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Insulin resistance is associated with Fibroblast Growth Factor-23 in stage 3–5 chronic kidney disease patients☆,☆☆

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ABSTRACT

Aim: To determine the associations between insulin resistance, fibroblast growth factor 23 (FGF-23), and coronary artery calcification (CAC) in chronic kidney disease (CKD) patients.
Introduction: FGF-23 is associated with atherosclerosis and cardiovascular disease, but its association with insulin resistance in CKD has not been explored.
Subjects: Cross sectional study of 72 stage 3–5 CKD patients receiving care in Ontario, Canada.
Materials and Methods: Insulin resistance was measured by the homeostasis model assessment of insulin resistance (HOMA-IR), FGF-23 was measured by carboxyl terminal enzyme linked immunoassay (ctFGF-23) and CAC was measured by multi-slice computed tomography.
Results: Median HOMA-IR was 2.19 μU/ml (interquartile range 1.19 to 3.94). Patients with HOMA-IR > 2.2 had greater ctFGF-23 (179.7 vs 109.6; $P = 0.03$), and 40% higher log CAC scores (2.09 ± 0.87 vs 1.58 ± 1.26; $P = 0.049$). Multivariable linear regression adjusted for 1,25 dihydroxyvitamin D, kidney function, and parathyroid hormone revealed insulin resistance was a risk factor for greater log ctFGF-23 levels (log HOMA IR $\beta = 0.37$; 95% confidence interval 0.14 to 0.59; $P = 0.002$).
Conclusions: Insulin resistant CKD patients demonstrated higher FGF-23 levels, and increased CAC, while PO_4 levels remained normal, suggesting a potential link between insulin resistance and PO_4 homeostasis in CKD.

1. Introduction

Micro-puncture studies have identified the transporter for renal proximal tubular phosphorus re-absorption, which is coupled with sodium (Greger, Lang, Marchand, & Knox, 1997): the apical type 2 sodium-dependent phosphorus co-transporter (NaPi-II). The NaPi-II co-transporter has various subtypes, but in humans, the NaPi-IIa is mainly responsible for phosphorus re-absorption (Prié & Friedlander, 2010). Maintenance of phosphorus homeostasis is mediated, in part, by the action of counter-regulatory hormones which act to influence renal phosphorus re-absorption. Parathyroid hormone (PTH) decreases the abundance of NaPi-II co-transporters, decreasing phosphorus re-absorption (Zhao & Tenenhouse, 2000). In contrast 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) increases NaPi-II co-transporter abundance (Katai et al., 1999), increasing renal phosphorus re-absorption. Fibroblast growth factor 23 (FGF-23) is a hormone secreted by osteoctyes and is one of the most important regulators of phosphorus homeostasis (Jüppner, Wolf, & Salusky, 2010). When secreted, FGF-23 acts to reduce renal phosphorus re-absorption, (thereby increasing renal phosphorus excretion), by reducing the expression of the kidney proximal tubule NaPi-II co-transporters (Shimada et al., 2004). In CKD patients, as nephron mass decreases, renal phosphorus elimination becomes impaired, and thus FGF-23 increases in an effort to maintain normo-phosphatemia (Gutierrez et al., 2005; Gutierrez et al., 2009). Consequently, it has been suggested

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that increased FGF-23, in CKD, is an early biomarker indicating renal phosphorus homeostasis is disrupted, even in the absence of hyperphosphatemia (Gutierrez et al., 2005; Gutierrez et al., 2009; Jüppner et al., 2010).

