Is Insulin Resistance a Risk Factor for the Progression of Chronic Kidney Disease?

Taner Bastürk^a Abdulkadir Unsal^b

^aDepartment of Nephrology, Bağcılar Education and Research Hospital, and ^bDepartment of Nephrology, Sisli Etfal Education and Research Hospital, Istanbul, Turkey

Key Words

Insulin resistance · Chronic kidney disease · Hypertension

Abstract

Background: The aim of this research was to establish whether there is a link between insulin resistance (IR) and glomerular filtration rate (GFR), and assess whether insulin-resistant subjects experience a more rapid deterioration in GFR. **Methods:** We enrolled 73 non-diabetic chronic kidney disease (CKD) stage 2–4 patients. All blood samples were taken after 10 h of overnight fasting. Fasting blood glucose (FBG), creatinine, uric acid, albumin, cholesterol, triglyceride, insulin, HbA1c, high-sensitivity C-reactive protein (hs-CRP) and intact parathyroid hormone (iPTH) levels as well as proteinuria were analyzed. Patients were followed up for a mean of 30 (24–35) months and renal and metabolic parameters were compared in conjunction with a homeostasis model assessment of IR (HOMA-IR) between the entry and the end of the study period. CKD progression was assessed by recording renal endpoints, which included end-stage renal disease, requiring renal replacement therapy, or overall mortality. **Results:** The study patients were divided into group 1 (n = 36), without IR, and group 2 (n = 37), with IR. Group 2 patients had a higher FBG (p = 0.003) and insulin level (p = 0.001) compared to group 1. The baseline and end of study systolic (p = 0.007) and diastolic (p = 0.001) blood pressures were decreased in group 1. In group 2, FBG (p = 0.008), HbA1c (p = 0.009), systolic (p = 0.024) and diastolic (p = 0.001) blood

pressures and CRP (p = 0.047) were decreased. In group 2, 8 patients reached renal endpoints while in group 1, 9 patients reached study endpoints. HOMA-IR was not significantly higher among 17 patients who reached the renal endpoint than among the 56 who did not. At baseline, those patients who reached the renal endpoint showed lower GFR (p = 0.001), higher iPTH (p = 0.004) and hs-CRP (p = 0.002) levels. **Conclusion:** There was no significant difference in GFR at the end of the study between patients who had or did not have IR. Furthermore, HOMA-IR was not significantly different in patients with or without renal endpoints.

Copyright © 2011 S. Karger AG, Basel

Introduction

Insulin resistance (IR) in advanced kidney disease has been well recognized since the seminal work by DeFronzo et al. [1] using hyperinsulinemic-euglycemic clamp techniques. IR as well as compensatory hyperinsulinemia are independently associated with an increased prevalence of chronic kidney disease (CKD) [1, 2]. Hyperinsulinemia has direct renal effects such as induced relaxation of the afferent arteriole, resulting in glomerular hyperfiltration and renal damage. There are many risk factors in the development of diabetic nephropathy. Non-glycemic factors, including genetic susceptibility, lipids and blood pressure, in the pathogenesis of diabetic nephropathy and IR play a central role [3]. High insulin levels stimulate an-

giogenesis and mesangial cell proliferation, associated with the development of diabetic nephropathy [4]. IR is thought to play a role in renal damage and kidney disease progression.

The aim of this study was to establish whether there is a link between IR and glomerular filtration rate (GFR), and assess whether insulin-resistant subjects experience a more rapid deterioration in GFR.

Methods

The study was performed in 73 patients with non-diabetic hypertensive CKD (stages 2–4), between June 2005 and September 2008. CKD patients were divided into two groups – those with and those without IR. The patients were followed up for a mean of 30 (24–35) months.

