrations with HDL-c.

RESULTS

Characteristics of the study subjects. A total of 62 women with SSc and 62 healthy women who served as controls were included in our study. Patients and controls were similar in age and race (the majority were Caucasian). Forty-four (70.9%) patients had a limited form of the disease and 18 (29.1%) had a diffuse form. Twelve (19%) patients had calcinosis and all patients had Raynaud Phenomenon. Data are shown in Table I.

Laboratory results. Laboratory tests of the patients and healthy controls included in the present study are shown in Table II. Laboratory markers of inflammation found at the time of the study were higher in women with SSc than in controls. In this regard, the mean CRP in SSc patients was 0.4 ± 0.4 mg/dl versus 0.2 ± 0.1 mg/dl in controls (p=0.007). Likewise, the mean ESR in the group of SSc patients was 21.1 ± 16 mm/1st hour versus 11.3 ± 10.2 mm/1st hour in controls (p=0.001). BNP levels were higher in patients with SSc (41.2 ± 27.5versus 28.3 ± 19.9 pg/ml in controls; p=0.003). Patients had lower levels of HDL-c [57.8 ± 15.5 versus 63.3 ± 13.1 mg/dl; p=0.03] than controls.

There were no significant differences in FGF23 levels between the patients and controls [78.2 ± 60.5 versus 80.3 ± 56.3 pg/ml; p = 0.662].

Cardiovascular disease risk factors. There were no differences between groups, regarding the presence of CV risk factors, with the exception of tobacco, which was more frequent in controls. Results are shown in Table I.

Association between FGF23 levels and cardiovascular risk factors in patients with Systemic Sclerosis. Figure 1 shows the correlation coefficients between FGF23 and other markers in patients with SSc. We found a statistically significant inverse relationship between FGF23 and HDL-c measurements (r= -0.27; p= 0.03) in women with SSc. In addition, in the linear regression model, higher FGF23 concentrations were associated with lower HDL-c [β = -1.45 95% CI (-2.81, -0.08); p < 0.05] (Figure 2).

However, there was no correlation of FGF23 levels with LDL-c, TG, age, BMI, waist circumference, or smoking status.

DISCUSSION

In the present study, there was no significant differences in FGF23 levels between the patients and controls, but we found a statistically significant inverse relationship between FGF23 and HDL-c measurements in women with SSc.

Systemic sclerosis is a multisystemic, immune-mediated disease that results in tissue fibrosis.[24] In fact, altered balance of the pro-angiogenic and anti-angiogenic activities in SSc causes an abnormal new vessel growth (angiogenesis) or defective repair processes with subsequent tissue ischemia and fibrosis.[25] Cardiovascular complications in SSc include peripheral vascular disease, cerebrovascular disease, coronary disease and primary myocardial disease.[26] Brain natriuretic peptide (BNP) level assessment has become a strong and well-recognized indicator of the cardiovascular risk in SSc.[27] In this regard, we have found higher BNP levels in SSc female patients compared to healthy controls. Elshamy et al.[28] reported a significant increase in the mean values of serum levels of N-terminal pro-brain natriuretic peptide in SSc patients compared to controls. In our SSc patients, HDL-c levels were statistically different from healthy controls, and this is in line with others reports.[29]

Fibroblast growth factor-23 (FGF23) is a 30 kDa secreted hormone glycoprotein that plays an important role in the complex and tightly regulated mechanism of mineral metabolism.[30] In healthy individuals, FGF23 is secreted from bone osteocytes in response to an increase in dietary phosphate.[31] FGF23 has been found to be associated with total body atherosclerosis and vascular dysfunction.[32,33] In our study, there was no significant difference in FGF23 serum levels between SSc patients and healthy controls, probably due to the small sample size. However, we found a statistically significant inverse relationship between FGF23 and HDL-c measurements, which was independent of age. Mirza et al.[34] examined the association between FGF23 concentrations and markers of the metabolic syndrome in two cohorts of predominantly older Caucasian patients from the Osteoporotic Fractures in Men Study (MrOS) and Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) study. Lower serum HDL-c and apoA1, along with higher triglycerides were found among patients with higher FGF23 measurements. Montford et al.[35] also observed a significant inverse association between FGF23 and HDL-c concentrations in dialysis patients that persisted after multivariate analysis. There is currently a paucity of evidence to support a biochemical mechanism by which FGF23 might control lipid regulation. An attractive theory is that FGF23 can signal through multiple fibroblast growth factor receptors (FGFRs) previously thought limited to other FGF19 subfamily members. In fact, FGF23 is closely related in structural homology to both FGF15/19 and FGF21.[36] FGF-15/19 signaling is primarily implicated in bile acid metabolism and gallbladder filling, while experimental data supports a role for FGF21 in regulation of lipolysis.[37] Though FGF23 has been shown to signal primarily through FGFR 1c, 3c, and 4c in the kidney, parathyroid gland, and choroid plexus of the brain,[38] in vitro studies demonstrate that FGF23 can signal through multiple FGFRs.[39]

There are several limitations in our study that should be considered. First, this study was a cross-sectional analysis that reflected the status of a population in a particular period. The cross-sectional design of this study does not allow drawing causal inferences. This study focused only in women with SSc; therefore, the findings of this study cannot be generalized to men with SSc. However, it has several strengths derived from the monocentric design of the study with the inclusion of consecutive SSc patients homogeneously evaluated and the careful analysis of data performed by a dedicated physician.

CONCLUSION

We report an association between circulating FGF23 and HDL-c in SSc female patients, representing a novel pathway linking high FGF23 to an increased cardiovascular risk. In this series there are higher levels of BNP and lower levels of HDL-c, and these results are relevant in the clinical practice because they should be monitored as known CV risk factors. These results suggest that FGF23 might have a role in the increased CV risk of patients with SSc. Larger studies should be conducted to explore this potential effect.

Disclosure

The authors did not receive any funding and have no conflicts of interest in conducting this study.

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