Impaired postprandial lipemic response in chronic kidney disease

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Dyslipidemia in chronic kidney disease (CKD) is usually characterized by hypertriglyceridemia. Here we studied postprandial lipemia in children and young adults to determine whether an increasing degree of CKD results in a proportional increase in triglyceride and chylomicron concentration. Secondary goals were to determine whether subnephrotic proteinuria, apolipoprotein (apo)C-III and insulin resistance modify the CKD effect. Eighteen fasting participants (mean age of 15 years, mean glomerular filtration rate (GFR) of 50 ml/min/1.73 m^2) underwent a postprandial challenge with a high fat milkshake. Triglycerides, apoB-48, insulin, and other markers were measured before and 2, 4, 6, and 8 hours afterward. Response was assessed by the incremental area under the curve of triglycerides and of apoB-48. The primary hypothesis was tested by correlation to estimated GFR. Significantly, for every 10 ml/min/1.73 m^2 lower estimated GFR, the incremental area under the curve of triglycerides was 17% greater while that of apoB-48 was 16% greater. Univariate analyses also showed that the incremental area under the curve of triglycerides and apoB-48 were significantly associated with subnephrotic proteinuria, apoC-III, and insulin resistance. In multivariate analysis, CKD and insulin resistance were independently associated with increased area under the curve and were each linked to increased levels of apoC-III. Thus, postprandial triglyceride and chylomicron plasma excursions are increased in direct proportion to the degree of CKD. Independent effects are associated with subclinical insulin resistance and increased apoC-III is linked to both CKD and insulin resistance.

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Dyslipidemia is frequent among individuals with chronic kidney disease (CKD), most commonly manifesting as hypertriglyceridemia with reduced high-density lipoprotein (HDL) cholesterol concentrations. CKD in adults is often associated with other diseases and comorbidities that affect lipid metabolism. Among children with CKD, primary renal disease is predominant yet the same dyslipidemia is seen, supporting the idea that it arises directly as a consequence of renal dysfunction.[1] Whereas multiple cardiovascular risk factors are present in the CKD population and the deleterious effect of each is difficult to isolate, multiple lines of evidence support a pathological role for dyslipidemia in this setting.[2] CKD is associated with a many fold increased risk of cardiovascular events and death attributable to cardiovascular disease, justifying its study.[3]

The mechanism by which renal disease leads to dyslipidemia remains an active area of inquiry. Hypertriglyceridemia could result from the following 2 broad processes: (i) increased secretion of triglycerides (TGs) as a component of very low-density lipoproteins (VLDL) or chylomicrons (CMs) from the liver or intestine, respectively or (ii) decreased utilization or catabolism of VLDL and CM TG. The latter mechanism is generally considered the more relevant one in CKD.[4,5] Past investigations have separated renal-insufficient patients and those with nephrotic syndrome; the latter routinely producing extreme dyslipidemia.

Most circulating TG is carried by apolipoprotein B (apoB)-containing lipoproteins. The liver synthesizes and secretes TG in VLDL, which each contain a single molecule of apoB-100. VLDL are metabolized to intermediate- and low-density lipoproteins during circulation. CM carry freshly absorbed dietary TG into the circulation following meals. Synthesized by the intestines and containing a single apoB-48 molecule, each CM delivers dietary TG to target tissues where lipolysis releases fatty acids for use as energy or storage. Lipoprotein lipase (LPL) is among the principal lipases involved; apoC-III inhibits the activity of LPL, slowing TG catabolism. As TG is removed from its core, the CM shrinks to a less buoyant "remnant" particle that is taken up by the liver where residual CM TG is either oxidized or recycled in VLDL.[4]

Even in the fasting state, CM remnants are increased among individuals with severe CKD, suggesting a defect in clearance.[6,7] Many of the catabolic mechanisms by which CM

TG are cleared following a meal parallel the clearance of VLDL TG.[8] Whereas the *in vivo* clearance of CM TG cannot be assessed independently from that of VLDL TG, the relative importance of hepatic synthesis is smaller in the postprandial state compared with fasting. Furthermore, because production of CM after a meal is closely related to the amount of TG ingested, a "fat tolerance test" is well suited to test the hypothesis that CKD impairs the clearance of CM and their TG and to explore potential mediators of this CKD effect. Two previous studies of 9 and 21 subjects, respectively, demonstrated defective postprandial clearance of TG and CM remnants among adult dialysis-dependent patients.[9,10] Impaired postprandial TG clearance was also shown in a group of 14 adults with less severe CKD, in whom insulin resistance inversely proportional to glomerular filtration rate (GFR) was also demonstrated.[11] Although elevated apoC-III is a consistent finding in all hypertriglyceridemic states, recent studies have linked delayed VLDL catabolism to increased apoC-III levels and delayed apoC-III catabolism to CKD.[12,13] To our knowledge, no previous study has investigated these abnormalities of triglyceride metabolism in children or (in any age group) whether these abnormalities are proportional to the degree of CKD. Finally, we do not believe any previous investigation has measured the extent, if any, to which proteinuria contributes to these associations in non-nephrotic patients.