The exclusion criteria were age <18 or >75 years, secondary hypertension (disorders of the adrenal gland, including Cushing's syndrome, hyperaldosteronism and pheochromocytoma, drugs such as corticosteroids, non-steroidal anti-inflammatory drugs, sleep apnea, coarctation of the aorta, thyroid problems), diabetes mellitus, previous kidney transplantation, serious systemic disease (systemic lupus erythematosus, periarteritis nodosa, etc.), chronic infections, neoplastic diseases or kidney failure (estimated GFR <15 ml/min per 1.73 m²).

All blood samples were taken after 10 h of overnight fasting. Fasting blood glucose (FBG), serum creatinine, uric acid, albumin, total cholesterol, triglyceride (TG) insulin, HbA1c, C-reactive protein (hs-CRP) and iPTH levels as well as proteinuria were analyzed. At the same time, blood pressure, weight, and height were measured.

FBG, total cholesterol, TG and albumin were assessed by enzymatic colorimetric assay, serum creatinine by kinetic colorimetric assay, iPTH levels by solid-phase, two-site chemiluminescent enzyme immunoassay on an Immulite automatic analyzer, insulin levels by electrochemiluminescence immunoassay, and hs-CRP by nephelometric assay on an E170 analyzer.

Creatinine clearance was calculated using the Cockcroft-Gault formula: $C_{cr} \text{ (ml/min)} = (140 - \text{age}) \times \text{measured weight (kg)} / (\text{plasma Cr} \times 72)$. The obtained value was multiplied by 0.85 in women. Body mass index (BMI = weight (kg)/height (m)²) was obtained from height and weight measurements.

Hypertension was defined as systolic (SBP) and diastolic (DBP) blood pressures of ≥ 140 and ≥ 90 mm Hg, respectively, or the use of antihypertensive medications. SBP and DBP were the average of three measurements taken with a brachial sphygmomanometer with the patient in the seated position. Patients were accepted as impaired fasting glucose (IFG): $100 \leq \text{IFG} < 126$ mg/dl, according to the 1997 ADA definition.

Renal function was defined according to the National Kidney Foundation Kidney Disease Outcome Quality Initiative (K/DOQI) definitions [5], therefore CKDs were defined according to the presence or absence of kidney damage and level of kidney function. Kidney damage was defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies. Among individuals with CKD, the

stage was defined by the level of GFR (stages 1–5). Urinary proteinuria concentration was determined by an immunoturbidimetric method. Proteinuria was defined as ≥ 300 mg/day.

IR was assessed by a homeostasis model assessment of IR (HOMA-IR: $\text{FBG (mg/dl)} \times \text{fasting serum insulin level (}\mu\text{U/l)} / 22.5$) measured at the beginning of the study. In the present analysis, patients were stratified into two groups according to baseline HOMA-IR (≥ 2.5): group 1 had levels below the median of the cohort while group 2 had levels above the median. Patients were followed up for a mean of 30 (24–35) months and renal and metabolic parameters were compared in conjunction with HOMA-IR between the entry and the end of the study period.

CKD progression was assessed by recording renal endpoints, doubling of serum creatinine or a 50% decrease of GFR end-stage renal disease requiring renal replacement therapy (hemodialysis, peritoneal dialysis or kidney transplantation) or mortality. 32.1% of our patients received renin-angiotensin system (RAS) blockers, 33.9% received RAS blockers and calcium channel blockers, 15% received calcium channel blockers, and 19% received other anti-hypertensive drugs (β -blockers, α -blockers). These drugs were maintained by changing the dosage or a diuretic (loop diuretic) was added throughout the study. Patients who were previously following a low-salt diet maintained it without modification throughout the study.

Statistical Analysis

Baseline characteristics of study participants are given as frequency (for sex), means $\pm$ SD (for age, BMI, FBG, fasting insulin, LDL and HDL cholesterol) and were compared using two tests, i.e. unpaired Student's *t* test (two-tailed) for parametric data analysis and the Mann-Whitney test or Wilcoxon test for non-parametric analysis. For research of associated factors, multivariate logistic regression analyses were used. Statistical analyses were performed using the SPSS package (release 15.0).

