FGF-23 is associated with insulin resistance in pre-dialysis CKD patients, and in obese, non-CKD patients

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Background

- Insulin is directly involved in renal phosphorus (PO_4) handling, increasing renal PO_4 re-absorption at the proximal tubule sodium-phosphate co-transporter type II (NaPi-2). [1]
- Previously, we have reported a positive association between insulin resistance (HOMA-IR) and FGF-23 in pre-dialysis CKD patients. [2]
- Fibroblast growth factor 23 (FGF-23) acts to reduce renal phosphorus re-absorption (increasing renal phosphorus excretion) by decreasing the expression of renal proximal tubule NaPi-II co-transporters.
- In CKD, as nephron mass decreases, renal phosphorus elimination becomes impaired, and FGF-23 increases to maintain normo-phosphatemia.
- Consequently, it has been suggested that increased FGF-23 is an early biomarker indicating renal phosphorus homeostasis is disrupted, even in the absence of overt hyperphosphatemia. [3]

Objectives

We wished to determine if the association between FGF-23 and insulin resistance could also be demonstrated in a non-CKD population.

Our primary hypothesis was insulin resistant CKD patients, and patients without CKD who are also insulin resistance, would demonstrate greater disruption in renal PO_4 homeostasis, detected by greater fibroblast growth factor-23 (FGF-23) levels.

Aim: Our primary objective was to compare the associations between insulin resistance and FGF-23 in non-CKD and CKD populations.

Methods

- Participants: Cross sectional study of 72 predialysis stage 3-5 CKD patients and 66 obese, non-diabetic, non-CKD patients receiving care in Ontario, Canada, Diabetic patients requiring insulin were excluded.
- Insulin resistance was assessed using the homeostasis model assessment of insulin resistance (HOMA-IR), and plasma carboxyl terminal FGF23 (ctFGF-23) was measured in duplicate by enzyme-linked immunosorbent assay. Kidney function was estimated (eGFR) using the abbreviated MDRD formula.

Results

- CKD patients were older, had greater systolic but lower diastolic blood pressure, lower eGFR, and had higher HOMA-IR and FGF-23 levels compared to non-CKD patients (see table1 below).
- By partial correlation, in CKD patients (N=72), accounting for kidney function (eGFR) and phosphorus level, ctFGF-23 was positively associated with HOMA-IR (r=0.4;P=0.001).
- This association remained in non-CKD patients (N=66) (r=0.26;P=0.04), and when considering all patients together (N=138) (r=0.25; P=0.003).

Table 1: Comparison of patient characteristics between CKD and Non-CKD patients

Variable	CKD (N=72)	Non-CKD (N=66)	P
Age	64 ± 14	59 ± 13	0.003
BMI	30.2 ± 8	32.1 ± 4	0.08
Waist (cm)	101.6 ± 22	109.3 ± 10	0.01
BP (SYS)	130.7 ± 16	124.9 ± 18	0.04
BP (DIA)	74..8 ± 12	79 ± 9.2	0.02

Results

Table 1: Comparison of patient characteristics (continued)

Variable	CKD (N=72)	Non-CKD (N = 66)	P
Glucose	5.8 ± 1.2	5.5 ± 1.0	0.06
Phosphorus	1.27 ± 0.24	0.95 ± 0.21	< 0.0001
eGFR	25.8 ± 13	63 ± 13	< 0.0001
HOMA-IR	2.66 (1.4 – 5)	2.15 (1.3 – 3)	0.02
ctFGF-23	132 (58-300)	67 (56-79)	< 0.0001

Conclusions

- These data suggest that obesity and insulin resistance impact on renal phosphorus handling, potentially by increasing renal phosphorus retention.
- Similar to our findings in pre-dialysis CKD patients, insulin resistance, in obese patients without CKD, was associated with increasing ctFGF-23 level.
- Increased FGF-23 is linked with cardiovascular events and vascular calcification in CKD, and thus disrupted renal phosphorus handling many impact on vascular health in earlier CKD stages.

Future directions: Studies directly evaluating urinary renal phosphorus excretion in insulin resistance are needed.

References

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