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ORIGINAL RESEARCH

Fibroblast Growth Factor 23 is Associated With Adiposity in Patients Receiving Hemodialysis: Possible Cross Talk Between Bone and Adipose Tissue

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Objective: Fibroblast growth factor 23 (FGF-23) may be involved in signaling between bone and adipose tissue in dialysis patients, but its role is uncertain. We sought to examine the association between FGF-23 and adiposity and whether this association is mediated in part by leptin.

Design/Setting: We performed univariate and multivariate linear regression analyses using data from 611 participants in a cohort of prevalent hemodialysis patients recruited from dialysis centers in Atlanta, GA and San Francisco, CA from 2009 to 2011. We also investigated the role of leptin in these relationships.

Subjects: Participants were aged ≥18 years, English or Spanish speaking, and receiving hemodialysis for at least 3 months.

Main Outcome Measures: Outcome measures of adiposity included body mass index, waist circumference, and body fat measured by bioelectrical impedance spectroscopy.

Results: Mean age was 56 ± 14 years, 39.8% were female, and median serum FGF-23 was 807 pg/mL. In fully adjusted models, FGF-23 was inversely associated with body mass index (−0.24 kg/m^2 per 50% higher FGF-23, 95% confidence interval [CI]: −0.38 to −0.10), waist circumference (−0.44 cm per 50% higher FGF-23, 95% CI: −0.79 to −0.08), and percent body fat (−0.58% per 50% higher FGF-23, 95% CI: −0.79 to −0.37). Leptin was inversely associated with FGF-23. Addition of leptin to body composition models attenuated the associations between FGF-23 and measures of adiposity, but FGF-23 remained significantly associated with percent body fat (−0.17% per 50% higher FGF-23, 95% CI: −0.32 to −0.02).

Conclusion: We found a negative association between FGF-23 and adiposity that appears to be mediated in part by leptin. As adipose tissue provides a "protective energy depot" for patients with chronic illness, a decrease in adipose tissue may be one mechanism in which higher FGF-23 levels may contribute to increased mortality in dialysis patients.

Introduction

FIBROBLAST GROWTH FACTOR 23 (FGF-23), a hormone secreted predominantly by osteoblasts and osteocytes, modulates mineral homeostasis by acting as a phosphatonin, altering renal secretion of phosphate, and suppressing 1,25-$(OH)_2$ vitamin D production. Emerging data from *in vitro* and animal models suggest that FGF-23 may also be involved in communication among different endocrine systems, including in adipose tissue and the pancreas.[1,2] The similarity of conserved domains in FGF-23 to those in FGF-19 and FGF-21, both of which are important in lipid and glucose metabolism, may underlie the effects of FGF-23 in adipose tissue. It is possible that leptin, an adipokine important in maintaining the homeostasis of adipose tissue, is involved in mediating this cross talk. Tsuji *et al.*[3] showed that injecting *ob/ob* mice with leptin increased transcription and serum concentration of FGF-23. In humans, there have also been cross-sectional and case control studies linking FGF-23 and adiposity. In cohorts of community-dwelling elderly individuals, FGF-23 was associated with higher body mass index (BMI), waist-hip ratio, and fat mass[4]; and in women presenting for bariatric surgery, FGF-23 was positively associated with BMI and leptin.[5]

Plasma FGF-23 concentration increases among patients with chronic kidney disease (CKD), perhaps as an initial adaptive mechanism to rising phosphorous levels. However, FGF-23 may escape counter-regulatory mechanisms as disease progresses to end-stage renal disease (ESRD),[6] and

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FGF-23 concentrations can be more than 100-fold higher among individuals with ESRD than among individuals without CKD. Higher concentrations of FGF-23 are associated with higher mortality among patients on dialysis.[7]

Montford *et al*.[8] found that in a cohort of ESRD patients, the relationship between FGF-23 concentration and body composition was contrary to those observed in animal models and in individuals without CKD; FGF-23 was inversely correlated with BMI in their analysis. To further investigate these seemingly paradoxical results, we examined the association of FGF-23 with adiposity measured by BMI and also with estimates of fat mass derived from bioelectrical impedance spectroscopy (BIS) and anthropometry in a prevalent hemodialysis cohort. In addition, we investigated whether the association of FGF-23 with adiposity is independent of leptin. We hypothesized that FGF-23 would be inversely associated with BMI, waist circumference, and percent body fat and that the association between FGF-23 and adiposity would be dependent on leptin.

