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Insulin resistance and postprandial triglyceride levels in primary renal disease

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Abstract

Background: Renal failure is associated with a range of metabolic abnormalities including insulin resistance and dyslipidemia. We examined the role of creatinine clearance (CrCl) and body composition in the development of insulin resistance in patients with primary renal disease and a variable degree of renal failure. We also determined the effect of a high-fat meal on postprandial triglyceride levels in a subgroup of these patients.

Methods: Forty-four patients with primary renal disease (men, 25; women, 19; age, 21-75 years) were compared to 44 controls matched for age, sex, and body composition. Renal biochemistry, plasma glucose, insulin, lipids, and nonesterified fatty acids were measured in the fasting state. Insulin sensitivity was calculated using the Homeostasis Model Assessment for Insulin Resistance (HOMA-R), and pancreatic beta-cell secretory capacity by HOMA-β. Fourteen normotriglyceridemic subjects from each group consumed an 80-g fat meal to examine their postprandial metabolic response.

Results: Although there was no significant difference between HOMA-R for the controls and the entire patient group ($P = .06$), HOMA-R was significantly higher in patients with CrCl less than 60 mL/min than those with CrCl greater than 60 mL/min or control subjects ($P < .01$ for each pair). Exponential analysis of the relationship between CrCl and HOMA-R and -β showed a line of best fit that was superior to that obtained by linear regression analysis ($P < .01$ and $P < .005$, respectively). HOMA-R in renal patients was correlated with several parameters of body composition, including central fat (kilogram) ($P < .005$). There was no difference in body fat parameters or HOMA-R for the patient and control subgroups undergoing a fat meal challenge. However, the patient subgroup showed a greater postprandial incremental rise in plasma triglycerides compared to controls ($P < .02$).

Conclusion: Patients with renal disease exhibit metabolic features typically associated with the metabolic syndrome. Insulin resistance increased with decline in renal function and was significantly higher in patients with CrCl less than 60 mL/min compared to subjects with CrCl greater than 60 mL/min or carefully matched controls. Renal patients also showed significant postprandial hypertriglyceridemia.
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1. Background

The metabolic syndrome, typically characterized by insulin resistance (IR), dyslipidemia, hypertension, and central adiposity, is associated with increased risk of vascular disease [1,2]. Some or all of these features may accompany renal disease, irrespective of etiology [3-6]. Hypertension and lipid abnormalities may occur relatively early in the evolution of renal disease [4], but the development of IR and its relationship to the nature of the renal abnormality and the degree of renal impairment remain contentious. Recent publications have suggested that reduction in insulin sensitivity may occur before the development of renal failure. Thus, Vareesangthip et al [7] observed IR in patients with adult polycystic kidney disease (PKD), irrespective of hypertension or renal impairment. On the basis of the previous studies linking abnormal membrane fluidity to IR [8,9], they suggested that a generalized change in membrane properties could influence insulin action in patients with adult PKD. Fliser et al [10] also observed IR and hyperinsulinemia in patients before the

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onset of renal failure. However, 42% of their patients had adult PKD raising the possibility that a membrane abnormality influenced the expression of IR.

The high prevalence of some or all features of the metabolic syndrome in the general community [11], irrespective of renal status, makes its definition more difficult in patients with mild or advanced renal disease. Moreover, data show that body composition exerts a major influence on metabolic features such as IR and dyslipidemia [12]. Hence, detailed analysis of this aspect is essential to distinguish those metabolic features attributable to renal disease from those preexisting in individual patients. However, most metabolic studies in patients with renal disease have relied on body weight and/or body mass index (BMI) as a means of matching patients with control subjects, even though these indices may not define those differences in composition that more precisely determine vascular risk. It is recognized, for example, that central adiposity is a better predictor of cardiovascular sequelae than either body weight or BMI [13]. Hence, the interpretation of previous studies of IR specifically and the metabolic syndrome in general in patients with renal disease is difficult because of incomplete definition of the metabolic phenotype of patients and controls. To clarify the impact of kidney disease and renal failure per se on IR and dyslipidemia, we examined 44 patients with various forms of primary renal pathology and a variable degree of renal impairment and 44 control subjects. They were carefully matched for body composition to separate the influence of adiposity on metabolic parameters from those effects that occur specifically with renal disease. Further examination of metabolic behavior was undertaken by administration of a high-fat meal to a subgroup of 14 normotriglyceridemic patients and 14 matched controls. Several studies emphasize the potential importance of postprandial hypertriglyceridamia in the development of vascular disease (eg, Refs [14,15]). This would appear to apply particularly to high-risk groups, such as those with chronic renal disease and diabetes.

