Renal Insulin Resistance Syndrome, Adiponectin and Cardiovascular Events in Patients with Kidney Disease: The Mild and Moderate Kidney Disease Study

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The relationship among insulin resistance, adiponectin, and cardiovascular (CV) morbidity in patients with mild and moderate kidney disease was investigated. Insulin sensitivity (Homeostasis Model Assessment of Insulin Resistance [HOMA-IR]) and adiponectin plasma levels were assessed in 227 nondiabetic renal patients at different degrees of renal dysfunction and in 76 healthy subjects of similar age and gender distribution and body mass index. In renal patients, association with prevalent CV events was evaluated, and incident CV events were evaluated in a prospective study. HOMA-IR was markedly higher in patients than in healthy subjects (3.59 ± 3.55 *versus* 1.39 ± 0.51; $P < 0.01$). In renal patients, HOMA-IR was significantly correlated with body mass index ($r = 0.477$; $P < 0.01$), triglycerides ($r = 0.384$; $P < 0.01$), adiponectin plasma levels ($r = -0.253$; $P < 0.01$), and age ($r = 0.164$; $P < 0.05$), but not with renal function (GFR by iod-thalamate clearance). Patients with previous CV events were significantly older, had higher HOMA-IR and serum triglycerides, and had lower adiponectin plasma levels (all $P < 0.05$). Logistic regression analysis revealed age ($P < 0.001$) and adiponectin ($P < 0.002$) as independent variables related to prevalent CV events. In the prospective study, median follow-up was 54 mo. Patients who experienced CV events had significantly higher serum glucose and lower adiponectin plasma levels (both $P < 0.05$). In patients with chronic kidney diseases, a syndrome of insulin resistance is present even in the earliest stage of renal dysfunction, and several components of this syndrome are associated with CV events. Moreover, hypoadiponectinemia is a novel putative CV risk factor in patients with mild and moderate renal failure.

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Experimental studies and studies in humans have revealed that the kidney is an important organ of glucose homeostasis (1–4). Diminished insulin-stimulated glucose uptake has been documented in uremic patients using the euglycemic clamp technique (5). Insulin resistance (IR) in renal patients is accompanied by hyperinsulinemia and glucose intolerance as well as by complex derangements of insulin secretion (6,7). Several explanations for the presence of IR in uremic patients have been proposed, such as deficiency of vitamin D, anemia, or putative uremic toxins (6,8,9). Results of recent small clinical studies have indicated that IR is present already in patients with mild degrees of renal dysfunction or even in patients with apparently normal renal function, *i.e.*, normal GFR (10–13). Thus, kidney disease *per se* seems to cause a syndrome of IR. An alternative or complementary explanation is suggested by the observation that in large population-based prospective studies, IR predicted chronic kidney disease (14). These findings did not attract much attention until a recent study indicated that IR is related to cardiovascular (CV) events in patients with terminal renal failure (15). For early renal failure, however, information on this point had not been available.

Adiponectin is a recently discovered adipokine that plays an important pathophysiologic role in patients with impaired glucose homeostasis (16,17). It is synthesized and secreted by adipose tissue and exhibits potent anti-inflammatory and antiatherosclerotic properties. Adiponectin is a component of a novel signaling network among adipocytes, insulin-sensitive tissues, and vasculature (16). Recently published prospective studies in a large male population with normal renal function and in patients with terminal renal failure revealed a significant relationship between adiponectin plasma levels and CV events (18,19). Such information had not been available for patients with mild to moderate renal failure, however.

To investigate IR further as well as adiponectin plasma levels in early phases of renal impairment, we assessed insulin sensitivity evaluating the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) and other metabolic variables in 227

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nondiabetic patients with mild and moderate kidney disease. We also analyzed potential confounders of insulin sensitivity, particularly body mass index (BMI), renal function (GFR by iod-thalamate clearance), and antihypertensive treatment. In a multicenter study with a cross-sectional as well as a prospective design, we evaluated prevalent CV events as well as incident CV events during a 7-yr follow-up. We further assessed the correlation of such CV events with components of the IR syndrome, particularly with adiponectin, as well as with classical CV risk factors.

Materials and Methods

Participants and Protocol

We examined 227 white patients who had chronic kidney diseases and were between 18 and 65 yr of age. They were recruited from eight nephrology departments in Germany, Austria, and South Tirol as described earlier (20). The study was approved by the institutional Ethic Committees, and all participants gave written informed consent. They had stable renal function for at least 3 mo before the study, and none of them was treated with immunosuppressive agents, fish oil, or erythropoietin. Additional exclusion criteria were serum creatinine concentration >6 mg/dl, diabetes of any type, malignancy, liver or infectious disease, nephrotic syndrome (defined as daily proteinuria >3.5 g/1.73 m^2), organ transplantation, allergy to ionic contrast media, and pregnancy.