An action of insulin that has not been widely studied is its direct involvement in renal phosphorus handling. Insulin also directly induces the NaPi-II, and is anti-phosphaturic, promoting increased renal phosphorus re-absorption (Murer, Hernando, Forster, & Biber, 2000). Insulin resistance is a condition characterized by an impaired physiological response of peripheral tissues to the metabolic effects of insulin action (Reaven, 2004), which occurs, in part, because of decreased insulin receptor expression in tissues that are involved in energy homeostasis (eg. liver and skeletal muscle)(Catena et al., 2003). The insulin receptor is expressed in the kidney, and ^{125}I-labeled insulin has the greatest binding (per length renal tubule) in the kidney proximal convoluted tubule (Hammerman, Rogers, Hansen, & Gavin, 1984). In the kidney, unlike skeletal muscle or hepatic tissue, the state of insulin resistance does not appear to involve down-regulation of insulin receptors. On the contrary, an important observation was made by Sechi et al. when they demonstrated that, despite insulin resistance, insulin receptor number remains preserved in the kidney (Sechi et al., 1996).

The relationship between insulin resistance and FGF-23 has not been investigated previously; however, Wahl et al. have observed that FGF-23 levels are greater in CKD patients who have diabetes (Wahl et al., 2012). Since insulin directly induces the NaPi-II, and is anti-phosphaturic, we sought to evaluate the impact of insulin resistance on FGF-23 levels in 72 pre-dialysis stage 3–5 CKD patients, while accounting for other hormones known to impact on renal NaPi-II expression and FGF-23: parathyroid hormone (PTH), and 1,25-dihydroxyvitamin D ($1,25(OH)_2D$). Our primary objective was to determine the association between insulin resistance and FGF-23 in stage 3–5 pre-dialysis CKD patients (not receiving insulin therapy). Our secondary objective was to explore the relationship between insulin resistance and coronary artery calcification in Stage 3–5 pre-dialysis CKD patients.

2. Materials and methods

In 2005, 174 pre-dialysis CKD patients were enrolled in a study of coronary artery calcification (CAC) in CKD (Holden et al., 2010). The full methods are described elsewhere (Holden et al., 2010), but patients were eligible to participate if they were greater than 18 years of age and had stage 3–5 CKD (not requiring dialysis and excluding acute kidney injury and insulin treated diabetes mellitus). All patients who had CAC scores measured in 2005 were invited to undergo repeat multi-slice CT (MSCT) scan for quantification of CAC in 2009, and had repeat clinical and biochemical assessments performed. Of the original 174 patients, 17 patients died, 31 patients progressed to dialysis, 5 were transplanted, 7 were discharged to the care of their family physician, 2 had moved, and 5 were lost to follow-up. This left 107 patients, and 95 agreed to participate. Of these, one CAC score was not interpretable due to motion artefact, and 22 patients were receiving insulin therapy and were excluded (as plasma insulin levels were being measured to determine HOMA-IR), leaving 72 patients who had data for CAC, insulin resistance, and FGF-23. All patients gave informed consent, and the study protocol was approved by the Queen's University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board.

National Kidney Foundation criteria were applied to diagnose CKD (National Kidney Foundation, 2004). Diagnoses of hypertension were documented as per 2006 Canadian Hypertension Education Program Guidelines (Hemmelgarn et al., 2006), and diabetes mellitus as per the Canadian Diabetes Association criteria (Canadian Diabetes Association Clinical Practice Guidelines Expert Committee, 2003). Metabolic syndrome was defined as fulfilling at least 3 of 5 criteria from the National Cholesterol Education Program Adult Treatment Panel III 2005 criteria (Grundy et al., 2005).

2.1. Laboratory Measures

Fasting blood samples taken in 2009 were analyzed at Kingston General Hospital's Core Laboratory, including serum creatinine (Jaffe rate method, Beckman Coulter UniCel DxC 800 SYNCHRON Clinical System assay, traceable to isotope dilution mass spectroscopy), glucose, phosphorus, total calcium, intact parathyroid hormone (iPTH),(chemoluminescent immunoassay, Beckman Coulter UniCel DxI 800 Access Immunoassay System, Beckman Coulter Inc., Fullerton CA), albumin, high-sensitivity C-reactive protein (hsCRP),(Beckman Coulter UniCel DxC 600/800 SYNCHRON Clinical System, Beckman Coulter Inc., Fullerton CA), total cholesterol, low density lipoprotein cholesterol (LDL), high density lipoprotein cholesterol (HDL), and triglycerides.