2. Materials and methods

2.1. Patients and controls

Forty-four subjects (men, 25; women, 19; age, 21-75 years) with accurately diagnosed renal disease were studied. There were 23 with primary glomerulonephritis (GN) (including 14 with mesangial immunoglobulin A [IgA] nephropathy and 4 with focal glomerulosclerosis), 8 with adult polycystic renal disease, 9 with various forms of chronic tubulointerstitial disease, and 4 with hypertensive nephrosclerosis. They were attending outpatient clinics in the Department of Nephrology, Prince of Wales Hospital, Sydney, Australia, and their renal status, including diagnosis, had been established previously. All were well at the time of study and were free of edema; none was receiving dialysis treatment. Subjects with diabetes, nephrotic syndrome (or proteinuria >2 g/d), or systemic forms of renal disease were excluded. None was receiving corticosteroids, β-blockers, lipid-lowering agents, or antidiabetic medications. Twenty-two patients were taking antihypertensive medications: 20 were receiving an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin II receptor antagonist and 12 of these subjects were also taking a dihydropyridine calcium channel blocker (CCB). Two patients were receiving a CCB alone. Patients with poorly controlled blood pressure were not considered for this study. Control subjects consisted of healthy volunteers without clinical or laboratory evidence of renal disease, diabetes, or other disorders likely to influence metabolic status. None was taking regular medications. They were matched with the patient group for age, sex, and body composition as described below. The St Vincent's and Prince of Wales Hospitals' Human Research Ethics Committees approved the study and all subjects gave written informed consent.

2.2. Study protocol

Patients and controls were studied in the morning after a 10-hour fast. They were asked to abstain from alcohol and vigorous exercise for 72 hours before the study. The following measurements were performed on venous blood, in the fasting state, on each subject: (i) plasma urea, creatinine, electrolytes, albumin, and globulin; (ii) plasma cholesterol, triglycerides, and high-density lipoprotein cholesterol (HDL-C); and (iii) plasma glucose and insulin. Creatinine clearance (CrCl) was calculated from a 24-hour urinary collection and plasma sample or by the Cockcroft-Gault formula. Twenty-four-hour urinary protein (gram) was measured on patients with proteinuria detectable by dipstick. A second measurement of fasting plasma glucose and insulin was undertaken within 1 to 2 weeks of the first visit.

2.3. Assessment of insulin sensitivity

Insulin resistance and pancreatic beta-cell secretory capacity were calculated using the Homeostasis Model Assessment for Insulin Resistance (HOMA-R) and beta-cell function (HOMA-β). Derivation of values for IR and fasting beta-cell function have been described previously [16] and validated under a range of clinical conditions including in the presence of renal impairment [17]. They were calculated from the average value obtained from the 2 measurements of fasting plasma glucose and insulin using the following formulae: HOMA-R = fasting glucose (mmol/L) × fasting insulin (mU/mL)/22.5 and HOMA-β = fasting insulin (mU/mL)/(fasting glucose [mmol/L] − 3.5).

2.4. Analysis of body composition

At the first visit, weight was measured to the nearest 0.1 kg using a digital electronic scale and height to the nearest 0.1 cm

using a stadiometer. Body mass index was calculated as weight (kilogram) divided by height (meter) squared (ie, kilogram per meter squared). Waist circumference (centimeter) was measured at the umbilicus. Whole-body dual emission x-ray absorptiometry (Lunar DPX-Lunar Radiation Corporation, Madison. Wis; Software Version 1.35y) was used to analyze body composition according to a 3 compartmental model, incorporating fat mass, lean tissue, and bone mineral content. The measurement of central body fat has been described elsewhere and includes all visceral and some subcutaneous abdominal fat [13].

2.5. Fat meal

Fourteen patients with CrCls ranging from 10.5 to 125.5 mL/min were selected to eat a high-fat meal, as described by Kriketos et al [18], to investigate their postprandial metabolic response. They had been shown previously to have normal fasting plasma glucose (ie, <6.1 mmol/L) and triglyceride levels (ie, <2.0 mmol/L) on at least 2 occasions. Control subjects, matched for age, sex, and body composition, consumed an identical fat meal containing approximately 80 g of dietary fat (40 g saturated), 19 g carbohydrate, and 47 g protein with an energy content of 4250 kJ. The meal was eaten within 20 minutes and accompanied by 600 mL of water. Patients were allowed free access to water through the testing period but no other food or beverage. Venous blood samples were taken before consumption and then at 15, 60, 120, 180, 240, and 360 minutes after the meal. These samples were used for the serial measurement of plasma insulin, glucose, triglycerides, and nonesterified fatty acids (NEFAs).