Results

Essential hypertension ($n = 23$), chronic glomerulonephritis ($n = 19$), polycystic kidney disease ($n = 14$), chronic pyelonephritis ($n = 9$), amyloidosis ($n = 5$) and obstructive nephropathy ($n = 3$) were the causes of CKD among the study patients. Demographic, clinical, and baseline laboratory data are shown in table 1.

The groups were defined as follows: Group 1 ($n = 36$) without IR (21 females, mean age 60 ± 13 years, median GFR 40.5 ± 17 ml/min per 1.73 m², BMI $26.9.7 \pm 4.2$), and group 2 ($n = 37$) with IR (17 females, mean age 57 ± 11 years, median GFR 44.4 ± 21.9 ml/min per 1.73 m², BMI 29.3 ± 7.8). Group 2 patients had a higher FBG ($102.78 \pm 7.92/98.28 \pm 8.82$ mg/dl, $p = 0.003$) and serum insulin level ($15.03 \pm 5.03/7.99 \pm 1.89$ $\mu\text{U/l}$, $p = 0.001$) compared to group 1, and the other parameters were not significantly different ($p > 0.05$) (table 2). 12 patients in group 2 had IFG, while no IFG was found in group 1.

At the end of the study, SBP ($140.36 \pm 16.8/129.29 \pm 15.37$ mm Hg, $p = 0.007$) and DBP ($83.21 \pm 10.2/72.14 \pm 8.32$ mm Hg, $p = 0.001$) were decreased in group 1. In group 2, FBG ($102.78 \pm 7.92/96.48 \pm 11.34$ mg/dl, $p = 0.008$), HbA1c ($5.64 \pm 0.48/5.42 \pm 0.41$, $p = 0.009$), SBP ($142.76 \pm 16.88/134.83 \pm 14.84$ mm Hg, $p = 0.024$) and DBP ($85.17 \pm 9.86/75.86 \pm 7.32$ mm Hg, $p = 0.001$) and hs-CRP ($7.95 \pm 6.27/5.42 \pm 3.84$ mg/l, $p < 0.047$) were decreased (table 2). In group 2, 8 of the IFG patients improved, 3 developed diabetes and were treated for type 2 diabetes mellitus, and 8 patients reached renal endpoints (1 died, 7 started dialysis). In group 1, 9 patients reached study endpoints (3 died, 6 started dialysis).

At the end of the study there was a statistically significant difference in GFR between the rest of group 1 ($n = 27$) and group 2 ($n = 29$) ($46.1 \pm 19.7/26.2 \pm 11.6$, $p = 0.001$). HOMA-IR was not significantly higher among 17 patients who reached the renal endpoint than among the 56 who did not. Patients who reached the renal endpoint showed lower GFR ($p = 0.001$), higher iPTH ($p = 0.004$) and hs-CRP ($p = 0.002$) levels (table 3).

Discussion

We found that there was no significant difference in GFR at the end of the study between patients who had or did not have IR. Furthermore, HOMA-IR was not significantly different in patients with or without renal endpoints. IR per se was not found to be a risk factor for the worsening of renal functions.

DeFronzo et al. [1] used the euglycemic insulin clamp technique in combination with titrated glucose and hepatic venous and femoral venous catheterization to examine the contribution of the liver versus peripheral tissues to the impaired insulin action observed in uremia. They concluded that suppression of hepatic glucose production by physiological hyperinsulinemia was not impaired and that insulin-mediated glucose uptake by the liver was normal in uremic subjects. Tissue insensitivity to insulin is the primary cause of IR in uremia [1].

IR is present in patients with a mild degree of renal dysfunction or even in patients with an apparently normal renal function, i.e. normal creatinine value and low GFR. Thus, kidney disease per se seems to cause an IR syndrome.