The purpose of this study was to investigate the effects of CKD on CM and TG metabolism following a single high-fat meal in a pediatric and young adult group and determine whether such effects vary with the degree of renal impairment. We hypothesized that CKD results in decreased clearance of CM and TG in proportion to the severity of reduction in renal function. We investigated the relevance of subnephrotic proteinuria and other potential mediators of impaired TG metabolism including apoC-III, insulin resistance, free fatty acid concentrations, and markers of inflammation, as well as anthropomorphic measures of adiposity. We also determined whether this "fat tolerance test" provides measures that are more sensitive to the effects of CKD as compared to fasting measures.

RESULTS

Cohort characteristics

The baseline characteristics and fasting lab values for the study group are shown in Table 1. All 3 subjects with a urine protein–creatinine ratio (uPCR) 2 to 3 mg/mg had congenital structural CKD and albumin levels of 4 g/dl or greater, and none manifested edema. The group was mostly teenagers with 2 participants under age 10 years (ages 5 and 9) and 1 over age 20 years (age 25). The HOmeostasis Model Assessment of Insulin Resistance Index (HOMA-IR) and body mass index *Z*-scores were elevated, though waist circumference was average. No subjects demonstrated fasting glucose levels >100 mg/dl or postprandial glucose levels >110 mg/dl. For descriptive purposes, Supplementary Figures S1 to S4 show postprandial levels of TG, insulin, free fatty acids, and HDL cholesterol.

Table 1 | Study population characteristics and baseline measures

	Fasting measures[a]	Normal range[b]
Age (yr)	15 ± 5	
GFR (ml/min/1.73 m^2)	53 ± 30	>70 by equation
Urine protein–creatinine ratio (mg/mg)	0.8 ± 1.0	<0.2
Serum albumin (g/dl)	4.5 ± 0.5	3–5
BMI (kg/m^2)	22 (18, 29)	(age-/sex-dependent)
BMI *Z*-score	1.07 ± 1.28	0 ± 2
Waist circumference *Z*-score	−0.05 ± 0.71	0 ± 2
Insulin (μIU/ml)	12.79 ± 6.5	5–15 (age-dependent)
HOMA-IR	2.40 (1.7, 3.8)	<2.5 (puberty-dependent)
Total TGs (mg/dl)	121 (90, 175)	<130 (age-dependent)
Total cholesterol (mg/dl)	176 ± 53	<200
HDL-C (mg/dl)	42 ± 7	>40 (guideline)
Non-HDL-C (mg/dl)	132 ± 51	<130 (guideline)
LDL-C (mg/dl)	81 ± 30	<100 (guideline)
VLDL-TG (mg/dl)	58 (42, 98)	
ApoA1 (mg/dl)	133 ± 21	104–225
ApoB (mg/dl)	84 ± 27	60–133
ApoB-48 (ng/l)	11.3 ± 5.3	1.4–9
ApoC-III (mg/dl)	12.4 ± 4.7	< ~9 (age-dependent)
Lp(a) (mg/dl)	17 (6, 59)	ULN 14.6 M/17.6 F
TNF-α (pg/ml)	2.5 ± 1.3	0.55–2.82
IL-6 (pg/ml)	1.5 ± 1.1	0.45–9.96
Free fatty acids (mM)	0.6 ± 0.5	0.1–0.6

Characteristics and fasting laboratory measures of the study group.
Apo, apolipoprotein; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, HOmeostasis Model Assessment of Insulin Resistance Index; f, female; IL, interleukin; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; Lp, lipoprotein; M, male; TG, triglyceride; TNF, tumor necrosis factor; ULN, upper limit of normal; VLDL, very low-density lipoprotein.
[a]Variation is described by either mean ± SD or median (IQR).
[b]Normal ranges or recommended levels are provided where available.

Association between GFR and AUCs of TG, apoB-48

Figure 1a and b demonstrates the associations between GFR and both total and incremental (above fasting level) postprandial TG clearance. Figure 1c and d demonstrates the same associations for CM clearance as measured by apoB-48 area under the curve ([AUC]; individual *P* values shown in figures). Table 2 provides estimates of effect size: for every 10 ml/min/1.73 m^2 lower GFR, the incremental AUC (iAUC) of TG was 17% (95% confidence interval [CI]: 4%–33%; $P < 0.05$) greater and the iAUC of apoB-48 16% (95% CI: 1%–33%; $P < 0.05$) greater. Multivariable models confirmed these effect sizes and significance.

Association between subnephrotic proteinuria and AUCs of TG, apoB-48

Figure 2a and b demonstrates the associations between uPCR and both total and incremental postprandial TG clearance. Figure 2c and d show the same associations for apoB-48 AUC. All relationships were quantitatively and statistically significant (individual *P* values shown in figures). Table 2 provides estimates of effect size: for each 50% increase in uPCR in the group, the iAUC of TG was 12% (95% CI: 6%–26%; $P < 0.005$) greater and the iAUC of apoB-48 was 15% (95% CI: 4%–27%; $P < 0.01$) greater.

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