2.6. Biochemical analyses

Plasma glucose was measured by the glucose oxidase method (Yellow Springs Instruments, Model 23 AM Glucose Analyser, Yellow Springs, Ohio). Plasma insulin was measured by radioimmunoassay (Linco RIA, Charles, Mo). Plasma total cholesterol, HDL-C, triglyceride, and NEFA concentrations were determined spectrophotometrically using enzymatic colorimetric kits (CHOD-PAP kit, Cfas HDL-C kit, GPO-PAP kit, Roche Diagnostics, Basel, Switzerland, and NEFA kit, Wako Inc, Japan). Inter- and intraassay coefficients of variation were less than 10% for these assays.

2.7. Statistical analyses

Differences among biochemical values, HOMA indices, and measurements of body composition between controls and patients were examined by unpaired t tests and, where appropriate, Mann-Whitney U test. Correlations between paired parameters including CrCl, HOMA-R and -β, and indices of body composition were examined by linear regression analysis (Spearman) with calculation of the coefficient r. The relationship between CrCl and HOMA-R and -β was also examined by exponential analysis and derivation of the line of best fit. The impact of renal impairment on IR was further examined after division of patients into those with relatively greater impairment, that is, CrCl less than 60 mL/min (n = 24) and those with CrCl greater than 60 mL/min (n = 20). Of the patients with CrCl less than 60 mL/min, 9 had primary GN (5 with mesangial IgA nephropathy), 5 had adult PKD, 7 had tubulointerstitial disease, and 3 had hypertensive nephrosclerosis. Fourteen of the patients with CrCl greater than 60 mL/min had primary GN(9 with mesangial IgA nephropathy), 3 had adult PKD, 2 had tubulointerstitial disease, and 1 had hypertensive nephrosclerosis. Differences in postprandial values, that is, compared to fasting levels, were examined by analysis of variance with Dunnett and Bonferroni post tests. Multivariate analysis was used to further examine the relative influence of the following parameters on HOMA-R in renal patients: age, sex, fasting cholesterol and triglycerides, central fat (kilogram), and CrCl less than 60 mL/min. Results are shown as mean ± SD unless indicated otherwise. Significance was taken as $P < .05$.

3. Results

Characteristics of the patient and control groups (each, n = 44) are shown in Table 1. The patient subgroups with a CrCl less than 60 and greater than 60 mL/min are also shown. There were no significant differences for BMI, waist circumference (centimeter), total fat (kilogram), % total fat, central fat (kilogram), % central fat, and fat-free mass (kilogram) between patients and controls or between patient subgroups. Also, body characteristics for each patient subgroup were comparable to those of the total control group. However, there was a significant difference in age and

Table 1
Body composition of controls and patients

	Age (y)	Sex (M:F)	Weight (kg)	BMI (kg/m^2)	Waist (cm)	Total fat (kg)	Total fat (%)	Central fat (kg)	Central fat (%)
Controls (n = 44)	47 ± 14	25:19	76.8 ± 15.6	26 ± 4	84 ± 13	23.5 ± 9.2	30.2 ±10.8	1.7 ± 0.8	32.0 ± 11.3
Patients (n = 44)	49 ± 13	25:19	72.5 ± 16.6	26 ± 5	90 ± 14	22.1 ± 10.1	30.7 ± 10.7	1.5 ± 1.1	31.7 ± 12.0
Patients CrCl <60 (n = 24)	54 ± 12*	17:7*	76 ± 19	26 ± 6	93 ± 16	22.6 ± 11.2	29.8 ± 11.4	1.8 ± 1.3	32.4 ± 13.1
Patients CrCl >60 (n = 20)	42 ± 12	8:12	69 ± 13	25 ± 4	86 ± 10	21.4 ± 8.9	31.6 ± 9.9	1.3 ± 0.7	30.7 ± 10.8

Data are expressed as mean ± SD.

* There were no significant differences between parameters except for the age and sex of patients with CrCl <60 mL/min vs CrCl >60 mL/min ($P < .01$).

Table 2
Fasting metabolic characteristics for controls and patients*

	Glucose (mmol/L)	Insulin (mU/L)	Cholesterol (mmol/L)	Triglycerides (mmol/L)	HDL-C (mmol/L)
Controls (n = 44)	4.7 ± 0.7	10.6 ± 7.9	4.8 ± 1.0	1.1 ± 0.6	1.2 ± 0.4
Patients (n = 44)	5.0 ± 0.4*	13.8 ± 9.2	5.2 ± 0.9	1.6 ± 0.8**	1.2 ± 0.3
Patients CrCl <60 (n = 24)	5.2 ± 0.4	17.9 ± 10.3	5.1 ± 1.0	1.8 ± 1.0	1.2 ± 0.4
Patients CrCl >60 (n = 20)	4.9 ± 0.3*	8.8 ± 3.8**	5.3 ± 0.8	1.4 ± 0.6	1.3 ± 0.3