Materials and Methods

Study Participants

ACTIVE/ADIPOSE (A Cohort Study To Investigate the Value of Exercise in ESRD/Analysis Designed to Investigate the Paradox of Obesity and Survival in ESRD) recruited 771 participants from 14 dialysis centers in metropolitan Atlanta, GA and the San Francisco Bay Area, CA from 2009 to 2011.[9] Participants were aged ≥18 year, English or Spanish speaking, and receiving hemodialysis for at least 3 months. Exclusion criteria were active malignancy, pregnancy, incarceration, or significant mental illness or dementia. The study was approved by the University of California, San Francisco and Emory University Institutional Review boards. The patients provided written informed consent to participate in the study. Only complete participant data with measurements of BMI, waist circumference, laboratory values, and BIS were included in the analysis.

Body Composition

Study personnel measured height using a stadiometer, and weight was recorded as the mean postdialysis weight from the previous 3 dialysis sessions. Waist circumference was measured above the hip bone while the patient was in a standing position. The mean of the 2 values was used in analyses.

Whole body BIS was performed before dialysis after the patient was in a supine position for at least 10 minutes. Electrodes were placed on the hand and foot on the side opposite the dialysis access, with the proximal and distal electrodes 5 cm apart. The instrument (SFB7: ImpediMed, San Diego, CA) scanned 256 frequencies between 4 and 1000 kHz, and 10 measurements were performed within a 1-minute period. Total body water was estimated using the resistance extrapolated to infinite frequency, and total body fat mass was calculated by subtracting total body water divided by 0.73 from the body weight. Percent body fat was calculated by total body fat mass divided by body weight.

Laboratory Values

Blood was collected before a dialysis session. Serum was separated, aliquoted, frozen at −80°C, and transferred to the central laboratory at UC Davis where samples were then stored at −196°C until analyzed. Serum FGF-23 concentration was measured by C-terminal ELISA using Millipore Sandwich ELISA assay (Millipore, St. Charles, MO). Interassay coefficient of variation (COV) was 2.45-11.31%, intra assay COV was 7.8-11.2%. Leptin and interleukin-6 (IL-6) were measured using Milliplex MAP Kit Human ADIPOKINE Magnetic Bead Panel 2 (Millipore, St. Charles, MO), allowing the simultaneous measurement of multiple biomarkers by an ELISA method (R&D Systems, Inc. Minneapolis, MN). The COV for leptin was 6.4%, and the intra-assay COV was 11.9%. The range for the IL-6 assay was 0-300 pg/mL, intra-assay COV was 4.5%, and interassay COV was 2.6%. Average values of the duplicate measures were used in analyses.

Statistical Analysis

We compared the characteristics of the subset of the cohort included in the analysis with those who were not included using chi-square analysis or *t* tests as appropriate. We used univariate and multivariate linear regression analysis to examine the relationship between natural log-transformed FGF-23 (ln-FGF-23) and BMI, waist circumference, and percent body fat individually. Next, we performed multivariate analysis, adjusting for age, race, dialysis vintage, serum phosphorus, and natural log-transformed serum IL-6 concentration. As inflammation is a regulator of FGF-23 level[10] and can also decrease adiposity, we have included IL-6 as a marker of inflammatory status. We also performed regression between ln-FGF-23 and natural log-transformed leptin (ln-leptin). Sex was not included in these models because of high correlation between sex, leptin, and adiposity. The unadjusted analysis was checked for departures from linearity graphically using a nonparametric locally weighted scatterplot smoothing (LOWESS) curve. The multivariable regression models were examined for linearity using a component plus residual plot. We confirmed that there was no nonlinear pattern in the component plus residual plot using natural-log transformed FGF-23 as the predictor, and the linear and LOWESS fits agree well, indicating a linear relationship.