Blood samples were stored at −80 °C, and after a single freeze–thaw cycle the following were measured from plasma in duplicate at the Ontario Cancer Biomarker Network, Toronto, ON, Canada: 1,25-dihydroxyvitamin D, enzyme immunoassay (Immunodiagnostic Systems Inc., Fountain Hills, Arizona), 25-hydroxyvitamin D, enzyme immunoassay (Immunodiagnostic Systems Inc., Fountain Hills, Arizona), insulin (single measure) Human Serum Adipokine (Panel B) Kit Protocol Immunoassay, (Milliplex Analytes, Millipore Corp, St. Charles, MI), and plasma carboxyl terminal FGF-23, (ctFGF-23) (measured in duplicate), enzyme-linked immunosorbent assay (ALPCO Diagnostics, Salem, NH).

The 4-variable MDRD Study equation (Levey et al., 1999), re-expressed for standardized creatinine (Levey et al., 2006), was used to estimate kidney function (estimated glomerular filtration rate (eGFR)). Albuminuria was detected by the urinary albumin-to-creatinine ratio (UACR). Weight and height data were collected on each individual to calculate body mass index (BMI) in kg/m^2. Abdominal obesity was defined as a waist circumference of >88 cm in women and >102 cm in men (Grundy et al., 2005). Insulin resistance was assessed using the following validated formula: homeostasis model assessment of insulin resistance (HOMA-IR) = (fasting glucose [mmol/l] × fasting insulin [μU/ml])/22.5 (Ascaso et al., 2003).

2.2. Coronary Artery Calcification Measurement:

CAC scores were evaluated using the General Electric (GE) VCT 64 slice helical CT scanner, (Waukesha, Wisconsin, USA) and data were processed by Smartscore software, version 3.5 from GE Medical Systems (Waukesha, Wisconsin, USA). The GE VCT 64 slice helical CT scanner scans and reconstructs 8 slices simultaneously, using a step and shoot technique. Each slice is 2.5 mm in thickness with no overlap. Images were acquired with prospective gating technique using a discrete algorithm (Wexler et al., 1996). The total CAC score was generated as per the Agatston method and reported in Agatston units (AU) (Agatston, Janowitz, & Hildner, 1990).

2.3. Statistical methods

Statistical differences between the levels of HOMA-IR were analyzed using the Student's t test, Chi square test or the Mann–Whitney test, as appropriate. Data are expressed as means and standard deviations, medians and inter-quartile ranges (IQR), or percentages, as appropriate. Statistical differences in FGF-23 among three groups were analyzed using the one-way ANOVA test. Bivariate analysis was performed to evaluate the associations between log FGF-23, insulin resistance (HOMA-IR) and other a priori chosen risk factors, including factors important in phosphorus homeostasis (iPTH, phosphorus, 25-hydroxyvitamin D, and 1,25-Dihydroxyvitamin D),

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CAC, BMI, abdominal obesity, age, kidney function, and albuminuria (UACR). FGF-23, CAC and HOMA-IR were logarithmically transformed to ensure normality for parametric testing. Multivariable linear regression was used to identify risk factors for disrupted renal phosphorus homeostasis (FGF-23), including iPTH, 1,25 Dihydroxyvitamin D, phosphorus, season blood work collected, eGFR, and HOMA-IR. All statistical analyses were performed using IBM SPSS Statistics 19.0.

3. Results

Table 1 describes baseline clinical characteristics of the 72 included study participants, compared based on severity of insulin resistance as per the median HOMA-IR for this CKD cohort (2.19 μU/mL (IQR 1.19 to 3.94)). Patients whose HOMA-IR was greater versus (vs) less than the median did not differ by age, sex, cardiovascular risk scores or kidney function (eGFR), However, patients with greater HOMA-IR had greater BMI, insulin levels, dyslipidemia, and glycosylated hemoglobin levels.

