Insulin Resistance, Inflammatory Biomarkers, and Adipokines in Patients with Chronic Kidney Disease: Effects of Angiotensin II Blockade

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Patients with chronic kidney disease (CKD) present a high prevalence of insulin resistance (IR). Some studies suggest that angiotensin II may influence some cellular pathways that contribute to the pathogenesis of IR and stimulate the release of proinflammatory cytokines. Fifty-two patients who had stages 3 and 4 CKD and no diabetes were administered an angiotensin receptor blocker (ARB), olmesartan (40 mg), for 16 wk. Before and after ARB treatment, metabolic and inflammatory parameters and adipokines were measured. IR was calculated by Homeostasis Model Assessment (HOMA) index. Baseline data were compared with data that were obtained from 25 healthy control individuals of similar age and normal renal function. Compared with control subjects, patients with CKD presented significantly higher BP and waist circumference, higher triglycerides and lower HDL levels, higher insulin levels, and higher mean HOMA index (6.0 ± 2.7 versus 2.9 ± 2.2 μU/mL × mmol/L; P < 0.001). In addition, patients with CKD had increased levels of high-sensitivity C-reactive protein, TNF-α, and IL-6. In patients with CKD, leptin was positively correlated to abdominal obesity, insulin levels, and IL-6, and adiponectin was inversely correlated to abdominal obesity and insulin levels. Olmesartan treatment resulted in a significant decrease of BP, urinary protein excretion, plasma glucose (99 ± 16 versus 92 ± 14 mg/dl; P < 0.05), insulin (23.1 ± 8.8 versus 19.9 ± 9; P < 0.05), HOMA index (6.0 ± 2.7 versus 4.7 ± 2.8; P < 0.05), and glycated hemoglobin (5.33 ± 0.58 versus 4.85 ± 0.81%; P < 0.01). At the same time, there was a significant reduction of high-sensitivity C-reactive protein levels, from 4.45 mg/L (2.45 to 9.00) to 3.55 mg/L (1.80 to 5.40; P < 0.05) and fibrinogen (412 ± 100 versus 370 ± 105 mg/dl; P < 0.05). There were no significant differences in adipokine levels after olmesartan treatment. These data demonstrate that patients with CKD have a high prevalence of IR, metabolic syndrome, and chronic inflammation and that the administration of the ARB olmesartan improves IR and inflammation markers in these patients. Plasma adipokine levels that are related to several metabolic risk factors in patients with CKD were not modified by ARB therapy.


Patients who have chronic kidney disease (CKD) present a high prevalence of metabolic syndrome (MS) and insulin resistance (IR) (1,2), which are associated with a high risk for diabetes (3) and cardiovascular disease (CVD) (4) and a high all-cause mortality (5). At the same time, cross-sectional and prospective (6) studies have demonstrated that MS is independently associated with an increased risk for CKD in adults without diabetes, and IR is already present in patients with mild degrees of renal dysfunction (7). This supports a close relationship between CKD and MS/IR syndrome and can contribute to a high risk for CVD related to early stages of CKD.

The MS is considered to be a proinflammatory state because it is associated with elevated levels high-sensitivity C-reactive protein (hs-CRP), IL-6 (8–10), fibrinogen (11), and plasminogen activator inhibitor-1 (11), all of which promote the development of atherosclerotic CVD. In addition, it is associated with alterations of cytokines that are produced in abdominal fat (12–16) (an increase in leptin levels and a reduction in those of adiponectin). These adipokines exert opposite effects on metabolism, as well as on the cardiovascular system. Leptin plays an important role in IR and in the development of arterial hypertension that is associated to obesity and MS (17). By contrast, adiponectin improves insulin sensitivity and presents anti-inflammatory and antiatherogenic properties (18).

Arterial hypertension frequently is present in patients with CKD; consequently, antihypertensive drugs are used commonly in these patients (19,20). However, not all of them exert similar effects on metabolic alterations that are observed in these patients. Diuretics are associated with hyperinsulinemia, hyperglycemia, and increased IR in renal patients (20), whereas renin-angiotensin system (RAS) blockers may have a beneficial effect on glucose metabolism. This effect could involve not only a reduction in hemodynamic stress but also additional metabolic mechanisms because it has been shown that at least one angiotensin II subtype I receptor blocker (ARB) at conventional oral dosing could act as a partial agonist of the peroxisome proliferator–activated receptor γ (PPAR-γ) (21). These drugs

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also have shown an anti-inflammatory effect in hypertensive patients with microinflammation (22). However, the effect of these drugs on metabolic and inflammatory alterations that are observed in patients who have CKD is not well established. Therefore, the aim of this study was to explore (1) the impact of CKD on metabolic and inflammatory variables as well as on adipokine levels in patients who have moderate CKD and no diabetes and (2) the effect of treatment with an ARB, olmesartan, on these parameters in patients with CKD. An age-matched group with normal renal function was used as a reference group.