The Hiyasama Study found a strong correlation between hyperinsulinemia and renal dysfunction in a study population of 1,065 men and 1,381 women, while a large sample of US adults participating in the Third National

Table 1. Baseline laboratory data of study subjects

Age, years	58.8 ± 12.3
Female/male	38/35
GFR, ml/min	42.5 ± 19.6
BMI	28.15 ± 6.36
FBG, mg/dl	101.25 ± 9.05
HbA1c, %	5.44 ± 0.39
Serum insulin, μ U/l	11.65 ± 5.72
HOMA-IR	2.94 ± 1.57
SBP, mm Hg	142.29 ± 16.17
DBP, mm Hg	85.4 ± 9.7
Uric acid, mg/dl	7.32 ± 1.96
Albuminemia, g/dl	4.21 ± 0.31
Total cholesterol, mg/dl	192.87 ± 35.27
Serum TG, mg/dl	165.9 ± 101.36
hs-CRP, mg/l	8.74 ± 6.2
iPTH, pg/dl	180.37 ± 163.27
Proteinuria, mg/day	580.43 ± 163.27

Health and Nutrition Examination Survey (NHANES III) showed a strong correlation between the HOMA index, plasma insulin and the risk of CKD [2]. Sit et al. [4] evaluated the prevalence of IR in 89 non-diabetic, non-obese patients with CKD. They reported IR in 48.3% of their CKD patients. In another study, IR was reported in 50% of such patients, irrespective of the underlying cause [7–10].

Kobayaski et al. [11] showed that IR is an important risk factor for the progression of renal disease among stage 3 CKD patients who they followed up for at least 3 years. Moreover, Ikee et al. [12] performed a 75 g oral glucose tolerance test in 23 non-diabetic CKD patients who had renal biopsies. All the vasculature, glomeruli and tubulointerstitial changes in the biopsy were evaluated. IR in particular had an effect on the tubulointerstitial and vascular changes.

Mohteshamzadeh et al. [13] followed up 106 CKD patients for 5 years who were divided into three groups according to their insulin sensitivity. As a result, it was clearly shown that IR is frequent among CKD patients and sometimes progresses to IFG and diabetes mellitus. On the other hand, there was no correlation between IR and GFR [13]. Similarly, Satirapoj et al. [14] demonstrated that IR had a correlation with BMI, TG and arterial blood pressure in CKD patients, but it did not have any correlation with GFR.

In our study, there was no significant difference in GFR at the end of the study in both groups. Moreover, there was no relation between IR and GFR. 12 of those patients with IR initially had IFG and 8 improved, where-

Table 2. Baseline and end of the study laboratory data of groups 1 and 2

	Group 1 ^a (n = 36)	Group 1 ^b (n = 28)	p	Group 2 ^a (n = 37)	Group 2 ^b (n = 28)	p
GFR, ml/min	40.5 ± 17	46.1 ± 19.7	NS	44.4 ± 21.9	48.6 ± 21.2	NS
BMI	26.9 ± 4.1	28.5 ± 3.4	NS	29.3 ± 7.8	28.2 ± 4.4	NS
FBG, mg/dl	98.2 ± 8.8	95.4 ± 10	NS	102.7 ± 7.9	96.4 ± 11.3	0.008
Serum insulin, μU/l	7.7 ± 1.8	7.9 ± 1.9	NS	15 ± 5.03	15.6 ± 8.8	NS
HOMA-IR	1.85 ± 0.4	1.86 ± 0.9	NS	3.98 ± 1.5	3.77 ± 2	NS
HbA1c, %	5.4 ± 0.39	5.5 ± 0.46	NS	5.6 ± 0.48	5.42 ± 0.41	0.009
SBP, mm Hg	140.3 ± 16.8	129.3 ± 15.3	0.007	142.6 ± 15.3	134.8 ± 14.8	0.024
DBP, mm Hg	83.2 ± 10.2	72.1 ± 8.3	0.001	85.17 ± 9.8	75.8 ± 7.5	0.001
Uric acid, mg/dl	7.6 ± 1.9	6.9 ± 2.1	NS	7.05 ± 2.1	6.76 ± 2.1	NS
Albuminemia, g/dl	4.1 ± 0.3	4.2 ± 0.2	NS	4.2 ± 0.3	4.2 ± 0.2	NS
Total cholesterol, mg/dl	194.6 ± 24.8	198.4 ± 40.1	NS	192.4 ± 43.2	201.2 ± 48.1	NS
Serum TG, mg/dl	154.8 ± 80	170.2 ± 78	NS	172.9 ± 128	159.8 ± 73	NS
hs-CRP, mg/l	7.9 ± 6.7	8.6 ± 10.5	NS	7.9 ± 6.2	5.4 ± 3.8	0.047
iPTH, pg/dl	165 ± 115	141 ± 114	NS	198 ± 223	120 ± 84	NS
Proteinuria, mg/day	650.2 ± 869	454.9 ± 553	NS	542.6 ± 660	309.6 ± 218	NS