Considering bone and mineral metabolism parameters, phosphorus levels were not elevated and were similar between the higher and lower HOMA-IR groups, as were calcium levels, and iPTH. Levels of 25-hydroxyvitamin D and 1,25 dihydroxyvitamin D were reduced overall, but were not significantly different between the higher and lower HOMA-IR groups. Of the 72 patients, 34% were prescribed oral calcium-based phosphorus binders (N = 25), 16% (N = 12) oral calcitriol, 23% (N = 17) oral calcidiol, and 2% (N = 2) Sevelamer. Prescription of Vitamin D or phosphorus binder did not differ based on insulin resistance group (data not shown).

Table 1
Comparison Clinical Characteristics of Study Participants (N = 72) by degree of insulin resistance (HOMA-IR).

Variable	HOMA IR < 2.2 (N = 36)	HOMA IR > 2.2 (N = 36)	P
Age (years)	63 ± 13	65 ± 15	0.64
Male sex	50 %	61 %	0.47
Body mass index (kg/m^2)	25.3 ± 4.3	35.1 ± 7.5	<0.0001
Abdominal waist circumference (cm)	90.6 ± 18.5	112.7 ± 19.3	<0.0001
eGFR (ml/min/1.73 m^2)	24.9 ± 13.5	26.8 ± 12.1	0.5
UACR (mg/g) (N = 68)	7.4 (2.3 - 41)	30.0 (2.4 - 40)	0.02
Hypertension	89 %	97 %	0.36
Systolic Blood Pressure (mmHg)	129.4 ± 15.1	130.0 ± 17.0	0.50
Diastolic Blood Pressure (mmHg)	74.33 ± 10.3	75.2 ± 13.1	0.75
Non insulin dependent Diabetes Mellitus	11 %	31 %	.08
Glucose (mg/dl)	98.2 ± 12.5	110.7 ± 2.5	0.01
Hemoglobin A1C %	5.8 ± 0.76	6.2 ± 0.93	0.01
Calcium (mg/dl)	9.06 ± 0.8	9.42 ± 1.1	0.15
Phosphorus (mg/dl)	3.96 ± 0.84	3.90 ± 0.65	0.77
Albumin (g/dl)	3.8 ± 0.38	3.7 ± 0.36	0.41
Total cholesterol (mg/dl) (N = 71)	162.4 ± 53.8	167.8 ± 48.0	0.65
HDL cholesterol (mg/dl) (N = 71)	46.8 ± 15.9	36.5 ± 8.1	0.001
LDL cholesterol (mg/dl) (N = 70)	97.1 ± 42.5	94.7 ± 38.7	0.80
Triglycerides (mg/dl) (N = 71)	52.6 ± 31.7	82.0 ± 44.9	0.002
Log hsCRP (mg/dL) (N = 71)	3.5 ± 0.5	6.1 ± .5	.03
25-Hydroxy Vitamin D (ng/mL)	23.9 (17-28)	21.7 (18-28)	0.64
1,25-Dihydroxyvitamin D (pg/mL)	21.1 (15-21)	20.8 (14-29)	0.45
ct-FGF-23 (RU/ml)	109.6 (46–216.5)	179.7 (91–560)	0.03
Insulin (pg/ml)	215 ± 82	662 ± 296	<0.0001
Fetuin (g/L) (N = 71)	0.62 ± 0.12	0.63 ± 0.15	0.89
Osteoprotegerin (pg/mL)	4.2 ± 1.9	3.6 ± 1.6	0.18
log Coronary artery calcification score (AU)	1.58 ± 1.26	2.09 ± 0.87	0.049
Intact parathyroid hormone (pg/ml)	75.4 (53 – 174)	93.3 (55– 201)	0.81