For avoiding interobserver differences, all patients were recruited by one physician who visited all participating centers. Patient history, including smoking habits, CV events, and antihypertensive treatment at baseline, was recorded by interview and confirmed by checking patient records. CV events were defined as myocardial infarction, aortocoronary bypass, percutaneous transluminal coronary angioplasty, angiographically verified stenosis of the coronary arteries, stroke, or a symptomatic stenosis of the peripheral arterial vessels (carotis, aorto-iliac, or femoral arteries). This was complemented by clinical examination, including assessment of BMI and BP. Hypertension was defined as BP >140/90 mmHg and/or antihypertensive medication. We also calculated pulse pressure as the difference between systolic and diastolic BP. Blood samples for measurement of routine chemistry, insulin, intact parathyroid hormone, high-sensitivity C-reactive protein (hsCRP), and adiponectin levels were taken after an overnight fast of at least 12 h. The samples were centrifuged immediately at 1500 × *g* and 4°C for 10 min, and the supernatants were stored in aliquots at −80°C until further use. In addition, GFR was assessed in all patients using the iod-thalamate clearance technique as described in detail elsewhere (20,21). Antihypertensive drugs (if present) were withheld on the day of the study to minimize interference with measurements of GFR. The primary cause of kidney disease was glomerulonephritis in 97 patients (biopsy confirmed in 90 patients), adult polycystic kidney disease in 37 patients, interstitial nephritis in 24 patients, other types of kidney disease in 43 patients, and unknown in 26 patients. For comparison, 76 healthy subjects of the same ethnic origin who were frequency-matched with respect to age, gender, and BMI were studied as well.

After the baseline investigation was completed, we followed the primary cohort of 227 patients in a prospective study, and we recorded all CV events in this period, *e.g.*, fatal and nonfatal myocardial infarction, aorto-coronary bypass, percutaneous transluminal coronary angioplasty, fatal and nonfatal stroke. The individual follow-up was terminated once a patient reached terminal renal failure that necessitated renal replacement therapy or the end of the observation period in 2003.

Measurements and Calculations

Plasma insulin concentrations were measured immunoenzymatically using an (ELISA with monoclonal insulin antibodies. The intra-assay and interassay coefficients of variation were 5.2 and 7.5%, respectively. Parathyroid hormone was measured with an immunoradiometric assay, and adiponectin plasma concentrations were measured with an ELISA (R&D Systems, Minneapolis, MN). All other measurements, including hsCRP, were performed using routine laboratory tests and certified methods. Insulin sensitivity was quantified using HOMA-IR: [plasma insulin (mU/L) × plasma glucose (mg/dl) − 405] (22). The results of the HOMA-IR index have been shown to correlate closely with those of the euglycemic clamp technique, and HOMA-IR has been used successfully for evaluation of insulin sensitivity in large studies that have examined different populations (14,23,24).

Statistical Analyses

Statistical analysis was performed with SPSS for Windows 12.01. Univariate comparisons of continuous variables between various groups were done by unpaired *t* test or the nonparametric Wilcoxon rank sum test in case of nonnormally distributed variables. Dichotomized variables were compared using Pearson χ^2 test. Correction for multiple comparisons was done when appropriate. Differences were considered as significant at $P < 0.05$. Data are presented as mean ± SD or as median and interquartile range for skewed variables. Furthermore, univariate correlation analysis was performed by Spearman correlation analysis. In addition, we assessed independent variables associated with CV events in the baseline cohort of renal patients using stepwise logistic regression analysis.

Results

HOMA-IR and Adiponectin in Renal Patients

Insulin sensitivity was lower, *i.e.*, HOMA-IR was significantly higher, in patients with kidney disease at study entry than in age-, gender-, and BMI-matched healthy subjects (Table 1). In parallel, the fasting plasma insulin concentration was significantly higher in renal patients compared with healthy subjects, reflecting concomitant hyperinsulinemia. Furthermore, serum total cholesterol concentration, triglycerides, and hsCRP were significantly higher in renal patients as compared with healthy control subjects. Adiponectin plasma levels were numerically lower in renal patients as compared with healthy control subjects, but the difference was NS (Table 1). Both systolic and diastolic BP values were significantly higher in renal patients. Antihypertensive drugs were taken by 179 (79%) patients: Diuretics ($n = 83$; 37%), angiotensin-converting enzyme inhibitors ($n = 123$; 54%), calcium channel blockers ($n = 78$; 34%), β receptor blockers ($n = 67$; 30%), and α-1 receptor blockers ($n = 36$; 16%). Patients who were taking antihypertensive drugs at baseline had significantly higher HOMA-IR (3.93 ± 3.91 *versus* 2.29 ± 0.77), serum glucose (100 ± 17 *versus* 91 ± 11 mg/dl), and insulin (14.8 ± 10.5 *versus* 10.3 ± 3.4 mU/L) concentrations than patients without antihypertensives (all $P < 0.01$). However, even patients without antihypertensive treatment had significantly higher HOMA-IR and serum glucose and insulin levels when compared with data of healthy control subjects (all $P < 0.01$; Table 1). Particularly the use of diuretics was associated with higher HOMA-IR (4.66 ± 5.08 *versus* 2.96 ± 1.95), serum glucose (103 ± 19 *versus* 95 ± 14 mg/dl), and insulin (16.9 ± 13.0 *versus* 12.2 ± 6.3 mU/L)

Table 1. Clinical and laboratory data of healthy subjects and patients with kidney diseases[a]