To investigate leptin as a possible mediator in the association of FGF-23 levels with measures of adiposity, we performed formal mediation analysis as follows: (1) Regression analysis with ln-FGF-23 as predictor of adiposity outcomes; (2) regression analysis with ln-FGF-23 as the predictor and the proposed mediator, ln-leptin as the outcome; (3) regression analysis with the proposed mediator, ln-leptin

as the predictor, and adiposity as the outcome; and (4) multiple regression analysis with ln-FGF-23 and the proposed mediator, ln-leptin, as predictors and adiposity as the outcome.[11] These analyses adjusted for possible confounders including age, race, dialysis vintage, serum phosphorus, and serum natural log-transformed IL-6. All statistical analysis was carried out with STATA, version 14.1 (STATA Corp, College Station, TX), and 2-tailed nominal *P*-values $< .05$ were considered to indicate statistical significance.

Results

Participant Characteristics

There were 771 patients in the ACTIVE/ADIPOSE cohort, of which 611 (80%) had measurements of BMI, waist circumference, laboratory values, and BIS and were included in the analysis. The mean age of participants in this analysis was 56 ± 14, 40% were female, 62% were black, and 23% were white. The median FGF-23 level was 807 pg/mL, with interquartile range 209-3,654 pg/mL. Participants included in the analysis were significantly younger and had a higher mean albumin concentration compared with those not included in the analysis (Table 1).

Association of FGF-23 With Measures of Adiposity

In univariate analysis, FGF-23 was inversely associated with BMI, waist circumference, and percent body fat (Table 2). In multivariate analysis, after adjusting for age, race, dialysis vintage, serum phosphorus level, and serum IL-6 level, we found that the inverse associations between FGF-23 and BMI (-0.24 kg/m^2 per 50% higher FGF-23, 95% confidence interval [CI]: -0.38 to -0.10), waist circumference (-0.44 cm per 50% higher FGF-23, 95% CI: -0.79 to -0.08), and percent body fat (-0.58% per 50% higher FGF-23, 95% CI: -0.79 to -0.37) remained statistically significant (Table 2).

Association of FGF-23 With Measures of Adiposity After Adjustment for Leptin

FGF-23 was inversely associated with leptin in univariate analysis (-0.21 pg/mL per 50% higher FGF-23, 95% CI: -0.29 to -0.14). Leptin was correlated with all measures of adiposity, as expected ($P < .001$ for all). Addition of leptin to the body composition models attenuated the association of FGF-23 with BMI and waist circumference, and those associations were no longer statistically significant. Addition of leptin also attenuated the association between FGF-23 and percent body fat, but there was still a statistically significant negative correlation (-0.17% body fat per 50% higher FGF-23, 95% CI: -0.32 to 0.02; Table 2). The mediation by leptin accounted for 52% of the association between FGF-23 and percent body fat.[12]

Discussion

In this prevalent cohort of adult men and women with ESRD receiving hemodialysis, we found that serum FGF-23 was inversely associated with adiposity as measured by BMI, waist circumference, and percent body fat after adjusting for age, race, dialysis vintage, serum phosphorus, and IL-6 concentrations. This association between FGF-23 and adiposity was partially mediated by leptin. Associations between FGF-23 and adiposity have been previously demonstrated.[4,5,8,13,14] Interestingly, FGF-23 is directly correlated with measures of adiposity in individuals with normal renal function. Although it may seem unexpected that the opposite (inverse) association was observed in our prevalent dialysis cohort, our results are in agreement with those of Montford *et al*.[8], who also observed an inverse relationship between FGF-23 and adiposity in ESRD. There are several mechanistic pathways that may explain