Materials and Methods

Participants and Laboratory Studies

Fifty-two patients (64% male) who had CKD and ranged in age from 36 to 86 yr were included. Patients were recruited in a single center from the metropolitan area of Madrid and had been referred for the first time to a study in a nephrology clinic because of renal failure: Estimated GFR (eGFR) <60 and >15 ml/min per 1.73 m², stages 3 and 4 Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines. Patients who had diabetes, had been treated with angiotensin-convert- ing enzyme inhibitors (ACEI) or ARB during the last 3 mo, and had serum creatinine >150 mg/dl were excluded from the study. All participants provided informed consent.

At the beginning of the study, all patients had BP values of ≥130/85 mmHg. History of cardiovascular events (myocardial infarction; coro- nary revascularization or stent; stroke; or peripheral artery stenosis in carotid, femoral, or aortoiliac arteries) was recorded, and a physical examination, which included BP, weight, height, and waist circumference, was performed. Blood samples were taken after at least 12 h of fasting for measurement of routine chemical determinations, insulin levels, and inflammatory markers: Serum fibrinogen, hs-CRP, IL-6, IL-1β, TNF-α, and adipokines (leptin and adiponectin). The samples were centrifuged immediately at 1500 × g and 4°C for 10 min, and the supernatant fraction was stored in aliquots at −80°C until further use. Albuminuria was determined in urine that was collected during the previous 24 h. The primary cause of kidney disease was vascular (42%), unknown (22%), glomerulonephritis (16%), adult polycystic kidney disease (12%), interstitial nephritis (8%), and other types of kidney disease (10%). In all patients, renovascular occlusive disease was ruled out by Doppler echography. None of the patients showed clinical or laboratory evidence of abnormal hepatic or infectious diseases in the last 3 mo before inclusion in the study. Twenty-five percent of them had history of ischemic heart disease, 8% of cerebral vascular disease, and 13% of peripheral arterial disease. Data for comparison was obtained in 25 healthy control individuals of similar age and normal renal function (eGFR >90 ml/min).

After initial screening, patients received a once-daily dose of olmesartan medoxomil 40 mg/d during 4 mo. Fifty-three percent of the patients received hepatic hydroxymethyl glutaryl-CoA reductase inhibitors, 28% received aspirin, 58% received diuretics, 39% received calcium channel blockers, 22% received β blockers, and 12% received α blockers. These drugs were maintained without changing the dosage throughout the study. Patients who were previously following a low-salt diet maintained it without modification throughout the study.

Measurements and Calculations

To define MS, clinical criteria by Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults, Adult Treatment Panel III (ATP III) (23) were used. According to the ATP III criteria, MS is identified by the presence of three or more of the following com- ponents:

- abdominal obesity, given as waist circumference >102 cm in men and >88 cm in women
- triglycerides ≥150 mg/dl
- HDL cholesterol <40 mg/dl in men and <50 mg/dl in women
- BP ≥130/≥85 mmHg
- fasting glucose ≥110 mg/dl

The eGFR was calculated according to age, weight, and gender using the Cockcroft-Gault formula (24). Plasma insulin was measured by RIA using a commercially available kit. Insulin sensitivity was quantified using Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) (25) on the basis of fasting insulin and glucose levels and according to the formula HOMA-IR = I × G/22.5, where I is insulin (µIU/ml) and G is glucose (mmol/L). HOMA-IR has been used successfully for evaluation of insulin sensitivity and has examined different pop- ulations, including subjects from a nearby metropolitan area, simi- lar to ours: No diabetes and with neither risk factors for MS nor family history of diabetes. Such populations were used as a refer- ence of normal values in our environment, considering an ab- normal HOMA-index >3.8 µU/ml × mmol/L (26).

Plasma IL-1β, IL-6, TNF-α, adiponectin, and leptin were mea- sured using quantitative sandwich enzyme immunoassay. A human specific mAb of IL-1β, IL-6, or TNFα, was precoated into microplates (R&D Systems, Minneapolis, MN). CRP plasma levels were measured with a highly sensitive latex-based turbidimetric immunoassay on a Hitachi analyzer (Sigma Chemical Co., St. Louis, MO).