	Healthy Subjects (n = 76)	Renal Patients (n = 227)
Gender (male/female [%])	51/25 (67/33)	154/73 (68/32)
Age (yr)	44.3 ± 13.0	45.7 ± 12.6
Body mass index (kg/m^2)	24.9 ± 2.9	25.2 ± 3.8
Serum creatinine (mg/dl)	0.92 (0.87 to 1.00)	1.61 (1.21 to 2.37)[b]
GFR (ml/min per 1.73 m^2)	—	63 (38 to 96)
Proteinuria (g/24 h per 1.73 m^2)	—	0.52 (0.18 to 1.42)
Intact parathyroid hormone (pmol/L)	4.1 (3.0 to 5.0)	6.0 (3.7 to 13.0)[b]
High-sensitivity C-reactive protein (mg/L)	0.91 (0.22 to 1.84)	1.50 (0.70 to 3.90)[b]
Systolic BP (mmHg)	123 ± 10	137 ± 21[b]
Diastolic BP (mmHg)	75 ± 7	87 ± 14[b]
Pulse pressure (mmHg)	48 ± 7	51 ± 15
Insulin (mU/L)	6.5 ± 2.3	13.9 ± 9.6[b]
Glucose (mg/dl)	86 ± 7	98 ± 17[b]
HOMA-IR index	1.39 ± 0.51	3.59 ± 3.55[b]
Adiponectin (μg/ml)	6.6 ± 2.8	6.1 ± 4.2
Total cholesterol (mg/dl)	191 ± 33	215 ± 45[c]
LDL cholesterol (mg/dl)	127 ± 26	136 ± 40
Triglycerides (mg/dl)	94 (74 to 124)	144 (101 to 223)[b]

[a]HOMA-IR, Homeostasis Model Assessment of Insulin Resistance.
[b]$P < 0.01$, healthy subjects *versus* renal patients.
[c]$P < 0.05$, healthy subjects *versus* renal patients.

compared with patients without diuretic treatment (all $P < 0.01$). Patients who were taking diuretics also had significantly higher BMI (26.6 ± 4.3 *versus* 24.3 ± 3.2 kg/m^2; $P < 0.01$) and more advanced renal failure (*i.e.*, lower GFR [55 ± 30 *versus* 78 ± 45 ml/min per 1.73 m^2; $P < 0.01$]).

In renal patients, HOMA-IR was significantly correlated with BMI ($r = 0.477$; $P < 0.01$), triglycerides ($r = 0.384$; $P < 0.01$), adiponectin blood levels ($r = -0.253$; $P < 0.01$), and age ($r = 0.164$; $P < 0.05$) but not with hsCRP ($r = 0.127$; $P = 0.06$) or GFR ($r = 0.007$; $P = 0.92$). To elucidate further the relationship between GFR and glucose metabolism, we stratified renal patients into three approximately equally large groups according to GFR—GFR >90, GFR between 45 and 90, and GFR <45 ml/min per 1.73 m^2—as done previously (20). Mean HOMA-IR and serum glucose and insulin concentrations did not differ significantly among the three groups of renal patients (Figure 1). However, it was significantly higher in all groups of patients as compared with healthy subjects, indicating marked insulin resistance in renal patients even when GFR is still normal. In contrast to HOMA-IR, adiponectin blood concentrations showed a significant inverse correlation with GFR ($r = -0.256$; $P < 0.01$). Furthermore, adiponectin plasma concentrations were significantly correlated with BMI ($r = -0.134$; $P < 0.05$), serum triglyceride ($r = -0.153$; $P < 0.05$), insulin ($r = -0.233$; $P < 0.01$), and glucose ($r = -0.168$; $P < 0.05$) levels but not with age ($r = 0.096$; $P = 0.15$), systolic ($r = -0.020$; $P = 0.77$) and diastolic ($r = 0.002$; $P = 0.98$) BP, or proteinuria ($r = 0.126$; $P = 0.058$).

CV Disease in Renal Patients at Study Entry

Table 2 presents data of renal patients with and without previous CV events at study entry. Patients who had experienced CV events in the past were predominantly male, were significantly older, and had significantly higher HOMA-IR and fasting serum insulin and triglyceride levels. In addition, they had markedly lower adiponectin plasma levels (Figure 2), and almost all took antihypertensive drugs. When we offered those variables to a stepwise logistic regression analysis, only age (odds ratio: 1.11; 95% confidence interval, 1.05 to 1.17; $P < 0.001$) and adiponectin plasma levels (odds ratio, 0.72; 95% confidence interval, 0.58 to 0.89; $P = 0.002$) were identified as predictors of prevalent CV events.