Table 1. Participant Characteristics

Characteristics	Study Participants (N = 611)*	Not Included (N = 160)†	*P*-Value
Age, years	56 ± 14	61 ± 14	.002
Sex, % female	39.8	45.0	.23
Race, %			.35
Black	62.5	56.9	
White	22.8	28.1	
Other	14.7	15.0	
Dialysis vintage, years	2.8 (1.3-5.4)	3.1 (1.5-5.7)	.49
BMI, kg/m^2	28.8 ± 7.0	29.6 ± 7.3	.86
Calcium, mg/dL	8.8 ± 0.9	8.7 ± 1.0	.20
Albumin, g/dL	4.0 ± 0.3	3.9 ± 0.4	<.001
Phosphorus, mg/dL	5.5 ± 1.7	5.4 ± 1.9	.19
FGF-23, pg/mL	807 (209-3,654)	531 (214-1,899)	.07
Leptin, pg/mL	17,509 (3,597-60,222)	17,131 (4,581-67,509)	.38

BMI, body mass index; FGF-23, fibroblast growth factor 23; BIS, bioelectrical impedance spectroscopy; SD, standard deviation.
Missing values: 12 missing BMI, 22 missing laboratory values, 83 missing waist circumference, and 111 missing BIS data.
*Numbers in mean ± SD or median (25th-75th).
†Cohort with any missing data for FGF-23, leptin, BIS data, BMI, or waist circumference.

Table 2. Association Between FGF-23 and BMI, Waist Circumference, and Percent Body Fat

Predictor: ln-FGF-23	Coefficient (95% CI)	*P*-Value
Univariate model*		
BMI, kg/m^2	−0.17 (−0.28 to −0.05)	.005
Waist circumference, cm	−0.49 (−0.78 to −0.19)	.001
Percent body fat, %	−0.64 (−0.82 to −0.47)	<.001
Multivariate model*,†		
BMI, kg/m^2	−0.24 (−0.38 to −0.10)	.001
Waist circumference, cm	−0.44 (−0.79 to −0.08)	.017
Percent body fat, %	−0.58 (−0.79 to −0.37)	<.001
Multivariate model with leptin*,‡		
BMI, kg/m^2	−0.02 (−0.13 to 0.09)	.74
Waist circumference, cm	0.05 (−0.23 to 0.33)	.72
Percent body fat, %	−0.17 (−0.32 to −0.02)	.02

CI, confidence interval; FGF-23, fibroblast growth factor 23; BMI, body mass index; IL-6, interleukin-6.

*Per 50% higher FGF-23 (pg/mL).

†Adjusting for age, phosphorus, race, dialysis vintage, and IL-6.

‡Adjusting for leptin, age, phosphorus, race, dialysis vintage, and IL-6.

the seemingly contradictory results in dialysis patients compared with those in individuals with preserved renal function.

Some authors have postulated that FGF-23 and adiposity could be related through leptin. Tsuji *et al.*[3] showed that injecting *ob/ob* mice with leptin led to an increase in FGF-23 transcription and higher serum levels. Thus, one would expect, and indeed studies in individuals without CKD have shown, that FGF-23 would be positively correlated with leptin, as well as with BMI and adiposity. However, we found a negative correlation between FGF-23 and leptin. One potential explanation for this finding is that high FGF-23 acts through an inhibitory feedback mechanism on leptin. Although the levels of hormones are commonly regulated through similar feedback pathways, a direct feedback signaling by FGF-23 on leptin have not yet been characterized. However, in our mediation analyses, adjusting for leptin did not completely attenuate the association between FGF-23 and percent body fat, suggesting that there may be leptin-independent as well as leptin-dependent pathways linking FGF-23 and adiposity.

