Adiponectin in Children with Chronic Kidney Disease: Role of Adiposity and Kidney Dysfunction

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Low serum adiponectin is a known cardiovascular risk in adult chronic kidney disease (CKD). However, adiponectin concentrations and their relation with other cardiovascular risks have not been studied in children with preterminal CKD. Forty-four children and adolescents who were aged 6 to 21 yr and had stages 2 to 4 CKD had serum adipocytes, lipoproteins, markers of inflammation, homocysteine, and insulin levels determined cross-sectionally. There were 29 lean (body mass index [BMI] <85th percentile) and 15 nonlean (BMI ≥85th percentile) patients. Mean serum adiponectin level was 30.6 ± 14.1 μg/ml (range 7.1 to 67.8 μg/ml). A total of 83% of patients had elevated adiponectin level. Despite similar kidney function, lean patients had significantly higher adiponectin levels than nonlean patients (34.1 ± 13.4 μg/ml versus 23.6 ± 13.3 μg/ml; P = 0.02). In univariate analysis, serum adiponectin negatively correlated with age (r = −0.34, P = 0.02), BMI (r = −0.47, P = 0.001), leptin (r = −0.41, P = 0.006), GFR (r = −0.39, P = 0.02), and insulin (r = −0.36, P = 0.01) and positively correlated with ApoA2 (r = 0.30, P = 0.04); no significant associations were found with markers of inflammation or homocysteine. Multivariate stepwise analysis showed that GFR (β = −0.008, P = 0.001), BMI (β = −0.16, P = 0.015), and age (β = −0.04, P = 0.018) independently predicted serum adiponectin levels. Separate analysis of lean patients showed no significant relations with age or BMI; only GFR independently predicted serum adiponectin level (β = −0.01, P = 0.0008). It is concluded that serum adiponectin is elevated in children and adolescents with stages 2 to 4 CKD and that decreased kidney function is a major determinant of elevated adiponectin concentrations. Despite overall elevated adiponectin, overweight patients display lower serum adiponectin levels and might be at risk for future cardiovascular complications.

A adiponectin, an anti-inflammatory cytokine, is a product of adipose tissue and is involved in regulation of lipid and glucose metabolism (1–3). Low serum adiponectin is strongly associated with known cardiovascular risk factors of dyslipidemia, insulin resistance, and inflammation. These associations suggest that higher adiponectin levels confer a protective effect against atherosclerosis. In the majority of human diseases, adiponectin serum concentration is decreased, yet, in chronic kidney disease (CKD), the serum level of adiponectin is increased beyond typical physiologic levels. How these elevated circulatory adiponectin levels interact with increased adiposity, insulin resistance, dyslipidemia, and inflammation, conditions that frequently are found in patients with CKD, is not understood clearly. Published studies that evaluated the relations between adiponectin and the above markers in CKD showed inconsistent and, sometimes, contradicting results.

To our knowledge, no previous published research described adiponectin levels in children with mild to moderate chronic renal insufficiency. The goals of this study, therefore, were to describe serum adiponectin levels in a cohort of children and adolescents with CKD stages 2 to 4; estimate the cross-sectional association of adiponectin levels with other potential cardiovascular markers such as other adipokines (leptin and resistin), lipids, hyperinsulinemia, and inflammation; and define the association of kidney dysfunction and adiposity with adiponectin levels.

Materials and Methods

The study population included 44 patients who were aged 6 to 21 yr and had CKD stage 2 to 4 (measured GFR 16 to 89 ml/min per 1.73 m²). The institutional review board of Cincinnati Children’s Hospital Medical Center approved the study, and informed consent was obtained for each study patient. The medical records were reviewed for age, gender, race, and cause of CKD. Routine clinical and laboratory data included height, weight, systolic BP (SBP), diastolic BP (DBP), serum creatinine, electrolytes, and hemoglobin. For controlling for differences in age, BP were indexed to the age-, gender-, and height-specific 95th percentiles for each patient; specifically, the measured SBP or DBP were divided by the age-, gender-, and height-specific 95th percentiles SBP or DBP. Hypertension was defined as indexed SBP or DBP ≥1.0. Kidney function was determined by measuring GFR using a single intravenous injection of Ioversol 74% (Optiray 350; Mallinckrodt, St. Louis, MO). Iodine in timed blood samples was measured by x-ray fluorescence analysis (Renalyzer PRX90; Diatron AB, Lund, Sweden), and GFR was