CV Disease during the Prospective Observation Period

A total of 177 (78%) patients from the baseline cohort could be assessed during the follow-up. Patients who were lost to follow-up ($n = 50$) had significantly better renal function than patients who were not lost for follow-up, *i.e.*, a higher mean GFR (91 ± 44 *versus* 64 ± 39 ml/min per 1.73 m^2; $P < 0.01$). Both groups did not differ significantly with respect to age, gender, HOMA-IR, and previous CV events (6 of 50 [12%] *versus* 22 of 177 [12%]), however. Patients who were lost to follow-up had moved away or were not referred by their private physicians for follow-up controls in the renal units. The median follow-up after completion of the baseline investigation was 54 mo (range, 1–82 mo), and during this follow-up, 29 patients reached terminal renal failure that necessitated renal

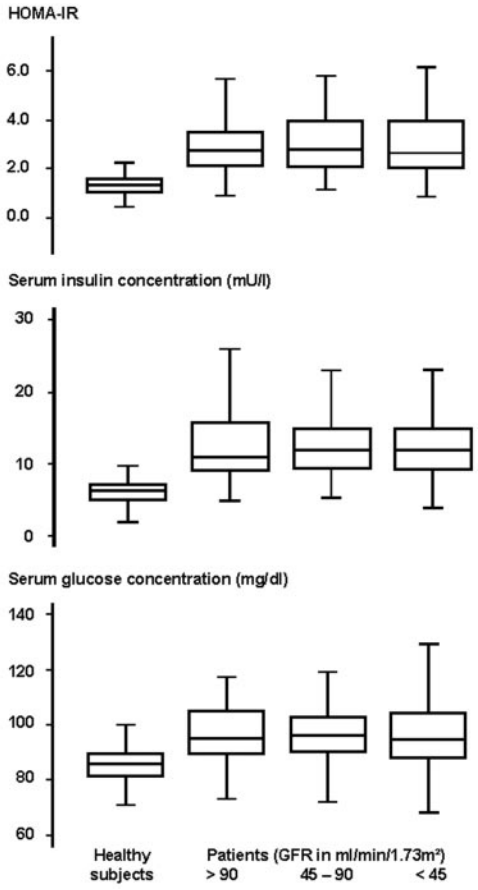

Figure 1. Boxplots of Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) and serum insulin and glucose concentrations in renal patients with GFR >90 ml/min per 1.73 m^2 ($n = 73$; GFR 119 ± 28 ml/min per 1.73 m^2), GFR between 45 and 90 ml/min per 1.73 m^2 ($n = 77$; GFR 65 ± 13 ml/min per 1.73 m^2), and GFR <45 ml/min per 1.73 m^2 ($n = 77$; GFR 28 ± 11 ml/min per 1.73 m^2). Mean HOMA-IR and serum insulin and glucose concentrations did not differ significantly among the three groups of renal patients but were significantly higher in all three groups as compared with healthy subjects ($P < 0.01$ by ANOVA).

replacement therapy. Five patients died during the follow-up period, none of them as a result of a fatal CV event, whereas 10 patients experienced a nonfatal CV event. Table 3 summarizes data in patients with and without CV events during the follow-up period. Patients with CV events were predominantly older men, who had significantly higher fasting serum glucose concentrations (*i.e.*, hyperglycemia) and pulse pressure. In addition, they had significantly lower adiponectin plasma levels (Figure 3).

Discussion

Mild and Moderate Impairment of Kidney Function: A Status of IR

The salient baseline finding of this study, comprising a large number of nondiabetic white patients with various kidney diseases, is the demonstration that kidney disease is accompanied by IR and other features of the classical metabolic syndrome, even when measured GFR is still within the normal range. Fasting blood glucose concentrations were considerably increased and significantly higher in renal patients than in healthy subjects. In a smaller cohort, we had previously documented that glucose intolerance is also a prominent component of this "renal insulin resistance syndrome" (11). Moreover, as in prediabetic patients with the metabolic syndrome, IR in renal patients is closely correlated with a higher BMI and increased triglyceride levels (25–28). The association of higher BMI, IR, hyperglycemia, and hypertriglyceridemia in patients with kidney disease is of interest because it suggests that this deleterious combination explains, at least in part, the excessive CV risk of renal patients. In line with this assumption is the observation that even mild hyperglycemia (*i.e.*, a serum glucose concentration in the upper normal range) contributes to atherosclerosis in apparently healthy subjects, particularly when associated with obesity and hypertension (27). Moreover, the presence of renal dysfunction *per se* has recently been recognized as an independent CV risk factor, and derangements of glucose metabolism associated with kidney disease may explain in part the increased CV risk associated with renal dysfunction, even in the absence of frank diabetes (29). Because our results demonstrate that IR is present even in renal patients who are matched with respect to BMI to healthy subjects, overweight seems to be only a factor aggravating an underlying metabolic disorder. We have examined only white patients with kidney diseases; studies in other populations such as black or Hispanic patients are necessary to clarify whether the results are generalizable to other ethnicities before general conclusions on the role of IR in kidney disease can be made. All participants were examined by a single investigator, contributing to the homogeneity of the data set obtained.

We found a significant correlation between IR on the one hand and the use of antihypertensive drugs on the other hand in our baseline cohort. Particularly, the use of diuretics was associated with hyperinsulinemia, hyperglycemia, and increased HOMA-IR in renal patients. This finding is reminiscent to results of intervention studies with (higher dose) diuretic treatment in patients with essential hypertension (30) and could result from a "diabetogenic" action of diuretics in renal patients as well. Despite the limitations of the cross-sectional nature of the analysis, our finding supports the notion that diuretics may aggravate preexisting IR in renal patients, particularly when high doses are administered. An alternative explanation could be that the need for aggressive antihypertensive (diuretic) treatment is highest in patients in whom the renal IR syndrome is most pronounced. This speculation would be in line with the finding of a significantly higher BMI in patients who are on diuretic treatment. Progressive kidney disease inevitably leads to "salt sensitive" hypertension as a result of reduced nephron mass, inappropriate activity of the renin-angiotensin system, and increased sympathetic activity. Hyperinsulinemia could conceivably contribute to the increase in BP, *e.g.*, via the antinatriuretic action of insulin (31). Insulin sensitivity, as documented by an increased HOMA-IR, was diminished even in patients whose GFR was still within the normal range. We had

