ORIGINAL RESEARCH

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

Janet M. Chiang, MD, George A. Kaysen, MD, PhD,† Anne L. Schafer, MD,* Cynthia Delgado, MD,‡ and Kirsten L. Johansen, MD‡*

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

*Division of Endocrinology, Department of Medicine, San Francisco VA Medical Center and University of California, San Francisco, California.

†Division of Nephrology, Department of Biochemistry and Molecular Medicine, University of California, Davis, California.

‡Division of Nephrology, Department of Medicine, San Francisco VA Medical Center and University of California, San Francisco, California.

Financial Disclosure: The authors declare that they have no relevant financial interests.

Support: See Acknowledgments on page XXX.

Address correspondence to Janet M. Chiang, MD, University of California, San Francisco, 400 Parnassus Ave, Ste 550, San Francisco, CA 94143. E-mail: Janet.chiang@ucsf.edu

1051-2276/$36.00

https://doi.org/10.1053/j.jrn.2017.12.010

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