It is also possible that extremely high FGF-23 levels have "off-target" effects through other pathways not yet identified. FGF-23 is part of the phylogenic FGF-19 subfamily, also comprised of FGF-21 and FGF-19. This unique subfamily of FGFs is hormone-like, and its members are important for maintaining energy, glucose, lipid, and mineral homeostasis.[1,2,15,16] FGF-21 stimulates lipolysis in white adipose tissue,[15-18] whereas FGF-19 is involved in the inhibition of bile acid synthesis[19] as well as in energy homeostasis by increasing metabolic rate and decreasing adiposity.[18,20] In the kidney, FGF-23 requires α-Klotho to bind and signal through FGF receptor 1c (FGFR1c). However, there is evidence that FGF-23 may not require α-Klotho to bind avidly to FGFR4, and non-α-Klotho–related direct binding to FGFR4 has been implicated in left ventricular hypertrophy.[21-23] Therefore, we speculate that in the setting of normal renal function and normal FGF-23 levels (40-60 pg/mL[24]), FGF-23 may signal through a leptin-mediated pathway in adipose tissues. However, in dialysis patients, FGF-23 levels rise to 100-fold higher, and we speculate that at those levels, it may be plausible for FGF-23 to signal through other FGF receptors such as through the FGF-21 or FGF-19 pathways in an α-Klotho–independent manner, leading to adipose tissue lipolysis.

Emerging data show that there are multiple endocrine factors communicating between bone, kidney, and adipose tissue to balance mineral and energy homeostasis.[25] These factors include FGF-23 and leptin, and recently, it has been recognized that adiponectin may also act on FGF-23 and Klotho to affect mineral metabolism.[26] The disturbance in balance between systemic levels of calcium, phosphate, and FGF-23 in ESRD may also lead to a disturbance in energy storage in fat. In dialysis patients, it has been shown repeatedly that obesity is associated with lower mortality in the ESRD population, in contrast to patients not on dialysis, a phenomenon known as the "obesity paradox".[23] One theory is that adipose tissue may act as a "protective" depot of energy and may be beneficial in the setting of inflammation or acute illness.[27,28] If high FGF-23 were to cause loss of protective adipose tissue, it might be detrimental in this vulnerable population and might provide a partial explanation for the association between high FGF-23 and higher mortality.

The limitations of this study include its observational and cross-sectional nature, which does not allow us to discern a causal relationship between FGF-23 and adiposity. Although we have proposed plausible mechanisms linking FGF-23 to adiposity, our study does not provide the *in vitro* or *in vivo* evidence that will be needed to confirm these mechanisms. Also, the proportion of black participants in our cohort was higher than that of the dialysis population in the United States. However, Jovanovich *et al.*[29] conducted a secondary analysis studying racial differences in markers of mineral metabolism and found no difference in FGF-23 level between whites and blacks with ESRD. In our analysis, we also did not find any statistically significant interactions between FGF-23 and race. Therefore, we also do not expect the association between plasma FGF-23 and adiposity to differ according to race. Residual renal function may be a possible confounder in this study. We were not able to directly adjust for this variable, but we adjusted for dialysis vintage as a surrogate, and our reported associations remained statistically significant.

In conclusion, we found that there is an inverse relationship between FGF-23 and adiposity that is different from what is seen in individuals with normal renal function. This paradoxical association could be due to off-target signaling of FGF-23 in the adipose tissue leading to

increased lipolysis of fat. This observation could add to our understanding of factors that lead to the obesity paradox in ESRD.

Practical Application

Multiple endocrine factors, including FGF-23 and leptin, communicate between bone, kidney, and adipose tissue to balance mineral and energy homeostasis. We show in this study that high levels of FGF-23 in dialysis patients may have off-target effects in adipose tissue, which could be a possible contributor to the obesity paradox seen in dialysis patients.

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