Table 2. Clinical and laboratory data of renal patients with and without previous CV events from the baseline cohort[a]

	CV Events (n = 28)	No CV Events (n = 199)
Gender (male/female [%])	24/4 (86/14)	130/69[b] (65/35)
Age (yr)	53.7 ± 6.5	44.5 ± 12.8[c]
Body mass index (kg/m²)	25.8 ± 4.0	25.1 ± 3.8
Current smoker (n)	5 (18%)	51 (26%)
Past smoker (n)	10 (36%)	47 (24%)
Serum creatinine (mg/dl)	1.76 (1.40 to 2.59)	1.60 (1.20 to 2.36)
GFR (ml/min per 1.73 m²)	53 (33 to 78)	64 (39 to 98)
Proteinuria (g/24 h per 1.73 m²)	0.58 (0.09 to 1.72)	0.56 (0.18 to 1.37)
High-sensitivity C-reactive protein (mg/L)	1.90 (0.90 to 4.70)	1.40 (0.60 to 3.90)
Intact parathyroid hormone (pmol/L)	9.2 (4.7 to 18.0)	5.7 (3.5 to 13.0)
Use of antihypertensive drugs (n)	27 (96%)	152 (76%)[b]
Systolic BP (mmHg)	138 ± 21	137 ± 21
Diastolic BP (mmHg)	86 ± 15	87 ± 14
Pulse pressure (mmHg)	52 ± 16	51 ± 15
Insulin (mU/L)	17.4 ± 18.9	13.4 ± 7.5[b]
Glucose (mg/dl)	100 ± 20	98 ± 16
HOMA-IR	5.12 ± 7.82	3.38 ± 2.49[b]
Adiponectin (μg/ml)	4.1 ± 1.8	6.4 ± 4.4[c]
Total cholesterol (mg/dl)	216 ± 48	214 ± 45
LDL cholesterol (mg/dl)	134 ± 49	137 ± 39
Triglycerides (mg/dl)	171 (114 to 332)	139 (98 to 213)[c]

[a]CV, cardiovascular.
[b]$P < 0.05$, patients with and without previous CV events.
[c]$P < 0.01$, patients with and without previous CV events.

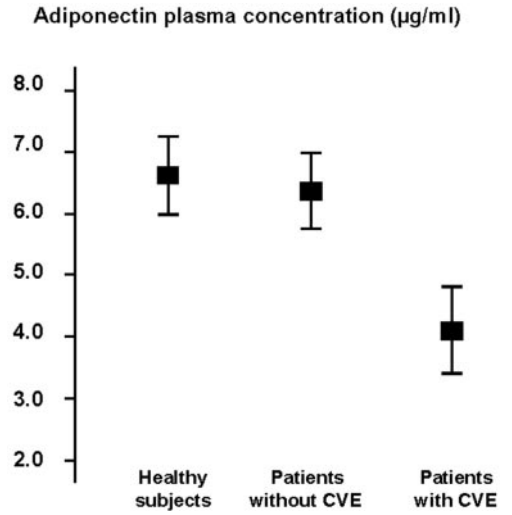

Figure 2. Adiponectin plasma concentrations in healthy subjects (n = 76) and in renal patients with (n = 28) and without (n = 199) cardiovascular events (CVE) at study entry. Mean adiponectin plasma concentration was significantly lower in renal patients with previous CVE as compared with healthy subjects and patients without previous CVE (both $P < 0.05$ by ANOVA). Data are presented as 95% confidence intervals of the mean.

previously argued, however, that because of single nephron hyperfiltration, whole-kidney GFR may not adequately reflect nephron loss (12). Furthermore, HOMA-IR was not correlated with renal function across a wide range of diminished GFR values. We also did not find a significant correlation between IR and complications of uremia such as anemia and secondary hyperparathyroidism (data not shown), although these conditions are associated with diminished glucose metabolism in patients with terminal renal failure (6,8,9).

In contrast to results in patients with type 2 diabetes (17), we found only a weak correlation between BMI or triglycerides with adiponectin plasma concentrations. In patients with the nephrotic syndrome, adiponectin plasma levels were found to be significantly higher than in nonnephrotic patients with kidney disease (32). In our patients with urinary protein excretion below the nephrotic range, we found only a marginal correlation between proteinuria and adiponectin plasma levels. However, we found significantly higher adiponectin plasma levels in 27 patients who had nephrotic syndrome and were not included in this study (10.8 ± 5.5 *versus* 6.1 ± 4.0 μg/ml in nonnephrotic patients included in this study; $P < 0.01$).

