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Brief Report

# Plasma FGF-21 and Sclerostin Levels, Glycemia, Adiposity, and Insulin Sensitivity in Normoglycemic Black and White Adults

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**Abbreviations:** 2hPG, 2-hour postload glucose; BMI, body mass index; ELISA, enzyme-linked immunosorbent assay; FGF, fibroblast growth factor; FPG, fasting plasma glucose; HOMA-B, homeostasis model assessment index of b-cell function; POP-ABC, Pathobiology of Prediabetes in A Biracial Cohort; T2D, type 2 diabetes.

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## Abstract

Increased circulating fibroblast growth factor (FGF)-21 and sclerostin levels have been reported in patients with type 2 diabetes (T2D). We assessed the association of FGF-21 and sclerostin with adiposity, glycemia, and glucoregulatory measures in healthy subjects. We studied 20 normoglycemic Black and White offspring of parents with T2D. Assessments included oral glucose tolerance test, insulin sensitivity (Si-clamp), insulin secretion (homeostasis model assessment index of b-cell function [HOMA-B]), and body fat (dual-energy X-ray absorptiometry). Fasting plasma FGF-21 and sclerostin levels were measured with enzyme-linked immunosorbent assays. The participants' mean ( $\pm$ SD) age was  $50.4 \pm 5.97$  years; body mass index (BMI)  $32.5 \pm 5.86$  kg/m<sup>2</sup>; fasting plasma glucose (FPG)  $96.1 \pm 5.21$  mg/dL, and 2-hour postload glucose  $116 \pm 5.45$  mg/dL. FGF-21 levels were similar in Black people vs White people ( $0.36 \pm 0.15$  ng/mL vs  $0.39 \pm 0.25$  ng/mL), men vs women ( $0.45 \pm 0.14$  vs  $0.44 \pm 0.07$  ng/mL), correlated positively with BMI ( $r = 0.23$ ,  $P = .05$ ) and waist circumference ( $r = 0.27$ ,  $P = .04$ ), and inversely with FPG ( $r = -0.26$ ,  $P = .05$ ). Sclerostin levels also were similar in Black people ( $33.5 \pm 17.1$  pmol/L) vs White people ( $34.2 \pm 6.41$  pmol/L), men vs women ( $35.3 \pm 9.01$  pmol/L vs  $32.3 \pm 15.8$  pmol/L), and correlated inversely with FPG ( $r = -0.11$  to  $-0.44$ ) but not adiposity measures. The correlation coefficient between Si-clamp values and FGF-21 levels was  $-0.31$  ( $P = .09$ ) compared with  $0.04$  ( $P = .89$ ) for sclerostin levels. FGF-21 and sclerostin levels were not correlated with each other or HOMA-B. Among healthy Black and White subjects, plasma FGF-21 and sclerostin showed differential associations with adiposity but concordant association with FPG levels.

**Key Words:** FGF-21, sclerostin, insulin action, beta-cell function, glucoregulation, race/ethnicity

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Fibroblast growth factors (FGFs) are ubiquitous polypeptides with protean biological actions [1]. FGF-21 is expressed widely in tissues (including liver, skeletal muscle, adipose, intestine) and has been shown to exert important metabolic effects, such as weight reduction and improvements in lipid profile and insulin sensitivity, in experimental models [1-3]. Limited human data indicate that FGF-21 levels are elevated in individuals with obesity, metabolic syndrome, or type 2 diabetes (T2D) [4, 5].

Circulating sclerostin levels increase with age, and higher levels have been reported in people with T2D than in control subjects [6, 7]. Sclerostin, an osteocyte-derived inhibitor of the wnt pathway, is an important regulator of bone turnover [8]. The TCF7L2 gene encodes a nuclear receptor for beta-catenin (a downstream mediator of the wnt signaling pathway), and variants at TCF7L2 are the most frequent T2D risk alleles in human populations [9, 10]. As impaired wnt signaling has been associated with increased fat accumulation and obesity, it is conceivable that circulating sclerostin levels (via wnt inhibition) might convey metabolic information regarding glucose regulation, adiposity, and bone turnover [6-12].