HOMA-IR = homeostasis model assessment of insulin resistance; eGFR = estimated glomerular filtration rate; UACR = urinary albumin to creatinine ratio; HDL = high density lipoprotein; LDL = low density lipoprotein; hsCRP = high sensitivity C-reactive protein; FGF-23 = fibroblast growth factor-23; AU = Agatston units; ctFGF-23 = carboxyl terminal FGF-23

Patients whose HOMA-IR was greater than 2.2 demonstrated higher ctFGF-23 levels and greater coronary artery calcification, versus CKD patients whose HOMA-IR was less than 2.2 (Table 1). Patients were classified into three categories according to the number of components of the metabolic syndrome: possessing 0–1 component (n = 5), 2–3 components (n = 29) or 4–5 components (n = 37). Log ctFGF-23 levels were compared according to the number of metabolic syndrome components, and were significantly higher as the number of metabolic syndrome components increased (P = 0.03). Because few patients had 0–1 component, the analysis was repeated comparing patients who had 0–3 components versus 4–5 components of the metabolic syndrome, and results were consistent, with log ctFGF-23 levels being 30% higher in the group with 4–5 components of metabolic syndrome (log ctFGF-23 2.31 ± 0.54 vs 2.01 ± 0.45; P = 0.02). Bivariate analysis (Table 2) demonstrated ctFGF-23 was positively correlated with HOMA-IR (r = 0.25; P = 0.04) as well as other markers of insulin resistance: abdominal waist circumference (r = 0.29, P = 0.02), and BMI (r = 0.33; P = 0.004).

Linear regression analysis was performed to explore the impact of insulin resistance on log ctFGF-23 levels, adjusted for risk factors known to influence FGF-23, including 1,25 Dihydroxyvitamin D, kidney function (eGFR, albuminuria (UACR)) and iPTH. The final adjusted model (Table 3) revealed increasing level of HOMA-IR was a risk factor for rising ctFGF-23 levels (log HOMA IR β = 0.43; 95% confidence interval 0.18 to 0.68; P = 0.001).

4. Discussion

The primary objective of this study was to determine the association between insulin resistance and FGF-23 levels in CKD patients, while accounting for other factors known to influence FGF-23 levels. In this study of 72 pre-dialysis CKD patients, CKD patients with greater levels of insulin resistance did not differ based on level of kidney function, 1,25 dihydroxyvitamin D or iPTH compared to CKD patients with lower levels of insulin resistance. However, CKD patients with greater insulin resistance had significantly higher log ctFGF-23 levels. The finding of higher ctFGF-23 levels in the setting of insulin resistance remained consistent in comparing patients based on the number of metabolic syndrome components. Moreover, results remained robust in the multivariable linear regression model determining risk factors for increased log ctFGF-23. Increasing log HOMA-IR was a predictor of log ctFGF-23, adjusted for eGFR, 1,25 dihydroxyvitamin D, and iPTH. Fernandez-Real et al. have reported similar findings in 314 non-CKD patients, where ctFGF-23 correlated with HOMA-IR (r = 0.35; P = 0.006) (Fernández-Real et al., 2013). Moreover, in a small sample of 10 male subjects, they described a

Table 2
Bivariate Analysis: log FGF-23 Correlates (N = 72).

Variable	r	P
Intact Parathyroid Hormone	0.43	<0.0001
eGFR	−0.75	<0.0001
log UACR (N = 68)	0.53	<0.0001
Phosphorus	0.50	<0.0001
1,25 dihydroxyvitamin D[a]	−0.45	<0.0001
Body Mass Index	0.33	0.004
Waist Circumference	0.29	0.02
Log HOMA-IR	0.25	0.04
25-Hydroxyvitamin D[a]	−0.21	0.07
Calcium	−0.15	0.22
Age	−0.08	0.50
Coronary artery calcification	−0.03	0.82

FGF-23 = fibroblast growth factor-23; eGFR = estimated glomerular filtration rate; UACR = urinary albumin to creatinine ratio; HOMA-IR = homeostasis model assessment of insulin resistance; HDL = high density lipoprotein.
[a] Spearman's rho.