* $P < .02$ (refers to total controls vs total patients or patients <60 vs >60 mL/min).
** $P < .001$ (refers to total controls vs total patients or patients <60 mL/min vs >60 mL/min).

sex between patients with CrCl less than 60 mL/min and those greater than 60 mL/min ($P < .01$ for each). Systolic and diastolic blood pressures between groups were also comparable: systolic blood pressure for controls was 124 ± 20 mm Hg and patients 129 ± 16 mm Hg; diastolic values were 80 ± 14 and 79 ± 10 mm Hg, respectively. Twelve of the patients with CrCl less than 60 mL/min were taking antihypertensive agents whereas 10 of the group with CrCl greater than 60 mL/min were receiving similar medications. Fasting values for plasma glucose, insulin, total cholesterol, triglycerides, and HDL-C are shown in Table 2 for both groups and each patient subgroup. Fasting triglycerides were significantly higher in the renal group ($P < .001$) although within the normal adult reference range (ie <2 mmol/L). No significant differences were observed for total cholesterol or HDL-C. Fasting glucose levels were higher in patients with CrCl less than 60 mL/min compared to those greater than 60 mL/min ($P = .02$; mean, 5.2 vs 4.9) whereas fasting levels of triglycerides were comparable between subgroups.

3.1. HOMA-R

The relationships between HOMA-R and various parameters of body composition are shown for controls, patients (ie, n = 44), and patient subgroups (ie, CrCl <60 and >60 mL/min) in Table 3. There were highly significant positive correlations among HOMA-R and weight, BMI, waist circumference, waist/hip ratio, and central fat (kilogram) for the entire control group ($P < .001$ for each).

Table 3
Correlation coefficient (r) between HOMA-R and parameters of body composition

	Controls (n = 44)	Patients (n = 44)	Patients CrCl <60 (n = 24)	Patients CrCl >60 (n = 20)
Weight (kg)	0.48*	0.39**	0.51***	0.13 (NS)
BMI (kg/m^2)	0.48*	0.32***	0.30 (NS)***	0.44 (NS)
Waist (cm)	0.56*	0.43**	0.55**	0.11 (NS)
Waist/hip	0.58*	0.44**	0.46***	−0.21 (NS)
Total fat (kg)	0.39**	0.32***	0.30 (NS)	0.70*
Total fat (%)	0.22 (NS)	0.17 (NS)	0.21 (NS)	0.74*
Central fat (kg)	0.54*	0.42**	0.43***	0.45***
Central fat (%)	0.43**	0.20 (NS)	0.09 (NS)	0.40 (NS)

NS, $P > .05$.
* $P < .001$.
** $P < .01$.
*** $P < .05$.

Significant correlations were also observed with the entire patient group: weight, waist, waist/hip ratio, and central fat (kilogram) (each $P < .01$); BMI and total fat (kilogram) (each $P < .05$). For patients with CrCl less than 60 mL/min, significant positive correlations were observed among HOMA-R and weight ($P < .05$), waist ($P < .01$), waist/hip ratio ($P < .05$), and central fat (kilogram) ($P < .05$); no significant correlations were observed with total fat (ie, % or kg), fat-free mass (data not shown in Table 3), or % central fat. For patients with CrCl greater than 60 mL/min, significant correlations were observed among HOMA-R and total fat (kilogram) ($P < .001$), % total fat ($P < .001$), and central fat (kilogram) ($P < .05$); no correlation was observed with fat-free mass or % central fat. Fig. 1 shows the relationship between central fat (kilogram) and the HOMA-R for all patients and controls. There was a highly significant correlation for both groups ($P < .005$ and 0.001) and slope values were comparable (controls, 0.99 ± 0.30; renal, 1.03 ± 0.13). However, the y-axis (HOMA-R) intercept was significantly higher in the renal group ($P < .01$). A significant correlation was also observed between HOMA-R and fasting triglycerides for the patient group ($r = 0.33$, $P < .05$).

There was a significant inverse linear correlation between CrCl and HOMA-R for the entire renal group (ie, n = 44; $r = -0.54$; $P < .001$). Exponential analysis of the relationship between CrCl and HOMA-R is shown in Fig. 2A. The r value was 0.63 and, as a line of best fit, was superior to linear regression analysis ($P < .01$). There was also a significant difference in HOMA-R between subgroups ($P < .01$) and between controls and patients with CrCl less than 60 mL/min ($P < .01$); there was no difference in HOMA-R values between patients with CrCl greater than 60 mL/min and control subjects (Fig. 3). No correlation was observed between CrCl and any parameter of body composition in the renal group. Of the 5 patients with HOMA-R greater than 6 (see Fig. 2A), 2 had primary GN and 1 each had adult PKD, hypertensive nephrosclerosis, and tubulointerstitial disease.