The results of this study in a sizable cohort of patients with kidney diseases confirm previous observations in smaller populations using different methodologic approaches (11–13). They clearly support the notion that kidney disease is associated with IR, hyperinsulinemia, and hyperglycemia and further under-

Table 3. Clinical and laboratory data of renal patients with and without CV events during follow-up

	CV Events (n = 10)	No CV Events (n = 167)
Gender (male/female [%])	9/1 (90/10)	109/58 (65/35)
Age (yr)	53.5 ± 7.1	45.9 ± 12.3
Body mass index (kg/m²)	26.1 ± 1.6	25.1 ± 3.8
Current smoker (n)	1 (10%)	33 (20%)
Past smoker (n)	1 (10%)	43 (19%)
Previous CV event	2 (20%)	20 (26%)
Serum creatinine (mg/dl)	1.96 (1.39 to 2.88)	1.70 (1.22 to 2.76)
GFR (ml/min per 1.73 m²)	39 (32 to 60)	57 (37 to 90)
Proteinuria (g/24 h per 1.73 m²)	0.30 (0.09 to 2.19)	0.72 (0.21 to 1.55)
High sensitivity C-reactive protein (mg/L)	1.10 (0.90 to 1.51)	1.70 (0.70 to 4.00)
Intact parathyroid hormone (pmol/L)	7.1 (5.9 to 15.6)	6.5 (3.9 to 15.3)
Systolic BP (mmHg)	148 ± 24	136 ± 20
Diastolic BP (mmHg)	89 ± 13	86 ± 13
Pulse pressure (mmHg)	59 ± 22	50 ± 15[a]
Use of antihypertensive drugs (n)	10 (100%)	133 (80%)
Insulin (mU/L)	14.1 ± 6.5	13.5 ± 9.9
Glucose (mg/dl)	110 ± 25	97 ± 15[b]
HOMA-IR	4.02 ± 2.86	3.43 ± 3.56
Adiponectin (μg/ml)	3.0 ± 1.3	6.5 ± 4.5[a]
Total cholesterol (mg/dl)	215 ± 33	216 ± 44
LDL cholesterol (mg/dl)	137 ± 29	138 ± 39
Triglycerides (mg/dl)	157 (106 to 286)	144 (104 to 221)

[a] $P < 0.05$, patients with and without CV events.
[b] $P < 0.01$, patients with and without CV events.

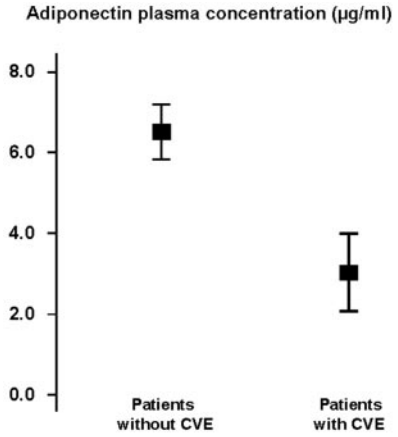

Figure 3. Adiponectin plasma concentrations in renal patients with (n = 10) and without (n = 167) CVE during follow-up. Mean adiponectin plasma concentration was significantly lower in renal patients with incident CVE as compared with patients without CVE. Data are presented as 95% confidence intervals of the mean.

line the currently not widely appreciated role of the kidney in glucose homeostasis (1–4,33). The important role of the kidney in glucose metabolism is well illustrated by the recent publication of Battezzati *et al.* (33); in anhepatic patients before liver transplantation, the rate of extrahepatic gluconeogenesis was similar to that of postabsorptive healthy subjects, pointing to the kidney as a major source of extrahepatic glucose production. Moreover, the results of this study shed light on the recently well-documented role of renal dysfunction as an independent CV risk factor in individuals without primary kidney diseases (29,34). Patients who had a history of nonfatal CV events not only were significantly older and predominantly male but also had significantly higher fasting insulin blood levels and HOMA-IR as a reflection of more severe IR as also seen in patients with the classical metabolic syndrome (25). In this context, the observation of a higher frequency of hypertension (and possibly of a metabolic syndrome) in families of patients with IgA glomerulonephritis is of definite interest (35).

IR and Adiponectin: Association with CV Disease

Components of the IR syndrome not only were associated with CV risk at baseline but also were significantly related to CV events during follow-up. In patients who experienced CV events during follow-up, hyperglycemia was present at study entry. In addition, they had markedly lower adiponectin plasma concentrations similar to the recent observations in a large male population with normal renal function (18) and in patients with terminal renal failure (19). The observation is remarkable, because in contrast to patients with terminal renal failure, baseline adiponectin levels were not significantly higher as compared with healthy subjects. We found a significant negative correlation between GFR and adiponectin plasma

levels, however, supporting the observation that adiponectin plasma concentrations increase in renal failure (19,36). Moreover, we found significantly lower adiponectin plasma levels in patients with prevalent as well as incident CV events. These results strongly support the notion that adiponectin is a vasoprotective factor and that in patients with mild to moderate renal dysfunction, hypoadiponectinemia is a CV risk factor, similar as in patients with the classical metabolic syndrome (16,37). We have to admit that because of the limited number of definite CV events during follow-up in our renal patients, the results obtained in the prospective part of the study have an explorative character and have to be confirmed in larger trials.