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Table 3
Multivariable Linear Regression Risk Factors for FGF-23 (N = 72) ($R^2 = 0.68$, $P < 0.0001$).

Factor	Beta co-efficient (95% Confidence Interval)	P
Log HOMA-IR	0.43 (0.18–0.68)	0.001
Each eGFR decline of 10 ml/min/1.73 m^2	−0.25 (−0.33–−0.17)	<0.0001
Log 1,25 dihydroxyvitamin D	−0.33 (−0.67–−0.009)	0.056
Log intact parathyroid hormone	0.07 (−0.14–0.28)	0.51
Age decade	−0.03 (−0.09–0.03)	0.30
Season blood work collected	0.10 (−0.07–0.28)	0.25
Phosphorus	0.15 (−0.28–0.59)	0.48
Urinary albumin to creatinine ratio	0.02 (−0.11–0.15)	0.75

HOMA-IR = homeostasis model assessment of insulin resistance; eGFR = estimated glomerular filtration rate

decrease in HOMA-IR and FGF-23 levels, pre- and post weight loss of approximately 20 kg, suggesting insulin resistance influences FGF-23 levels (intact FGF-23: 32.7 pg/ml pre weight loss versus 24.2 pg/ml post weight loss, P = 0.03; HOMA-IR 4.2 per weight loss versus 2.5 post weight loss, P = 0.04) (Fernández-Real et al., 2013).

The literature linking FGF-23, atherosclerosis, and measures of obesity is limited; however, most studies report positive associations between FGF-23 and such co-morbidities in adult population with and without CKD (Balci et al., 2010; Gutierrez et al., 2009; Kerr et al., 2013; Mirza et al., 2010; Wahl et al., 2012). To our knowledge, this is the first study to demonstrate a positive association between insulin resistance and FGF-23 in an adult CKD population. A previous study of 162 pre-dialysis CKD patients reported elevated FGF-23 levels were associated with vascular calcification (CAC) and left ventricular hypertrophy (Gutierrez et al., 2009). Similarly, a study of 128 hemodialysis patients demonstrated FGF-23 correlated with carotid artery intima media thickness (Balci et al., 2010), and we reported a statistically significant association between epicardial fat volume and FGF-23 in 94 pre-dialysis CKD patients (Kerr et al., 2013). Another study in elderly individuals with normal renal function, demonstrated FGF-23 levels were significantly higher in subjects with increased BMI, waist circumference and total body fat mass as measured by dual x-ray absorptiometry (Mirza et al., 2010). Finally, Wahl et al. evaluated FGF-23 levels in diabetic CKD patients, and determined diabetes status was a significant predictor for FGF-23 level in a multivariable adjusted regression model (Wahl et al., 2012). Our results are consistent with these findings, and suggest a link between obesity, insulin resistance, and bone and mineral metabolism. The biological mechanism accounting for these associations are unknown; however, it is plausible, given insulin's ability to increase renal phosphorus reabsorption by inducing the renal NaPi-II co-transporter, that insulin resistance may influence renal phosphorus handling in CKD patients. Thus, we hypothesize insulin resistance may contribute to disrupted renal phosphorus homeostasis, which is detectable clinically by increased FGF-23 levels. Further studies are necessary to explore this hypothesis.

In the pediatric population, Wojcik et al. demonstrated an inverse correlation between FGF-23 and insulin resistance in a study of obese adolescents (mean age 14 years) without CKD (Wojcik et al., 2012). A separate study by Wojcik et al. also showed FGF-23 levels were lower in obese insulin resistant adolescents without CKD versus obese non-insulin resistant controls (Wojcik et al., 2012), suggesting higher FGF-23 is associated with lower insulin resistance. These results differ from our results, where we report increasing insulin resistance (HOMA-IR) is positively associated with ctFGF-23.