^a Baseline study laboratory data of the two groups. ^b End of study laboratory data of the two groups.

Table 3. Patients who did or did not reach renal endpoint (RE) laboratory data

	Reached RE (n = 56)	Did not reach RE (n = 17)	p
GFR, ml/min	46.1 ± 19.7	26.2 ± 11.6	0.001
BMI	28.1 ± 6.6	28 ± 5.2	NS
FBG, mg/dl	100.68 ± 8.64	103.14 ± 10.44	NS
Serum insulin, μU/l	11.3 ± 5.5	11.3 ± 7.4	NS
HOMA-IR	2.83 ± 1.5	2.94 ± 1.9	NS
SBP, mm Hg	141.7 ± 16.9	144.1 ± 13.7	NS
DBP, mm Hg	84.5 ± 10.2	88.2 ± 8.1	NS
hs-CRP, mg/l	7.5 ± 6.4	12.7 ± 5.4	0.002
iPTH, pg/dl	148.2 ± 138	288 ± 247	0.004

as 3 progressed to overt diabetes. Carbohydrate metabolism disorders may be found in patients who have CKD, therefore this group of patients should be screened for diabetes. Those patients reaching renal endpoints had low GFR, high iPTH and hs-CRP levels. They did not demonstrate a statistically significant difference in terms of HOMA-IR. Furthermore, 22.2% of IR patients and 24.3% of non-IR patients progressed to endpoints. IR per se was not found to be a risk factor for worsening of renal functions.

IR is frequently observed in patients with essential hypertension, and the RAS has been demonstrated to modulate the status of IR. Arterial hypertension is frequently

present in patients with CKD, consequently antihypertensive drugs are commonly used in these patients. 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, whereas ACEI and angiotensin II receptor antagonists are the ones that have been shown to improve insulin sensitivity. This improvement in insulin sensitivity that is achieved with RAS blockers has been related to a decreased incidence of new-onset type 2 diabetes [15–18].

De Vinuesa et al. [19] demonstrated that patients with moderate CKD have a high prevalence of IR, and that the administration of the ARB olmesartan improves glucose metabolism and insulin sensitivity. 66% of our patients received RAS blockers. Baseline and the end of the study data revealed that SBP and DBP, proteinuria, FBG and HbA1c were decreased. HOMA-IR and GFR did not reveal any significant changes.

Conclusions

There was no significant difference in GFR at the end of the study between patients who had or did not have IR. Furthermore, HOMA-IR was not significantly different in patients with or without renal endpoints. IR per se was not found to be a risk factor for the worsening of renal functions.