Statistical Analyses

Statistical analysis was performed with SPSS 12 for Windows (SPSS, Chicago, IL). Kolmogorov-Smirnov test was used for analysis of the normality of the distribution of the parameters. Univariate comparison of continuous variables between groups was done by t test for normally distributed variables and Mann-Whitney and Wilcoxon tests for skewed variables. x² was used for categorical variables. Pearson corre- lation was calculated to find a correlation between two variables. Values were expressed as mean ± SD or median and interquartile range. Differences were considered as significant at P < 0.05.

Results

Forty-nine patients completed the study after 4 mo of treat- ment. Three patients discontinued the study: One because of gastrointestinal intolerance, another because of a worsening of renal function as a result of spontaneous atheroembolism, and the third was excluded because analytical determinations were not performed.

MS, HOMA-IR, Biomarkers, and Adipokines in Renal Patients and Control Group with Normal Renal Function

Table 1 shows the characteristics of patients with CKD in comparison with control subjects with normal renal function. Although no differences existed according to age, gender, body mass index, and fasting glucose levels, patients with renal failure (mean eGFR 42 ± 17 ml/min per 1.73 m²) had higher mean waist circumference, insulin levels (P < 0.05), HOMA-IR index (P < 0.001), and triglycerides (P < 0.001) and lower HDL cholesterol levels (P < 0.05). A total of 79% of the patients with CKD and only 20% of the control group had high HOMA-IR levels >3.8 µU/ml × mmol/L. These data are related to the fact
that 23 (44%) of 52 patients with renal disease had MS (three or more MS components; ATP III), versus only five (20%) of 25 of the subjects with normal renal function. In patients with CKD, the number of MS components was positively related to HOMA-IR, as it has been described in other populations without associated nephropathy. Patients with CKD, compared with control group patients, showed an inflammatory system activated with higher serum hs-CRP ($P < 0.001$), TNF-$\alpha$ ($P < 0.05$) and IL-6 levels ($P < 0.001$). No differences were observed in leptin and adiponectin levels between both groups (Table 1).

However, patients with stage 4 CKD (eGFR $< 30$ ml/min) had significantly higher adiponectin levels than the control subjects with normal renal function ($22.2$ [14 to 35] versus $13.9$ [10 to 23]; $P < 0.05$).

In patients with CKD, leptin was positively correlated to BMI ($r = 0.411$, $P < 0.01$), waist circumference ($r = 0.377$, $P < 0.05$), and insulin levels ($r = 0.29$, $P < 0.05$; Figure 1). Leptin also was positively correlated to IL-6 ($r = 0.40$, $P < 0.01$). Conversely, adiponectin was inversely correlated to BMI ($r = -0.371$, $P < 0.05$), waist circumference ($r = -0.326$, $P < 0.05$), and insulin levels ($r = -0.29$, $P < 0.05$; Figure 2). Patients who had CKD with MS (three or more MS components; ATP III) had lower levels of adiponectin and higher levels of leptin compared with patients without MS (Figure 3).

**Effects of Olmesartan in Patients with CKD**

In patients who had CKD and were treated with 40 mg of olmesartan, a decrease in BP and proteinuria was observed. Neither BMI nor waist circumference was modified. Fasting glucose levels were reduced, as well as insulin, HOMA-IR, and

![Figure 1](image-url)  
*Figure 1. Relationship between leptin plasma levels and waist circumference (left) and insulin (right) in 52 patients with chronic kidney disease (CKD).*