Like sclerostin, FGF-21 is a regulator of bone turnover [13-15]. Higher FGF-21 levels in older adults are associated with lower bone mineral density [13], and administration of FGF-21 induces aberrant bone microstructure in rats [14] and alters the expression of markers of bone turnover in humans [15]. However, reports of simultaneous measurement of FGF-21 and sclerostin are lacking, and it is unknown whether their circulating levels are correlated. Furthermore, the human data on insulin sensitivity in relation to FGF-21 and sclerostin levels have been based mostly on surrogate estimates of insulin action using the ratio of fasting plasma glucose (FPG) and insulin levels. In this pilot study, we used the more robust hyperinsulinemic euglycemic clamp method to measure whole-body insulin sensitivity and assessed ethnic patterns in the expression of FGF-21 and sclerostin and their relationships with metabolic function. We analyzed plasma FGF-21 and sclerostin levels simultaneously in plasma specimens from healthy African American (Black) and European American (White) adults with parental history of T2D.

## Materials and Methods

### Study Subjects

We analyzed plasma levels of FGF-21 and sclerostin in healthy offspring of parents with T2D (N = 20; 10 African Americans, 10 European Americans; 10 men, 10 women) with mean ( $\pm$ SD) age of  $50.4 \pm 6.0$  years. Data collected at baseline were analyzed for the present report. The study subjects were a subsample from participants

in the Pathobiology of Prediabetes in A Biracial Cohort (POP-ABC) study [16-18]. Eligibility criteria for the POP-ABC study included individuals in good overall health, aged 18-65 years, of self-reported non-Hispanic White (European American) or non-Hispanic Black (African American) race/ethnicity ancestry who had 1 or both biological parents with T2D. Participants were required to undergo a screening 75-g oral glucose tolerance test to document absence of diabetes and to confirm normal FPG ( $<100$  mg/dL [5.6 mmol/L]) and normal glucose tolerance (2 hour plasma glucose [2hPG]  $<140$  mg/dL [7.8 mmol/L]) status [16-18]. Excluded from participation were persons with a history of diabetes and those taking medications known to alter blood glucose or body weight [16-18].

The POP-ABC study protocol was approved by the University of Tennessee Institutional Review Board, and all participants gave written informed consent before initiation of the study.

### Assessments

Enrolled participants arrived at the University of Tennessee General Clinical Research Center after an overnight fast for baseline assessments, which included a structured medical interview and a general physical examination; and measurement of weight, height, waist circumference, and blood pressure [13-15]. The body mass index (BMI) was calculated as the weight in kilograms divided by the height in meters squared. Total fat mass and trunk fat mass were measured using dual-energy X-ray absorptiometry (Hologic, Bedford, MA).

Fasting plasma specimens were obtained for measurement of glucose (FPG), insulin, FGF-21, and sclerostin levels, and stored at  $-80^{\circ}\text{C}$  until assay.

### Insulin Sensitivity and Beta-cell Function

We measured insulin sensitivity with the hyperinsulinemic euglycemic clamp procedure, as previously described [19, 20]. In brief, participants who had fasted overnight received a primed, continuous intravenous infusion of regular insulin (2 mU/kg/min; 14.4 pmol/kg/min) for 180 minutes while blood glucose concentration was maintained at approximately 100 mg/dL (5.6 mmol/L) with a variable-rate dextrose (20%) infusion. Arterialized blood specimens for measurement of glucose and insulin levels were obtained every 10 minutes. The rate of total insulin-stimulated glucose disposal (M) was calculated for the past 60 minutes of insulin infusion, and corrected for steady-state plasma insulin levels, to derive the insulin sensitivity index (Si-clamp) [19, 20]. The homeostasis model assessment index of b-cell

function (HOMA-B) was derived from fasting glucose and insulin concentrations [21].

### Biochemical Measurements

Plasma human FGF-21 concentration was measured by enzyme-linked immunosorbent assay (ELISA), using a commercial kit (Millipore, Billerica, MA). The human FGF-21 ELISA is RRID:AB\_2783729. The sensitivity of the FGF-21 assay was 15.6 pg/mL and the intra-assay coefficient of variation was 3.6%. Plasma sclerostin concentration was measured by ELISA using a commercial kit (ALPCO Immunoassays, Salem, NH). The human sclerostin ELISA is RRID:AB\_2801530. The sensitivity of the sclerostin assay was 2.6 pg/mL and the intra-assay coefficient of variation was 5%. Both ELISA kits employed goat antihuman antibodies for the respective immunoassays. All specimens were assayed in duplicate in a single batch.

### Statistical Analysis

Data are reported as mean  $\pm$  SD. Continuous variables were analyzed using unpaired t tests and the chi-squared test was used for categorical variables. Linear regression models and Pearson correlation coefficients were used to analyze the associations between FGF-21 and sclerostin levels and measures of glycemia, adiposity, insulin sensitivity, and insulin secretion. Statistical significance was set at  $P < .05$ . All statistical analyses were performed using Statview (SAS Institute Inc., Cary, NC).