3.2. HOMA-β

A significant inverse linear relationship between CrCl and HOMA-β was observed in patients with renal disease (n = 44, $r = -0.36$, $P < .02$). Exponential analysis of the relationship between CrCl and HOMA-β is shown in Fig. 2B. The r value was 0.56 and, as a line of best fit,

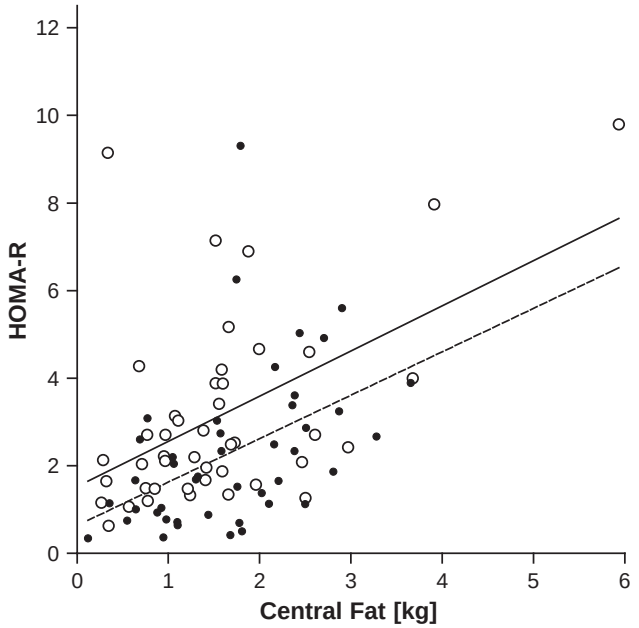

Fig. 1. Regression analysis of HOMA-R vs central fat (kilogram) in patients with renal disease and control subjects (n = 44 for each group). There was a significant correlation for both patients (r = 0.42, P < .005) and controls (r = 0.54, P < .001) and the slopes of the regression lines were comparable. However, the y-axis intercept was higher in the renal group (1.5 vs 0.6, P < .01), confirming an increment in the degree of IR for any given amount of central fat. Open circle indicates renal disease; filled circle, control subjects.

was superior to linear regression analysis (P < .005). Values for HOMA-β were significantly higher in patients with CrCl less than 60 mL/min than those with CrCl greater than 60 mL/min (P < .02), suggesting that insulin secretion was responsive to increasing IR.

3.3. Fat meal

The 14 patients and 14 control subjects given a high-fat meal were also closely matched for age, sex, BMI, waist circumference, % total fat, and central fat. Creatinine clearance in the renal subgroup ranged from 10.5 to 125.5 mL/min. Although still in the normal range, fasting triglycerides were higher in the patient subgroup: 1.15 ± 0.49 vs 0.70 ± 0.30 mmol/L in controls (P < .01). Fig. 4 shows that the postprandial changes in plasma insulin, glucose, and NEFAs were comparable for the 2 groups. However, there was a greater incremental rise in postprandial triglycerides in patients with renal disease (P = .02; Fig. 4).

4. Discussion

There was a striking exponential relationship between HOMA-R and CrCl in the renal group (Fig. 2A). Moreover, HOMA-R in patients with a greater degree of renal impairment (ie, CrCl <60 mL/min) was significantly higher than in their milder counterparts or controls. This higher HOMA-R was accompanied by an increase in insulin secretory capacity as analyzed by HOMA-β. However, this subgroup had higher fasting blood glucose levels than patients with CrCl greater than 60 mL/min, even though mean values for both subgroups remained within the normal range. Although the mean age and frequency of male subjects were greater in patients with CrCl less than 60 mL/ this group did not differ from the other patient subgroup or controls in terms of formal assessment of body composition. By contrast to previous studies that have examined the