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TABLE 1. Pearson correlation coefficients (R) of variables in the analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adiponectin</th>
<th>Age</th>
<th>BMI</th>
<th>GFR</th>
<th>Leptin</th>
<th>Insulin</th>
<th>ApoA2</th>
</tr>
</thead>
<tbody>
<tr>
<td>R Adiponectin</td>
<td>1.0</td>
<td>−0.34</td>
<td>−0.47</td>
<td>−0.34</td>
<td>−0.41</td>
<td>−0.36</td>
<td>0.30</td>
</tr>
<tr>
<td>P</td>
<td>0.03</td>
<td>0.001</td>
<td>0.02</td>
<td>0.006</td>
<td>0.01</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>R Age</td>
<td>—</td>
<td>1.0</td>
<td>0.38</td>
<td>−0.30</td>
<td>0.17</td>
<td>0.28</td>
<td>−0.26</td>
</tr>
<tr>
<td>P</td>
<td>0.01</td>
<td>0.04</td>
<td>0.25</td>
<td>0.06</td>
<td>0.09</td>
<td></td>
<td></td>
</tr>
<tr>
<td>R BMI</td>
<td>—</td>
<td>—</td>
<td>1.0</td>
<td>0.02</td>
<td>0.74</td>
<td>0.47</td>
<td>−0.09</td>
</tr>
<tr>
<td>P</td>
<td>0.89</td>
<td>&lt;0.0001</td>
<td>0.001</td>
<td>0.52</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R GFR</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>1.0</td>
<td>−0.008</td>
<td>0.02</td>
<td>−0.06</td>
</tr>
<tr>
<td>P</td>
<td>0.95</td>
<td>0.87</td>
<td>0.71</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R Leptin</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>1.0</td>
<td>0.44</td>
<td>0.002</td>
<td>0.58</td>
</tr>
<tr>
<td>P</td>
<td>0.002</td>
<td>0.58</td>
<td>0.31</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R Insulin</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>1.0</td>
<td>0.15</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>0.002</td>
<td>0.58</td>
<td>0.31</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R ApoA2</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>1.0</td>
<td></td>
</tr>
</tbody>
</table>
all patients showed that GFR (β = −0.008, P = 0.001), BMI (β = −0.16, P = 0.015), and age (β = −0.04, P = 0.018) concurrently and independently were associated with serum adiponectin levels.

Further analysis demonstrated a bimodal response in the relationship between adiponectin and BMI (Figure 1). Therefore, detailed analysis according to lean versus nonlean status was performed. There were 29 lean (BMI <85th percentile) and 15 nonlean BMI (≥85th percentile) patients. The comparisons of demographic, clinical, and laboratory characteristics between lean and nonlean patients are presented in Table 2. Nonlean patients had a significantly higher level of insulin, leptin, and triglycerides. There was no significant difference between groups in kidney function. Despite similar kidney function, lean patients had significantly higher adiponectin levels than nonlean patients (Table 2). Univariate analysis of lean patients only (n = 29) showed significant negative correlation of adiponectin with GFR (r = −0.57, P = 0.001). No significant associations of adiponectin were found with age (r = −0.14, P = 0.44), BMI (r = −0.07, P = 0.72), leptin (r = 0.04, P = 0.85), or insulin levels (r = −0.02, P = 0.92). Multivariate analysis of lean patients only showed that only lower GFR independently predicted higher serum adiponectin level (β = −0.01, P = 0.0008). In contrast, significant associations of adiponectin with age (r = −0.67, P = 0.006), BMI (r = −0.47, P = 0.043), insulin (r = −0.54, P = 0.036), HDL (r = 0.57, P = 0.021), and homocysteine (r = −0.64, P = 0.012) were demonstrated in nonlean patients. In these patients, GFR did not predict adiponectin level.

**Discussion**

High adiponectin levels were found previously in children who were on chronic peritoneal dialysis (7). The results of our study demonstrated that the serum level of adiponectin was increased in almost every patient in the cohort of children with mild to moderate CKD compared with normal values in children (6), and it was inversely correlated with kidney function. Similar observations from other studies that serum adiponectin concentrations inversely correlate with the degree of renal insufficiency (8) and that the highest levels are found in patients with ESRD (9–11) suggest that decreased renal clearance is the likely cause of elevated serum adiponectin. A recent small study by Marchlewskia et al. (12) corroborated this hypothesis. The authors showed significantly higher plasma adiponectin level and a decrease in ApM1 gene expression by adipocytes in 10 adults with ESRD compared with healthy adults. The results of the study suggest that elevated circulatory adiponectin, as a result of decreased clearance, induces a negative feedback mechanism on the ApM1 gene expression by adipocytes, resulting in a proportional adjustment of the protein expression. Thus, as in the conditions with decreased plasma adiponectin levels, such as obesity and type 2 diabetes, but through the different mechanism may be a decreased adipose tissue production of adiponectin in patients with CKD.