## Results

### Baseline Characteristics of the Study Population

The demographic and baseline characteristics of study participants are summarized in Table 1. The mean

age was  $51.3 \pm 4.92$  years in African Americans and  $49.5 \pm 7.03$  years in European Americans. The mean BMI and lean body mass did not differ significantly by race/ethnicity but African American participants had lower mean values for waist circumference and trunk fat mass, and a trend toward lower total fat mass than European Americans. Both groups did not differ significantly in other baseline characteristics, including FPG, 2hPG, and blood pressure (Table 1).

### Ethnicity and Sex

Table 2 summarizes values for plasma FGF-21 and sclerostin by ethnicity and sex. The mean plasma FGF-21 level was  $0.36 \pm 0.15$  ng/mL in African Americans vs  $0.39 \pm 0.25$  ng/mL in European Americans ( $P = .72$ ). The mean plasma sclerostin level was  $33.5 \pm 17.1$  pmol/L in African Americans vs  $34.2 \pm 6.41$  pmol/L in European Americans ( $P = .91$ ). There were no significant differences in plasma FGF-21 and sclerostin levels between men and women in the entire study population or within each ethnic group (Table 2).

### Body Composition Measures

Plasma FGF-21 levels correlated positively with BMI ( $r = 0.23, P = .05$ ) and waist circumference ( $r = 0.27, P = .04$ ), and showed similar trends for total fat mass ( $r = 0.17, P = .49$ ) and trunk fat mass ( $r = 0.20, P = .43$ ) that did not reach statistical significance. Sclerostin levels showed nominally inverse correlations with BMI ( $r = -0.21$ ), waist circumference ( $r = -0.11$ ), total fat mass ( $r = -0.21$ ), and trunk fat mass ( $r = -0.15$ ) that did not reach statistical significance. Neither FGF-21 ( $r = 0.05, P = .83$ ) nor sclerostin ( $r = 0.026, P = .91$ ) levels showed any correlation with lean body mass.

**Table 1.** Baseline characteristics of study participants

Characteristic	African American	European American	P
Number (M/F)	10 (5/5)	10 (5/5)	
Age (years)	$51.3 \pm 4.92$	$49.5 \pm 7.03$	.52
Waist circum. (cm)	$96.3 \pm 6.60$	$106.3 \pm 9.51$	.013
BMI (kg/m <sup>2</sup> )	$30.3 \pm 5.25$	$34.7 \pm 5.80$	.091
SBP (mmHg)	$131 \pm 20.0$	$129 \pm 14.3$	.78
DBP (mmHg)	$76.2 \pm 7.90$	$76.6 \pm 6.60$	.86
Total fat mass (kg)	$26.7 \pm 11.5$	$37.6 \pm 12.7$	.057
Trunk fat mass (kg)	$13.6 \pm 6.06$	$20.4 \pm 6.29$	.024
Lean body mass (kg)	$58.6 \pm 10.5$	$56.4 \pm 13.1$	.68
FPG (mg/dL)	$96.4 \pm 5.74$	$95.7 \pm 4.90$	.77
2hPG (mg/dL)	$112 \pm 22.9$	$111 \pm 14.3$	.46

To convert plasma glucose from mg/dL to mmol/L, divide by 18.

2hPG, 2-hour post-load plasma glucose; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose.

## Glycemic and Glucoregulatory Measures

FGF-21 levels correlated inversely with FPG ( $r = -0.26$ ,  $P = .05$ ) and 2hPG ( $r = -0.36$ ,  $P = .04$ ) and showed a trend toward inverse correlation with whole-body insulin sensitivity (Si-clamp,  $r = -0.31$ ,  $P = .09$ ), but there was no association with HOMA-B, a measure of insulin secretion ( $r = -0.04$ ,  $P = .88$ ). Sclerostin levels also showed inverse correlation with FPG ( $r = -0.44$ ,  $P = .03$ ) and a trend toward inverse correlation with 2hPG ( $r = -0.34$ ,  $P = .15$ ) values (Fig. 1). However, sclerostin levels showed no discernible association with Si-clamp ( $r = 0.04$ ,  $P = .89$ ) or HOMA-B ( $r = 0.06$ ,  $P = .81$ ) values.

Figure 1 shows the associations of FGF-21 and sclerostin with FPG, waist circumference, and insulin sensitivity. Notably, plasma levels of FGF-21 and sclerostin were not correlated in our study population ( $r = 0.05$ ,  $P = .83$ ).