References

- DeFronzo RA, Alvestrand A, Smith D, Hendler R, Hendler E, Wahren J: Insulin resistance in uremia. *J Clin Invest* 1981;67:563–568.
- 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* 2003;14:469–477.
- Orchard TJ, Chang YF, Ferrell RE, Petro N, Ellis DE: Nephropathy in type 1 diabetes: a manifestation of insulin resistance and multiple genetic susceptibilities? Further evidence from the Pittsburgh Epidemiology of Diabetes Complication Study. *Kidney Int* 2002;62:963–970.
- Knight SF, Imig JD: Obesity, insulin resistance, and renal function. *Microcirculation* 2007;14:349–362.
- National Kidney Foundation (K/DOQI): Clinical practice guidelines for chronic kidney disease: evaluation, classification and stratification. *Am J Kidney Dis* 2002;39:S1–S266.
- Sit D, Kadiroglu AK, Kayabasi H, Yilmaz ME: The prevalence of insulin resistance in nondiabetic nonobese patients with chronic kidney disease. *Adv Ther* 2006;23:988–998.
- Kubo M, Kiyohara Y, Kato I, et al: Effect of hyperinsulinaemia on renal function in a general Japanese population – The Hiyasama Study. *Kidney Int* 1999;55:2450–2456.
- Vareesangthip K, Tong P, Wilkinson R, Thomas TH: Insulin resistance in adult polycystic kidney disease. *Kidney Int* 1997;52:503–508.
- Fliser D, Pacini G, Engelleiter R, Kautzky-Willer A, Prager R, Franek E, Titz E: Insulin resistance and hyperinsulinemia are already present in patients with incipient renal disease. *Kidney Int* 1998;53:1343–1347.
- Hjelmsaeth J, Hartmann A: Insulin resistance in patients with adult polycystic kidney disease. *Nephrol Dialysis Transplant* 1999;14:2521–2522.
- Kobayashi H, Tokudome G, Hara Y, Sugano N, Endo S, Suetsugu Y, Kuriyama S, Hosoya T: Insulin resistance is a risk factor for the progression of chronic kidney disease. *Clin Nephrol* 2009;71:643–651.
- Ikee R, Hamasaki Y, Oka M, Maesato K, Mano T, Moriya H, Ohtake T, Kobayashi S: Glucose metabolism, insulin resistance, and renal pathology in non-diabetic chronic kidney disease. *Nephron Clin Pract* 2008;108:c163–c168.
- Mohteshamzadeh M, Wong C, Whitaric R, Thomas S: Is there a link between insulin resistance and chronic kidney disease in men with treated hypertension? Analysis of 5-year data. *Am J Nephrol* 2009;29:116–122.
- Satirapoj B, Supasyndh O, Boonyavarakul A, Luesutthiviboon L, Choovichian P: The correlation of insulin resistance and renal function in non-diabetic chronic kidney disease patients. *J Med Assoc Thai* 2005;883:S97–S104.
- Yildiz A, Hursit M, Celik AV, Kayacan SM, Yazici H, Akkaya V, Gu AO, Karsidag K: Doxazosin but not amlodipine decrease insulin resistance in patients with chronic renal failure: a prospective, randomized controlled study. *Clin Nephrol* 2002;58:405–410.
- Becker B, Kronenberg F, Kielstein JT, Haller H, Morath C, Ritz E, Fliser D, for the MMKD Study: Insulin resistance syndrome, adiponectin and vascular events in patients with kidney disease: the mild and moderate kidney disease study. *J Am Soc Nephrol* 2005;16:1091–1098.
- Benson SC, Perhadsingh HA, Ho CI, Chittiboyina A, Desai P, Pravenec M, Qi N, Wang J, Avery MA, Kurtz TW: Identification of telmisartan as a unique angiotensin II receptor antagonist with selective PPAR- γ modulating activity. *Hypertension* 2004;43:993–1002.
- Matayoshi T, Kamide K, Takiuchi S, et al: Relationship between insulin resistance and the renin-angiotensin system: analysis for patients with essential and renovascular hypertension. *Clin Exp Hypertens* 2007;29:479–487.
- De Vinuesa SG, Goicoechea M, Kanter J, et al: Insulin resistance, inflammatory biomarkers, and adipokines in patients with chronic kidney disease: effects of angiotensin II blockade. *J Am Soc Nephrol* 2006;17(suppl 3):S206–S212.