While it is difficult to make comparisons between a non-CKD pediatric population under-going bone growth, versus an adult CKD population, we can make the following observations which may account, in part, for these discrepant findings. Yasin et al., in a study of 81 patients less than 25 years of age, demonstrated that predictors of intact FGF-23 vary according to age (Yasin, Liu, Chau, Madrenas, & Filler, 2013). While insulin resistance was not assessed in the Yasin study, it is intriguing that statistically significant associations for intact FGF-23 were only demonstrated in patients greater than 13 years of age. Bacchetta et al. have reported similar results in a study of 227 children. Considering the subset without CKD (N = 115), intact FGF-23 levels were increased only in patients greater than 15 years of age; whereas, ctFGF-23 levels were not (Bacchetta et al., 2010). These results suggest that the FGF-23 assay type, and patient age, and growth status may impact on FGF-23 levels, and the resulting magnitude and direction of associations between FGF-23 and other covariates may differ in these circumstances. The difference between FGF-23 levels in the Wojcik study were measured by intact FGF-23 ELISA (Wojcik, Janus, et al., 2012), and were not appreciably elevated in either group (median level 9.8 pg/ml in insulin resistant compared to 11.9 pg/ml in non insulin resistant controls). We measured ctFGF-23, which may be a preferred method for CKD populations (Devaraj, Duncan-Staley, & Jialal, 2010). Also, the association we report between HOMA-IR and ctFGF-23 remained robust in a multivariable model adjusted for other factors affecting FGF-23: kidney function, 1,25 dihydroxyvitamin D, and PTH.

Our secondary objective was to determine if patients with increased insulin resistance have increased CAC scores, and we demonstrated that log CAC scores were 40% higher in patients in the higher HOMA-IR group. We (Garland et al., 2008), and others (Kobayashi et al., 2008), have reported that CKD patients who have elevated BMI, diabetes mellitus, or insulin resistance have an increased burden of vascular calcification; however, the biological mechanisms accounting for the accelerated vascular calcification in this setting remain incompletely described. It is possible that the renal phosphorus homeostasis is more severely disrupted in CKD patients with insulin resistance, which over time may contribute to the observed accelerated vascular calcification in these patients. Although our results demonstrated higher CAC scores in CKD patients with greater insulin resistance, our study was not designed to address the cellular mechanism(s) for this observation.

This study has strengths and limitations. The main strength is the identification of a novel, potentially modifiable manifestation of insulin resistance in CKD patients, which if correct, could be broadly applied given the prevalence of insulin resistance and diabetes mellitus in the CKD and general populations. Limitations include the sample size, and the cross sectional design prevents the ability to determine causality from our findings. Finally, although our results demonstrate higher ctFGF-23 levels in patients with insulin resistance, we cannot definitely link these findings to alterations in renal phosphorus handling, as urinary phosphorus excretion measures are not available. FGF-23 is one of a number of known fibroblast growth factors (FGF). Another FGF hormone, FGF-21, regulates glucose metabolism and levels are reportedly increased in obese patients with diabetes (Chavez et al., 2009), metabolic syndrome (Zhang et al., 2008), and in patients with CKD (Stein et al., 2009). Whether shared common elements between the structure of FGF-23 and FGF-21 (Itoh & Ornitz, 2008) could also be a factor in contributing to the association we report between HOMA-IR and FGF-23 has not been studied.

In conclusion, we describe an association between insulin resistance and ctFGF-23 in pre-dialysis CKD patients, which remained robust across different statistical methods. These findings support our hypothesis that CKD patients with greater insulin resistance have higher FGF-23 levels, possibly indicating insulin resistance may contribute to the severity of disrupted renal phosphorus homeostasis in CKD. Studies are needed to confirm this potential mechanism, and to determine whether insulin resistance therapy including dietary intervention might improve renal phosphorus handling in CKD, and over the longer term, CAC development.

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