## Discussion

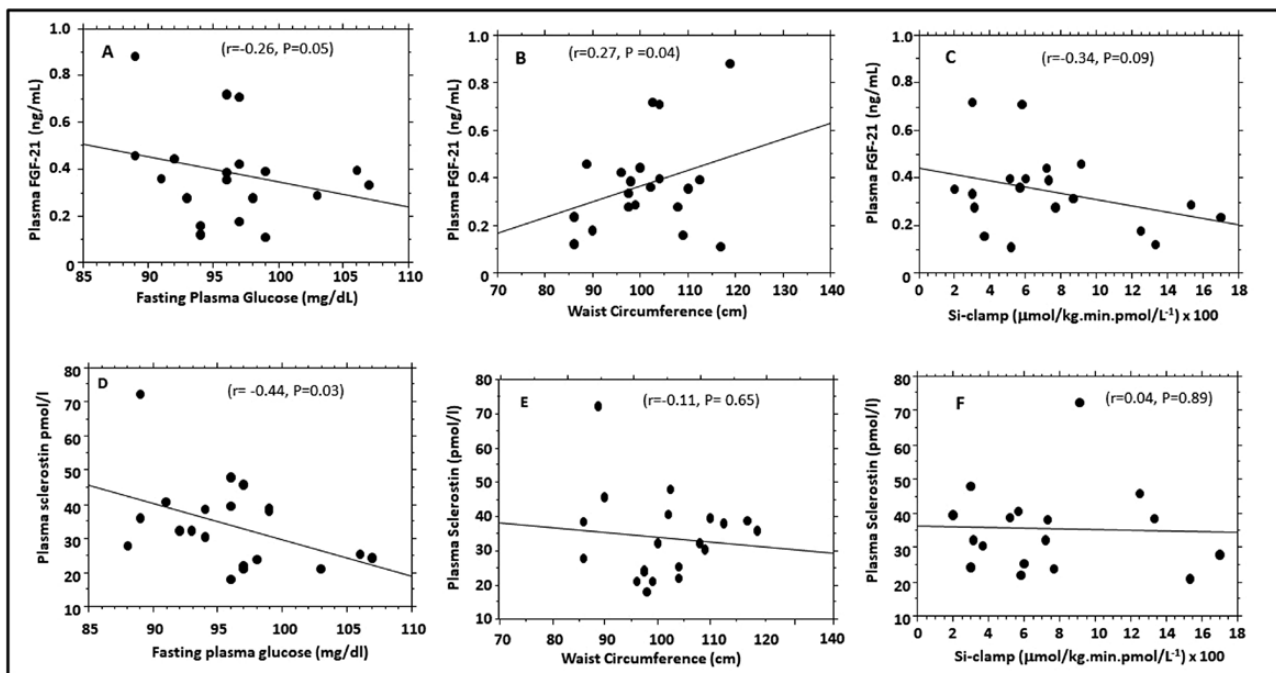
In the present report, we found no ethnic or sex disparities in the circulating levels of FGF-21 and sclerostin among

healthy African Americans and European Americans with parental history of T2D. We observed that plasma FGF-21 levels were positively correlated with BMI and waist circumference, whereas the levels of sclerostin showed no statistically significant correlations with adiposity measures. Interestingly, both FGF-21 and sclerostin levels showed inverse correlations with FPG. Additionally, FGF-21 levels showed an insignificant trend toward inverse correlation with insulin sensitivity, but we observed no discernible association between sclerostin levels and insulin sensitivity. Plasma levels of FGF-21 and sclerostin did not show any association with insulin secretion (HOMA-B). Because we found no correlation between plasma levels of FGF-21 and sclerostin in our study population, we infer that each analyte may be an independent predictor of ambient glycemia, presumably acting via different mechanisms.

Our findings are in accord with previous reports of elevated FGF-21 levels in people with obesity [4, 5]. Based on its reported metabolic actions, our finding that higher FGF-21 levels predicted lower plasma glucose levels is physiologically congruent. The related finding that participants with

**Table 2.** Mean plasma FGF-21 and sclerostin levels by ethnicity and sex

	African American	European American	P value
FGF-21 (ng/mL)	0.36 ± 0.15	0.39 ± 0.25	.72
Sclerostin (pmol/L)	33.5 ± 17.1	34.2 ± 6.41	.9
	Women	Men	
FGF-21 (ng/mL)	0.44 ± 0.07	0.45 ± 0.14	.17
Sclerostin (pmol/L)	32.3 ± 15.8	35.3 ± 9.01	.60