### Table 1. Demographics and laboratory characteristics of control group (normal renal function) and patients with CKD

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Control Group ($n = 25$)</th>
<th>Patients with CKD ($n = 52$)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male/female)</td>
<td>15/10</td>
<td>33/19</td>
<td>NS</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>67.2 ± 13.0</td>
<td>71.0 ± 11.0</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (kg/m$^2$)</td>
<td>28.0 ± 5.0</td>
<td>29.1 ± 4.0</td>
<td>NS</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>95.3 ± 11.1</td>
<td>98.3 ± 12.8</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>GFR (ml/min per 1.73 m$^2$)</td>
<td>97.7 ± 12.3</td>
<td>42.0 ± 17.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Glucose (mg/dl)</td>
<td>96.7 ± 11.0</td>
<td>99.2 ± 16.0</td>
<td>NS</td>
</tr>
<tr>
<td>Insulin (mU/L)</td>
<td>16.1 ± 4.4</td>
<td>23.1 ± 8.8</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>HOMA-IR index ($\mu$U/ml × mmol/L)</td>
<td>2.9 ± 2.2</td>
<td>6.0 ± 2.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>96.4 ± 38.0</td>
<td>137.2 ± 44.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dl)</td>
<td>61.5 ± 118.0</td>
<td>56.4 ± 13.0</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>hs-CRP (mg/L)</td>
<td>1.5 (1.0 to 3.2)</td>
<td>4.4 (2.4 to 9.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IL-6 (pg/ml)</td>
<td>2.39 (1.1 to 4.1)</td>
<td>4.8 (2.9 to 9.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IL-1$\beta$ (pg/ml)</td>
<td>1.3 ± 0.5</td>
<td>1.3 ± 0.6</td>
<td>NS</td>
</tr>
<tr>
<td>TNF-$\alpha$ (pg/ml)</td>
<td>5.07 ± 2.7</td>
<td>8.2 ± 3.6</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Leptin (ng/ml)</td>
<td>20.0 (12.0 to 57.0)</td>
<td>19.0 (10.0 to 66.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Adiponectin (mg/L)</td>
<td>13.9 (10.0 to 23.0)</td>
<td>14.2 (10.0 to 25.0)</td>
<td>NS</td>
</tr>
</tbody>
</table>

*BMI, body mass index; CKD, chronic kidney disease; HOMA-IR, Homeostasis Model Assessment of Insulin Resistance; hs-CRP, high-sensitivity C-reactive protein.*
glycated hemoglobin (Table 2). The percentage of patients with fasting glucose <110 mg/dl increased after treatment (before treatment 73%; after treatment 92%). On the basis of the definition for MS by the National Heart, Lung, and Blood Institute and the American Heart Association report (21), the fasting plasma glucose threshold is recommended to be lowered to ≤100 mg/dl. The percentage of patients with fasting glucose <100 mg/dl increased from 60% at baseline to 73% at 4 mo of therapy with olmesartan. The percentage of patients with IR (HOMA index >3.8 µU/ml × mmol/L) at baseline, 79%, decreased after olmesartan treatment, to 56%.

During olmesartan treatment, there was a significant reduction of CRP levels, from 4.45 mg/L (2.45 to 9) to 3.55 mg/L (1.8 to 5.4) and fibrinogen (412 ± 100 versus 370 ± 105 mg/dl; P < 0.05) without significant changes in other inflammatory biomarkers. There were no significant differences after olmesartan treatment in BMI, triglycerides, and HDL and LDL cholesterol, and no changes in adipokine levels were observed after olmesartan therapy (Table 2).

**Discussion**

The present data confirmed previous studies that showed a high prevalence of IR (79%) and MS (44%) in patients with renal disease (1,2,6,7) as they also presented other metabolic alterations, including abdominal obesity, glucose intolerance, hypertriglyceridemia, and low levels of HDL cholesterol. This high prevalence can be explained by the close relationship between CKD and MS/IR syndrome because not only does impaired renal function contribute to the development of IR (7), but also IR and concomitant hyperinsulinemia may contribute to CKD progression (2,6) and CVD in patients with renal dysfunction (5,27–29). In addition and confirming previous results, the present study shows that CKD is associated with an inflammatory state, because the patients presented high levels of inflammatory biomarkers (30,31). This inflammatory state also could explain the high incidence of atherosclerotic complications in patients with CKD because atherosclerosis is considered a chronic vascular inflammatory disorder (32). Although in comparison with healthy control subjects with normal renal function, no changes were observed in the median plasma levels of adipokines (leptin or adiponectin) considering the whole group of patients with CKD, however, patients with stage 4 CKD (eGFR <30>15 ml/min) had significant higher adiponectin levels than control subjects with normal renal function. Markedly increased levels of adiponectin have been found in patients with ESRD (27); although the reason that adiponectin levels are increased in patients with severe CKD is not evident, our data also support the observation that kidneys seem to play a role in the biodegradation and elimination of adiponectin (27).