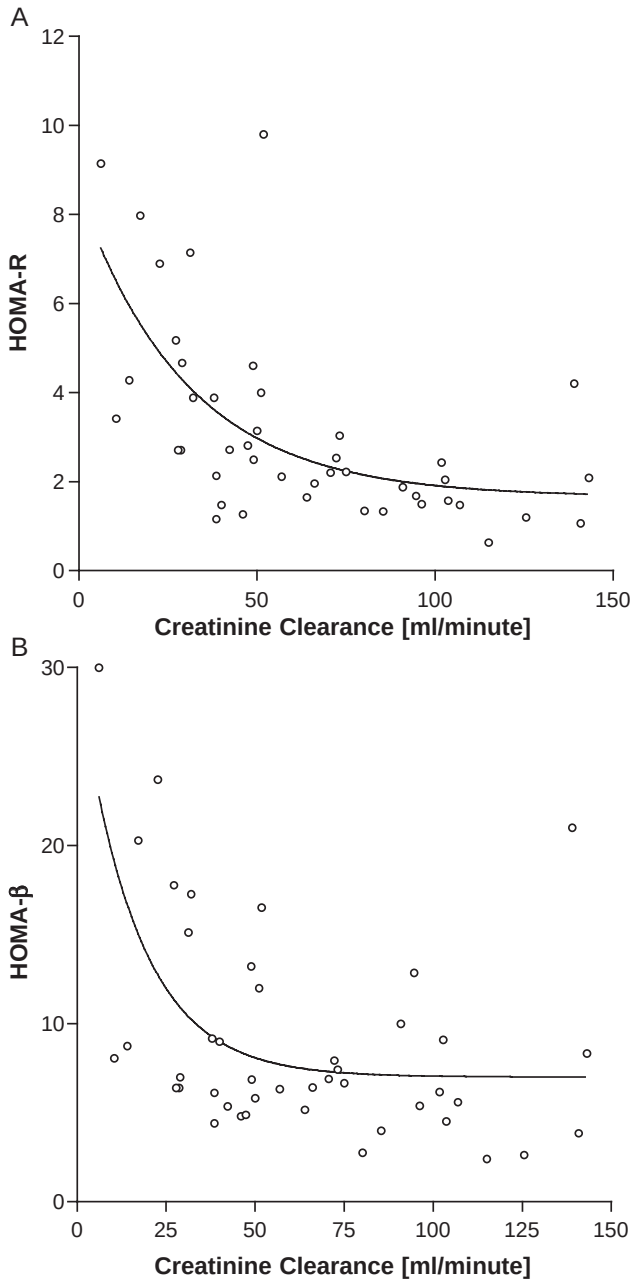

Fig. 2. The relationship between CrCl (ml/min) and (A) HOMA-R and (B) HOMA-β in patients with renal disease (n = 44). Exponential analysis revealed lines of best fit that were superior to linear regression analysis (r = 0.63, P < .01 and r = 0.56, P < .005, respectively). There were also significant inverse linear correlations between both pairs of parameters: CrCl vs HOMA-R (r = −0.54; P < .001); CrCl vs HOMA-β (r = −0.36; P < .02).

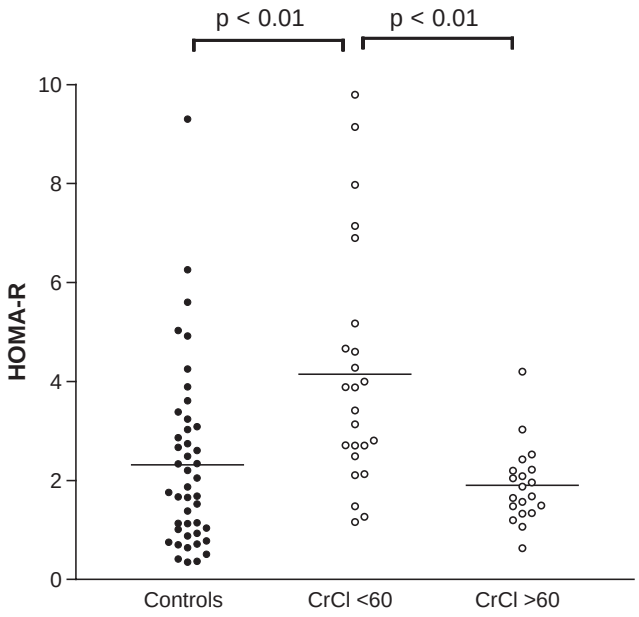

Fig. 3. Values for HOMA-R in control subjects, renal patients with CrCl less than 60 mL/min (n = 24), and patients with CrCl greater than 60 mL/min (n = 20). There was a significant difference between controls and patients with CrCl less than 60 mL/min (t = 3.49; P < .01) and between patients with CrCl greater than 60 mL/min and less than 60 mL/min (t = 3.44; P < .01). There was no significant difference between control subjects and patients with CrCl greater than 60 mL/min. Filled circle indicates control subjects; open circle, renal patients.

relationship between renal function and IR, all patients and control subjects were comprehensively analyzed for body composition. Other reports have confined matching to weight, waist circumference, and BMI, none of which accurately demonstrate differences in body fat distribution. In this study, changes in IR in the subgroup with CrCl less than 60 mL/min occurred independently of body composition, there being no correlation between CrCl and BMI or measurements of body fat. It was also notable that close matching for these parameters, including both central and total body fat, resulted in differences between other phenotypic parameters including weight, waist circumference, and lean body mass: the renal group showed a 6-cm higher waist measurement despite a lower mean body weight (see Table 1), and the latter coincided with a 2.9-kg lower lean body mass in the patient group. As shown in Fig. 1, the presence of renal failure was responsible for an increment in the degree of IR related to any given amount of central fat.