Recent studies indicate that abnormally low serum adiponectin should be considered as an important cardiovascular risk in patients with CKD. This assumption is based on the following facts: (1) Lower versus normal serum levels of adiponectin are associated with increased cardiovascular morbidity and mortality; (2) adiponectin may be protective by displaying anti-inflammatory and antiatherogenic properties. Low serum adiponectin levels are independently associated with increased prevalence and severity of coronary artery disease in men (13,14), hypertension (15), development of coronary and carotid artery atherosclerosis in general population (16), and progression of coronary artery calcification in adults with and without type 1 diabetes (17). Becker et al. (8) demonstrated that plasma adiponectin levels are an inverse predictor of cardiovascular outcomes among adults with mild and moderate CKD. Similar results have been shown in adults with ESRD in the study by Zoccali et al. (9). It is interesting that, in this study, on average, adiponectin levels were increased, in comparison with healthy subjects, not only among patients who experienced relatively few cardiovascular events but also among those who developed cardiovascular complications in large proportions. It currently is not clear why patients with ESRD need supraphysiologic levels of circulatory adiponectin to exhibit a cardioprotective effect.

The relations between adiponectin and metabolic or inflammatory outcomes in patients with CKD are not well elucidated. Guebre-Egziabher et al. (18) studied 48 patients with CKD (GFR 54 ± 25; range 12 to 107 ml/min per 1.73 m^2) and found no relation between adiponectin and insulin or adiponectin and CRP but strong positive associations between adiponectin and leptin. Becker et al. (8) in a study of 227 adults without diabetes and with CKD showed no significant relation between adiponectin and CRP but, in contrast to a previous study, significant inverse associations of adiponectin with insulin and triglycerides. In addition, significant negative associations, in contrast to Guebre-Egziabher et al. (18), between plasma adiponectin and leptin levels were shown in studies of patients with ESRD by Zoccali et al. (9) and Stenvinkel et al. (10). No association between serum adiponectin and CRP was found in the study by Zoccali et al. (9), whereas Stenvinkel et al. (10)
demonstrated significant negative associations between these two biomarkers. Both of these studies showed significant positive associations between adiponectin and HDL cholesterol and negative associations between adiponectin and triglycerides. Axelsson et al. (19) hypothesized that a reduction of renal mass might contribute to retention of proinflammatory adipokines, thereby generating adipokine imbalance. Such an imbalance may contribute to insulin resistance and dyslipidemia, which are common features of ESRD. In our study, no significant association was found between markers of inflammation and serum adiponectin level. This might be because the markers of chronic inflammation were elevated in very few patients in the study, perhaps indicating that young patients in our study were healthier than previously reported in studies of adults.

The variables that were associated with adiponectin level were different in lean and nonlean patients. In lean patients, only the degree of kidney dysfunction determined serum adiponectin level. These results are different from other pediatric studies. Böttner et al. (20) studied 200 normal-weight children and determined that in healthy lean boys, adiponectin levels significantly declined in parallel with physical and pubertal development (age, BMI), subsequently leading to significantly reduced adiponectin levels in adolescent boys compared with girls. In our study, no such relations were seen. As in the majority of studies of obese children and adolescents, we found significant associations of serum adiponectin with BMI, HDL, and serum insulin in our nonlean patients. It is interesting that the degree of kidney dysfunction did not significantly influence the serum adiponectin level in overweight patients. These results indicate that the relations between adiponectin, adiposity, and metabolic abnormalities become evident only in overweight children regardless of kidney function and continue to strengthen with increased adiposity. The results also might indicate that increased level of adiponectin in overweight children with CKD might not be protective against increased cardiovascular risk.

Acknowledgments
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Disclosures
None.

References
4. Stake G, Monclair T: A single plasma sample method for


Obesity is a subject of much concern because children as well as adults have increased adiposity and associated kidney dysfunction. In addition to the observations of Mitsnefes et al. in this month’s *CJASN*, de Boer et al. link central obesity microalbuminuria and changes in creatinine clearance in diabetes in this month’s issue of *JASN* (pp. 235–243).