Recent data indicated that fat itself, particularly in the abdomen, is a source of cytokines that produce endothelial damage (16) and that favors and perpetuates IR. Leptin, released by adipocytes, has an anorectic effect and modulates energy expenditure. It plays an important role in insulin sensitivity and in the development of arterial hypertension that is associated with obesity and MS (17). In the present study, no increase in leptin levels was found in patients with moderate CKD in relation to normal control subjects. Adiponectin, a protein that is secreted exclusively by adipocytes and implicated in atherosclerosis and IR pathogenesis, has raised considerable interest recently. It has been demonstrated that this protein has effects on monocyte adhesion to endothelium, cytokine production by macrophages, and several processes that are related to atherosclerotic plaque formation (6), and its action would be insulin sensitizing and antiatherogenic (14). In human studies, plasma adiponectin levels are negatively correlated with obesity and waist-to-hip ratio, IR (15), and CVD (16,18,27). It was demonstrated recently that in the earliest stages of kidney diseases, even before GFR is decreased, low blood adiponectin levels are associated with cardiovascular events. Blood adiponectin levels in our patients with moderate renal failure showed not to be significantly different from those of control subjects with normal renal function. However, patients with more renal insufficiency, stage 4 CKD, had higher adiponectin plasma levels, supporting the observation that kidneys seem to play a role in the biodegradation and elimination of adiponectin (27).
In agreement with data that were obtained in patients with obesity and type 2 diabetes (15,16), the present study shows that patients with CKD and MS have lower levels of adiponectin and higher levels of leptin compared with patients without MS. In addition, leptin is tightly positively correlated with abdominal obesity, insulin levels, and IL-6, and adiponectin was negatively related to abdominal obesity and insulin levels. It is suggested that these metabolic alterations in patients with CKD may favor arterial thrombotic/inflammatory complications, because it was proposed recently that hyperadiponectinemia is a novel putative cardiovascular risk factor in patients with mild and moderate renal failure (21). However, this relation is shifted upward in patients with severe CKD, who present with increased levels of adiponectin, suggesting that other factors may play a role in the regulation of plasma concentration of adipokines in renal failure (27).

As expected, the present data show that treatment with olmesartan in patients with moderate renal failure reduced not only arterial pressure but also proteinuria, which are widely recognized risk factors of cardiovascular and renal damage progression. In addition, it improved glucose sensitivity. These data confirmed previous observations in humans and experimental animals without renal disease that showed that RAS blockers are able to ameliorate the metabolic adverse effects that are observed in MS (33–38). However, to our knowledge, this is the first study to analyze the effect of ARB on IR that is associated with kidney disease. We do not know whether this effect is shared by all ARB or is specific to olmesartan and independent of its angiotensin AT1 receptor–blocking activity (35).

Besides changes in hemodynamic forces, additional mechanisms could be involved in the beneficial effects of olmesartan on IR because not all of the antihypertensive drugs ameliorate insulin sensitivity (35,36): In fact, α blockers, ACEI, and angiotensin II receptors antagonists are the ones that have been shown to improve it. By contrast, diuretics and β blockers worsen insulin sensitivity. The mechanisms that are involved in this improvement in insulin sensitivity may include increase of blood flow and microcirculation in skeletal muscles and, thereby, enhancement of insulin and glucose delivery to the insulin-sensitive tissues, facilitating insulin signaling at the cellular level and improvement of insulin secretion by the β cells (37). One of these additional mechanisms could involve PPAR-γ (33,34) because it has been shown that AT1 receptor blockers also can exert a partial agonist activity on PPAR-γ and thereby improve insulin signaling.

This improvement in insulin sensitivity that is achieved with RAS blockers (37) has been related to a decrease incidence of new-onset type 2 diabetes. In a recent meta-analysis of the randomized, controlled, clinical trials using ACEI or ARB to prevent new-onset type 2 diabetes as a primary or secondary end point, it was concluded that ACEI and ARB have a significant ability to reduce the occurrence of new-onset type 2 diabetes among patients with hypertension, coronary artery disease, and heart failure (39).