Several previous reports document the presence of IR in patients with renal failure. However, few have undertaken measurements of IR in conjunction with detailed quantitation of body composition, which is now recognized as a major contributor to insulin sensitivity [13]. Some reports have focused on patients immediately before [19] or after the commencement of dialysis treatment [20]; the latter provides a range of confounding variables in the analysis of IR. Other papers have examined a specific diagnostic category and have not addressed the influence of renal failure per se on insulin sensitivity [7]. The Homeostasis Model Assessment Index was used to quantitate IR in our patients. This simple method obviates the risks of venous injury that could occur with the euglycemic clamp technique in patients with advancing renal disease and requirements for long-term dialysis access. HOMA indices have been validated previously in patients with chronic renal failure [17] and Shinohara et al [21] have shown that IR acts as an independent predictor of cardiovascular mortality in patients with end-stage renal failure.

The finding of an exponential relationship between HOMA-R and CrCl in patients with renal disease differs from data reported by Fliser et al [10] who found patients with mild renal disease (ie, normal CrCl) to be insulin resistant compared to control subjects, matched for BMI but no other parameters of body fat composition. They observed that IR did not worsen as renal function deteriorated. An intravenous glucose tolerance test with frequent sampling was used to quantitate IR and the study involved patients with immunological renal disease (ie, mesangial IgA nephropathy) and adult PKD. These differing observations could reflect the less exacting approach to phenotypic matching of subjects and the use of data from the intravenous glucose challenge. Moreover, patients with PKD may exhibit a specific membrane effect on insulin sensitivity that is independent of renal impairment [7]. Fliser et al also found IR in patients with mesangial IgA nephropathy before the onset of renal failure, although this disorder has not been examined in detail by other groups. In our study, 9 such patients resided in the subgroup with CrCl greater than 60 mL/min; their HOMA-R values were comparable to the control group. Eidemak et al [22] investigated 29 patients with glomerular filtration rates of 11 to 43 mL/min by a 120-minute hyperinsulinemic euglycemic clamp; diagnoses included adult PKD, chronic GN, hypertensive nephrosclerosis, and tubulointerstitial disease. They demonstrated reduced insulin sensitivity in the patient group but did not analyze the influence of the degree of renal impairment on IR. Several groups have acknowledged the altered metabolism of insulin and glucose in the presence of chronic renal failure and the potential for prolonged insulin action to affect glucose disposal. Such abnormalities could influence the interpretation of data obtained by the clamp technique, thus providing further endorsement of the use of HOMA. Although most work concludes that peripheral failure of glucose transport is the main contributor to IR in renal disease, it is probable that some patients with advanced renal failure also exhibit a degree of pancreatic beta-cell insufficiency. Studies of glucose tolerance in patients on chronic hemodialysis, for example, show a wide range of tolerance among patients with nondiabetic renal disease, with the highest insulin response being observed in patients where normal glucose tolerance has been maintained [23].