With respect to some classical CV risk indicators, our results on CV events in renal patients differ to some extent from findings in other populations. In contrast to some studies in the classical metabolic syndrome, serum hsCRP concentration as a putative indicator of microinflammation was not associated with CV events in patients with mild to moderate renal dysfunction (25,28). Furthermore, self-reported smoking was not a predictor of CV events. The percentage of current smokers among our patients was similar to the local population.

In conclusion, a syndrome of IR is present in the earliest stages of kidney disease even before GFR is decreased. In renal patients, IR is associated with low adiponectin blood levels similar to what is found in patients with the metabolic syndrome (16,17). In the latter, the link between IR and related metabolic derangements, and CV morbidity and mortality has been well documented (25). The results of this study suggest that this relationship also holds true in patients with mild and moderate renal dysfunction. In addition, hypoadiponectinemia is a novel putative CV risk factor in patients with early stages of chronic kidney disease.

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References

1. Wirthensohn G, Guder WG: Renal substrate metabolism. *Physiol Rev* 66: 469–497, 1986
2. Stumvoll M, Chintalapudi U, Perriello G, Welle S, Gutierrez O, Gerich J: Uptake and release of glucose by the human kidney. Postabsorptive rates and responses to epinephrine. *J Clin Invest* 96: 2528–2533, 1995
3. Cersosimo E, Garlick P, Ferretti J: Insulin regulation of renal glucose metabolism in humans. *Am J Physiol* 276: E78–E84, 1999
4. Meyer C, Stumvoll M, Dostou J, Welle S, Haymond M, Gerich J: Renal substrate exchange and gluconeogenesis in normal postabsorptive humans. *Am J Physiol* 282: E428–E434, 2002
5. DeFronzo RA, Alverstrand A, Smith D, Hendler R, Hendler E, Wahren J: Insulin resistance in uremia. *J Clin Invest* 67: 563–572, 1981
6. Alvestrand A: Carbohydrate and insulin metabolism in renal failure. *Kidney Int* 52[Suppl 62]: S48–S52, 1997
7. Feneberg R, Sparber M, Veldhuis JD, Mehls O, Ritz E, Schaefer F: Altered temporal organization of plasma insulin oscillations in chronic renal failure. *J Clin Endocrinol Metab* 87: 1965–1973, 2002
8. Kautzky-Willer A, Pacini G, Barnas U, Ludvik B, Streli C, Graf H, Prager R: Intravenous calcitriol normalizes insulin sensitivity in uremic patients. *Kidney Int* 47: 200–206, 1995
9. Spaia S, Pangalos M, Askepidis N, Pazarloglou M, Mavropoulou E, Theodoridis S, Dimitrakopoulos K, Milionis A, Vayonas G: Effect of short-term rHuEPO treatment on insulin resistance in haemodialysis patients. *Nephron* 84: 320–325, 2000
10. Eidemak I, Feldt-Rasmussen B: Kanstrup IL, Nielsen SL, Schmitz O, Strandgaard S: Insulin resistance and hyperinsulinemia in mild to moderate progressive chronic renal failure and its association with aerobic work capacity. *Diabetologia* 38: 565–572, 1995
11. Fliser D, Pacini G, Engelleiter R, Kautzky-Willer A, Franek E, Ritz E: Insulin resistance and hyperinsulinaemia are present already in patients with incipient renal disease. *Kidney Int* 53: 1243–1247, 1998
12. Vareesangthip K, Tong P, Wilkinson R, Thomas TH: Insulin resistance in adult polycystic kidney disease. *Kidney Int* 52: 503–508, 1997
13. Kato Y, Hayashi M, Ohno Y, Suzawa T, Sasaki T, Saruta T: Mild renal dysfunction is associated with insulin resistance in chronic glomerulonephritis. *Clin Nephrol* 54: 366–373, 2000
14. Chen J, Muntner P, Hamm LL, Fonseca V, Batuman V, Whelton PK, He J: Insulin resistance and risk of chronic kidney disease in nondiabetic US adults. *J Am Soc Nephrol* 14: 469–477, 2003
15. Shinohara K, Shoji T, Emoto M, Tahara H, Koyama H, Ishimura E, Miki T, Tabata T, Nishizawa Y: Insulin resistance as an independent predictor of cardiovascular mortality in patients with end-stage renal disease. *J Am Soc Nephrol* 13: 1894–1900, 2002
16. Goldstein BJ, Scalia R: Adiponectin: A novel adipokine linking adipocytes and vascular function. *J Clin Endocrinol Metab* 89: 2563–8256, 2004
17. Hotta K, Funahashi T, Arita Y, Takahashi M, Matsuda M, Okamoto Y, Iwahashi H, Kuriyama H, Ouchi N, Maeda K, Nishida M, Kihara S, Sakai N, Nakajima T, Hasegawa K, Muraguchi M, Ohmoto Y, Nakamura T, Yamashita S, Hanafusa T, Matsuzawa Y: Plasma concentrations of a novel, adipose-specific protein, adiponectin, in type 2 diabetic patients. *Arterioscler Thromb Vasc Biol* 20: 1595–1599, 2000
18. Pischon T, Girman CJ, Hotamisligil GS, Rifai N, Hu FB,