In the present study, olmesartan was able to reduce inflammatory parameters such as hs-CRP and fibrinogen, as has been reported in patients with essential hypertension (22). However, we were not able to demonstrate any significant effect of olmesartan on other inflammatory biomarkers in patients with CKD as had been observed already in hypertensive patients with normal or slightly reduced renal function (22). Blockade of the renin-angiotensin-aldosterone system in hypertensive patients should result in reduced inflammatory markers, and patients who are treated with angiotensin type 1 receptor blockers present diminished plasma concentrations of systemic markers of oxidative stress as well as of TNF-α (40). In a recent study, angiotensin type 1 receptor blockers seemed to exert stronger systemic anti-inflammatory effects than ACEI (41). The underlying mechanisms of increased levels of inflammatory biomarkers and their changes in response to angiotensin blockade in hypertensive patients are not fully understood. It has been proposed that elevated concentrations of CRP are mediated by cytokines that are produced in adipose tissue (42). Although we demonstrated a tight relationship between leptin and IL-6, that adipokine levels were unrelated to CRP and other inflammatory biomarkers and the lack of effect of olmesartan on adipokine levels despite the reduction that was observed in CRP concentration do not favor this hypothesis. Whether this lack of effect of olmesartan on inflammatory cytokines and adipokines is a consequence of the patient’s characteristics, time or duration of treatment, or dosage is not possible to know at this time.
Table 2. Clinical and laboratory characteristics of patients with CKD, before and after treatment with olmesartan (40 mg/d)\textsuperscript{a}

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Baseline</th>
<th>After Olmesartan</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg/m\textsuperscript{2})</td>
<td>28.9 ± 4.8</td>
<td>28.9 ± 4.5</td>
<td>NS</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>98.3 ± 12.8</td>
<td>97.7 ± 11.7</td>
<td>NS</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>158 ± 23</td>
<td>137 ± 21</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>84 ± 15</td>
<td>75 ± 9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>GFR (ml/min per 1.73 m\textsuperscript{2})</td>
<td>42 ± 17</td>
<td>39.8 ± 13.0</td>
<td>NS</td>
</tr>
<tr>
<td>Proteinuria (mg/24 h)</td>
<td>2.29 ± 2.04</td>
<td>1.21 ± 1.19\textsuperscript{c}</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Glucose (mg/dl)</td>
<td>99.2</td>
<td>100</td>
<td>0.05</td>
</tr>
<tr>
<td>Insulin (mU/L)</td>
<td>23.1 ± 8.8</td>
<td>19.9 ± 9.0</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>HOMA-IR index</td>
<td>6.0 ± 2.7</td>
<td>4.7 ± 2.8</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Glycated hemoglobin (%)</td>
<td>5.33 ± 0.58</td>
<td>4.8 ± 0.81</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dl)</td>
<td>56 ± 13</td>
<td>56 ± 12</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>137 ± 44</td>
<td>139 ± 49</td>
<td>NS</td>
</tr>
<tr>
<td>hs-CRP (mg/L)\textsuperscript{b}</td>
<td>4.45 (2.45 to 9.0)</td>
<td>3.55 (1.8 to 5.4)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>IL-6 (pg/ml)\textsuperscript{b}</td>
<td>4.8 (2.9 to 9.6)</td>
<td>4.5 (2.5 to 7.6)</td>
<td>NS</td>
</tr>
<tr>
<td>IL-1\beta (pg/ml)</td>
<td>1.3 ± 0.6</td>
<td>1.4 ± 0.4</td>
<td>NS</td>
</tr>
<tr>
<td>Fibrinogen (mg/dl)</td>
<td>412 ± 100</td>
<td>370 ± 105</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>TNF-\alpha (pg/ml)</td>
<td>8.2 ± 3.6</td>
<td>7.8 ± 3.2</td>
<td>NS</td>
</tr>
<tr>
<td>Leptin (mg/ml)\textsuperscript{b}</td>
<td>19.0 (10.0 to 66.0)</td>
<td>20.3 (10.2 to 53)</td>
<td>NS</td>
</tr>
<tr>
<td>Adiponectin (mg/L)\textsuperscript{b}</td>
<td>14.2 (10.0 to 25.0)</td>
<td>13.4 (8.9 to 25.0)</td>
<td>NS</td>
</tr>
</tbody>
</table>

\textsuperscript{a}DBP, diastolic BP; SBP, systolic BP.
\textsuperscript{b}Median (25th to 75th percentiles).
\textsuperscript{c}Data refer to 14 patients with proteinuria >300 mg/d at baseline.

**Conclusion**

Data that were revealed in the present study confirm the high prevalence of MS, hyperinsulinemia, and IR in patients with moderate CKD. This, together with the associated chronic inflammatory state, may contribute to an excess of cardiovascular risk described in these patients. Adipokines in patients with CKD are related, leptin positively and adiponectin negatively, to several metabolic risk factors. Treatment with the angiotensin receptor antagonist olmesartan improves glucose metabolism and insulin sensitivity and decreases some inflammatory parameters in these patients, but adipokine levels (leptin/adiponectin) are not modified by this treatment.

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