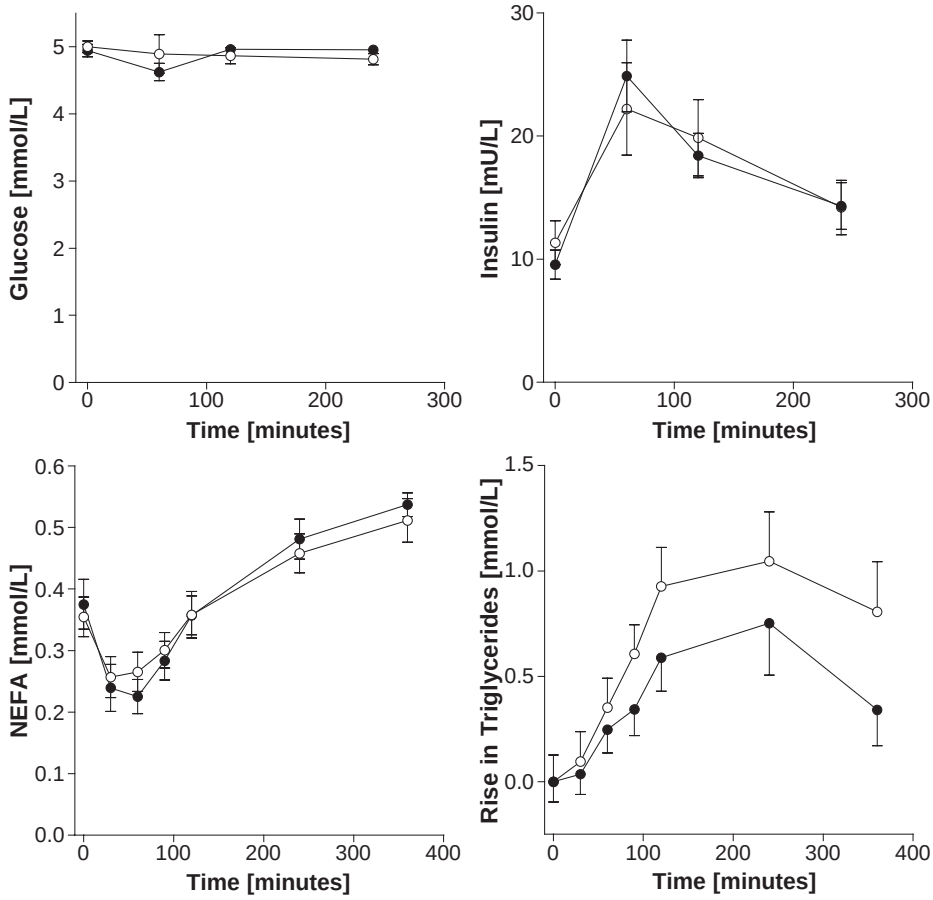

Fig. 4. Fasting and postprandial data in control subjects (n = 14) and renal patients (n = 14) given a high-fat meal. Serial values (mean ± SD) for plasma glucose, insulin, NEFAs, and incremental change in plasma triglycerides are shown for sampling periods up to 360 minutes postprandially. There was no significant difference between groups for glucose, insulin, or NEFAs. However, there was a greater incremental rise in postprandial triglycerides in the group with renal disease compared to controls (P = .02). Filled circle indicates control subjects; open circle, renal patients.

The patients with renal disease exhibited postprandial hypertriglyceridemia despite fasting levels within the normal range. This occurred in the presence of careful matching with healthy controls and a slightly lower central fat mass in the renal group. This postprandial lipid intolerance has been observed in normoglycemic subjects with a strong family history of type 2 diabetes [24], and it is acknowledged that patients with renal failure develop a complex dyslipidemia that resembles that observed in type 2 diabetes. Postprandial lipoprotein metabolism is abnormal in renal failure [25], and this is reflected in the typical dyslipidemic profile of elevated fasting triglycerides and low HDL-C. The accumulation of partially metabolized triglyceride-rich particles results from impaired lipoprotein lipase activity, as may occur in hyperinsulinemic states [26]. Our failure to demonstrate lower fasting HDL-C levels in the patient group could reflect the small number of subjects studied and the fact that their fasting triglyceride levels were normal at the time of the fat meal challenge. We did not find a difference in postprandial insulin or NEFA response between groups (see Fig. 4), which probably reflects their close matching for body composition and the relatively nonobese subjects randomly chosen for study. Additional testing with a meal higher in carbohydrate but with similar fat content might demonstrate further differences in the presence of IR (Milner et al, unpublished observations).

Twenty-two patients with renal disease had effectively treated hypertension, the majority receiving either an ACE inhibitor or an angiotensin II receptor antagonist. It would be anticipated that the mechanism(s) of high blood pressure in this group would differ from that observed in patients with essential hypertension, a common accompaniment of other features of the metabolic syndrome. Moreover, the use of ACE inhibitors has been reported to improve IR [27,28]. There have been no reports of a significant influence of dihydropyridine CCBs on IR. We could not exclude a contribution from primary hypertension to the blood pressure status of our patients, and this study did not attempt to define the mediators of hypertension in the renal group. However, a disproportionate percentage of patients with essential hypertension will also have IR, and this has been linked to the progressive decrease of glomerular filtration in some of

these subjects [29]. It should also be emphasized that despite the use of medications likely to improve insulin sensitivity, patients with renal impairment (ie, CrCl <60 mL/min) still displayed significant IR compared to their counterparts with milder renal disease. (There was no significant difference in the usage of antihypertensive agents in the 2 patient subgroups).

In summary, the data show that IR is significantly influenced by the degree of renal failure in patients with primary forms of renal disease and is associated with an increase in insulin secretion. We did not demonstrate significant IR in patients with CrCl greater than 60 mL min when compared to a carefully matched control population without renal disease. These results emphasize the need for careful evaluation of body composition when examining the metabolic associations of renal failure. However, the data do not exclude the potential for coexisting features of the primary metabolic syndrome to further influence the progress of chronic renal disease. Such metabolic abnormalities are prevalent in many communities worldwide and have been shown to have the potential to accelerate micro- and macrovascular disease. Hence, the IR associated with renal disease could be an important independent determinant of the progression of renal failure, irrespective of diagnosis, as it seems probable that a degree of renal cortical ischemia is common to all major forms of progressive renal injury [30].

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