Rimm EB: Plasma adiponectin levels and risk of myocardial infarction in men. *JAMA* 291: 1730–1737, 2004
19. Zoccali C, Mallamaci F, Tripepi G, Benedetto FA, Cutrupi S, Parlongo S, Malatino LS, Bonanno G, Seminara G, Rapisarda F, Fatuzzo P, Buemi M, Nicocia G, Tanaka S, Ouchi N, Kihara S, Funahashi T, Matsuzawa Y: Adiponectin, metabolic risk factors, and cardiovascular events among patients with end-stage renal disease. *J Am Soc Nephrol* 13: 134–141, 2002
20. Kronenberg F, Kuen E, Ritz E, Konig P, Kraatz G, Lhotta K, Mann JF, Muller GA, Neyer U, Riegel W, Riegler P, Schwenger V, von Eckardstein A: Apolipoprotein A-IV serum concentrations are elevated in patients with mild and moderate renal failure. *J Am Soc Nephrol* 13: 461–469, 2002
21. Gaspari F, Perico N, Matalone M, Signorini O, Azzollini N, Mister M, Remuzzi G: Precision of plasma clearance of iohexol for estimation of GFR in patients with renal disease. *J Am Soc Nephrol* 9: 310–313, 1998
22. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC: Homeostasis model assessment: Insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 28: 412–419, 1985
23. Hanley AJ, Williams K, Stern MP, Haffner SM: Homeostasis model assessment of insulin resistance in relation to the incidence of cardiovascular disease: The San Antonio Heart Study. *Diabetes Care* 25: 1177–1184, 2002
24. Bonora E, Targher G, Alberiche M, Bonadonna RC, Saggiani F, Zenere MB, Monauni T, Muggeo M: Homeostasis model assessment closely mirrors the glucose clamp technique in the assessment of insulin sensitivity: Studies in subjects with various degrees of glucose tolerance and insulin sensitivity. *Diabetes Care* 23: 57–63, 2000
25. Reilly MP, Rader DJ: The metabolic syndrome: More than the sum of its parts? *Circulation* 108: 1546–1551, 2003
26. Body mass index and cardiovascular disease in the Asia-Pacific Region: An overview of 33 cohorts involving 310 000 participants. *Int J Epidemiol* 33: 751–758, 2004
27. Thomas GN, Chook P, Qiao M, Huang XS, Leong HC, Celermajer DS, Woo KS: Deleterious impact of "high normal" glucose levels and other metabolic syndrome components on arterial endothelial function and intima-media thickness in apparently healthy Chinese subjects: The CATHAY study. *Arterioscler Thromb Vasc Biol* 24: 739–743, 2004
28. Fruchart JC, Nierman MC, Stroes ES, Kastelein JJ, Duriez P: New risk factors for atherosclerosis and patient risk assessment. *Circulation* 109[Suppl 1]: III15–III19, 2004
29. Sarnak MJ, Levey AS, Schoolwerth AC, Coresh J, Culleton B, Hamm LL, McCullough PA, Kasiske BL, Kelepouris E, Klag MJ, Parfrey P, Pfeffer M, Raij L, Spinosa DJ, Wilson PW; American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention: Kidney disease as a risk factor for development of cardiovascular disease: A statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. *Circulation* 108: 2154–2169, 2003
30. Opie LH, Schall R: Old antihypertensives and new diabetes. *J Hypertens* 22: 1453–1458, 2004
31. Stenvinkel P, Ottosson-Seeberger A, Alvestrand A: Renal hemodynamics and sodium handling in moderate renal insufficiency: The role of insulin resistance and dyslipidemia. *J Am Soc Nephrol* 5: 1751–1760, 1995
32. Zoccali C, Mallamaci F, Panuccio V, Tripepi G, Cutrupi S, Parlongo S, Catalano F, Tanaka S, Ouchi N, Kihara S, Funahashi T, Matsuzawa Y: Adiponectin is markedly increased in patients with nephrotic syndrome and is related to metabolic risk factors. *Kidney Int Suppl* 84: S98–S102, 2003
33. Battezzati A, Caumo A, Martino F, Sereni LP, Coppa J, Romito R, Ammatuna M, Regalia E, Matthews DE, Mazzaferro V, Luzi L: Nonhepatic glucose production in humans. *Am J Physiol Endocrinol Metab* 286: E129–E135, 2004
34. Mann JFE, Gerstein HC, Dulau-Florea I, Lonn E: Cardiovascular risk in patients with mild renal insufficiency. *Kidney Int* 63[Suppl 84]: S192–S196, 2003
35. Schmid M, Meyer S, Wegner R, Ritz E: Increased genetic risk of hypertension in glomerulonephritis? *Hypertension* 8: 573–577, 1990
36. Stenvinkel P, Marchlewska A, Pecoits-Filho R, Heimburger O, Zhang Z, Hoff C, Holmes C, Axelsson J, Arvidsson S, Schalling M, Barany P, Lindholm B, Nordfors L: Adiponectin in renal disease: Relationship to phenotype and genetic variation in the gene encoding adiponectin. *Kidney Int* 65: 274–281, 2004
37. Tan KCB, Xu A, Chow WS, Lam MCW, Ai VHG, Tam SCF, Lam KSL: Hypoadiponectinemia is associated with impaired endothelium-dependent vasodilation. *J Clin Endocrinol Metab* 89: 765–769, 2004