**Figure 1.** Association of plasma fibroblast growth factor-21 (A,B,C) and sclerostin (D,E,F) levels with fasting glucose, waist circumference, and insulin sensitivity (Si-clamp) in healthy offspring of parents with type 2 diabetes.

low insulin sensitivity tended to have higher FGF-21 levels compared with those who had greater insulin sensitivity suggests that elevated FGF-21 levels might be a counter-regulatory response to the ambient insulin-resistant state. Indeed, the finding of elevated FGF-21 levels in obese, insulin-resistant subjects has led to the notion of FGF-21 resistance [22]. The latter notion is analogous to compensatory hyperleptinemia in obesity [23]. Thus, the association between FGF-21 levels and plasma glucose observed in our study participants is likely related to ambient insulin sensitivity.

Circulating levels of the osteoclast-derived sclerostin, an endogenous inhibitor of the wnt signaling pathway, have been reported to be elevated in people with T2D [6, 7]. However, data on the pattern of sclerostin expression in healthy persons in relation to ethnicity and metabolic function are scant. Thus, our finding of similar plasma sclerostin levels in African American and European American men and women extends previous reports. The lack of sex-specific differences in circulating sclerostin levels in our study is in discord with previous reports showing higher levels in men than in women [6] or vice versa [24]. These conflicting findings might be related to uncontrolled factors that alter the expression of sclerostin. In 1 study, after adjusting for age, bone mineral content, physical activity, BMI, and renal function, sclerostin levels did not differ significantly by sex [25].

Although the mechanism(s) and significance of the observed associations between sclerostin and glycemia are unclear, it is plausible that sclerostin might be a peripheral marker or mediator of the complex interactions among TCF7L2 gene expression, wnt signaling, adipogenesis, and bone and glucose metabolism [6-12]. The lack of association between sclerostin levels and whole-body insulin sensitivity or HOMA-B suggests that the relationship between sclerostin and blood glucose observed in the present study is likely not mediated by classical glucoregulatory mechanisms involving insulin action and secretion. In a recent report, pre- and postoperative serum levels of sclerostin showed associations with changes in glycemic profile and body composition after sleeve gastrectomy [26]. Interestingly, postsurgery increase in serum sclerostin was associated with a reduction in lean mass (likely due to increased bone turnover), without any association with measures of insulin sensitivity [26]. Sclerostin inhibition with monoclonal antibodies is an emerging strategy for the treatment of osteoporosis [27]. So far, clinical trials have not reported blood glucose abnormalities during chronic inhibition of endogenous sclerostin with monoclonal antibodies [27].

The strengths of the present study include the well-matched cohort of African American and European American participants, simultaneous measurement of FGF-21 and sclerostin, and the direct measurement of

whole-body insulin sensitivity with the hyperinsulinemic euglycemic clamp. Previous reports in humans had utilized surrogate measures to estimate insulin sensitivity [4, 5, 26]. The major limitation is the small sample size, which affected statistical power in achieving significance in some of the correlations that were observed. Further, the use of HOMA-B provided information on basal but not dynamic (glucose-stimulated) insulin secretion. Despite the small sample size, it is reassuring that the circulating levels of FGF-21 and sclerostin recorded in our study were in the range reported in larger studies. The mean plasma FGF-21 level observed in our cohort,  $0.36 \pm 0.15$  ng/mL in African Americans (BMI  $30.3 \pm 5.25$ ) and  $0.39 \pm 0.25$  ng/mL in European Americans (BMI  $34.7 \pm 5.80$ ), were in agreement with the report by Zhang et al. that showed a mean serum FGF-21 level of  $0.336$  ng/mL in 97 overweight Chinese adults (BMI  $29.2 \pm 6$ ) [4]. Similarly, the mean plasma sclerostin levels observed in the present study ( $33.5 \pm 17.1$  pmol/L in African Americans and  $34.2 \pm 6.41$  pmol/L in European Americans) are comparable with the mean value of  $42.8 + 16.5$  pmol/L reported by García-Martín et al. in a group of 50 healthy Caucasian men and women [6]. Of note, participants in the latter report [6] were slightly older (mean age 56.4 years) than our study population (mean age ~50 years).

In summary, circulating levels of FGF-21 and sclerostin showed directionally concordant associations with plasma glucose but discordant associations with adiposity measures among healthy offspring of parents with T2D, without evidence of ethnic or sex disparities.

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## Additional Information

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**Data Availability:** All data generated or analyzed during this study are included in this published article.

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