Abnormalities of Glucose Metabolism in Patients With Early Renal Failure

Leonardo A. Sechi, Cristiana Catena, Laura Zingaro, Alessandra Melis, and Sergio De Marchi

Abnormalities of glucose metabolism and hyperinsulinemia have been demonstrated in patients with end-stage renal disease and may contribute to the development of atherosclerotic complications in these patients. In the present study, we investigated the stage of renal failure in which abnormalities of glucose metabolism develop and whether these abnormalities were associated with an increased prevalence of cardiovascular events in patients with early renal failure. In 321 untreated essential hypertensive patients, we assessed renal function by measuring 24-h creatinine clearance, urinary protein excretion, and microalbuminuria; we assessed cardiovascular status by clinical and laboratory tests; and we measured plasma glucose, insulin, and C-peptide levels at fasting and after a 75-g oral glucose load. To evaluate insulin sensitivity, a hyperinsulinemic-euglycemic clamp was performed in a subgroup of 104 patients. Patients with creatinine clearance <30 ml · min^{-1} · 1.73 m^{-2}, severe hypertension, BMI <30 kg/m^2, and diabetes or family history of diabetes were excluded. Hypertensive patients were found to be hyperinsulinemic when compared with 92 matched normotensive subjects. Early renal failure (creatinine clearance <90 ml · min^{-1} · 1.73 m^{-2}) caused by hypertensive nephrosclerosis was detected in 116 of 321 patients. Analysis of patients with varying degrees of renal function impairment demonstrated increased plasma glucose and insulin response to oral glucose load, decreased fasting glucose-to-insulin ratio, and reduced sensitivity to insulin only in those patients with creatinine clearance <50 ml · min^{-1} · 1.73 m^{-2}. Parameters of glucose metabolism were not correlated with creatinine clearance and microalbuminuria. Prevalence of atherosclerotic cardiovascular events was significantly related to reduction of creatinine clearance, but parameters of glucose metabolism were comparable in patients with and without evidence of atherosclerotic damage. Thus, in patients with hypertensive nephrosclerosis and early impairment of glomerular filtration, alterations of glucose metabolism become evident only when creatinine clearance is <50 ml · min^{-1} · 1.73 m^{-2} and are not related to microalbuminuria and cardiovascular complications. *Diabetes* 51:1226–1232, 2002

From the Hypertension Unit, Internal Medicine, Department of Clinical and Experimental Pathology and Medicine (DPMSC), University of Udine, Udine, Italy.

Address correspondence and reprint requests to Leonardo A. Sechi, MD, Hypertension Unit, Department of Internal Medicine, University of Udine School of Medicine, Ospedale Civile, Padiglione Medicine, 33100 Udine, Italy. E-mail: sechi@uniud.it.

Received for publication 9 August 2001 and accepted in revised form 14 January 2002.

AUC, area under the curve; GFR, glomerular filtration rate; i-PTH, intact parathyroid hormone; MCR, metabolic clearance rate; OGTT, oral glucose tolerance test.

Cardiovascular events are a major cause of death in patients with end-stage renal failure (1,2). In these patients, several common atherogenic risk factors, such as age, hypertension, diabetes, and dyslipidemia (3) are combined with factors more specifically related to the uremic state, such as increased serum levels of fibrinogen (4), homocysteine (5), and lipoprotein(a) (6). Some of these risk factors can be detected early in the course of renal failure (4,6) and may contribute to the development of cardiovascular complications in patients with mild impairment of renal function (7).

Several lines of evidence suggest that hyperinsulinemia may be an important risk factor for the development of atherosclerosis in the general population (8,9), and abnormalities in glucose metabolism have been recognized in uremic patients (10–12). Many of these patients have mild fasting hyperglycemia and an abnormal response to an oral glucose tolerance test (OGTT), whereas some patients maintain euglycemia at the expense of hyperinsulinemia, indicating the presence of decreased sensitivity to insulin (13). Therefore, insulin resistance and the compensatory hyperinsulinemia might contribute to the development of cardiovascular complications in end-stage renal patients.

Longitudinal (7) and cross-sectional studies (6) indicate that cardiovascular morbidity is increased in patients with mild renal failure, but little information is available about glucose metabolism in these patients. This study was designed to investigate at what stage of renal failure abnormalities of glucose metabolism develop and whether these abnormalities are associated with an increased prevalence of cardiovascular events.

RESEARCH DESIGN AND METHODS

A total of 321 untreated essential hypertensive patients (aged 53 ± 12 years; 184 men, 137 women), who were referred to the outpatient clinic of our department, were included in a cross-sectional study. High blood pressure (systolic blood pressure ≥160 mmHg and/or diastolic blood pressure ≥95 mmHg) was measured at least twice on two different occasions and subsequently confirmed on at least two more visits during the next 4 weeks. Blood pressure was measured by a mercury sphygmomanometer (14) after each subject had been supine for 15 min. The average of three readings obtained in 5 min was recorded. The patients seen at our clinic include individuals with all grades of hypertension living in Northeast Italy and are representative of hypertensive patients in this geographic area (15). Exclusion criteria were age <30 or >75 years; BMI >30 kg/m^2; severe hypertension, as defined by diastolic blood pressure of ≥115 mmHg; pregnancy; diabetes or family history of diabetes; renal failure with creatinine clearance <30 ml · min^{-1} · 1.73 m^{-2} body surface area; and presence of other diseases or treatments that might interfere with glucose metabolism. Renovascular and endocrine causes of hypertension were excluded on the basis of exhaustive laboratory testing (16). Renal function was assessed by measurement of 24-h creatinine clearance,

TABLE 1
Clinical, lipid, and glucose metabolism parameters of the hypertensive patients and control subjects

	Control subjects	Hypertensive patients	*P*
n	92	321	
Age (years)	52 ± 18	53 ± 12	0.532
Sex (M/F)	48/44	184/137	0.448
Systolic blood pressure (mmHg)	125 ± 13	168 ± 24	<0.001
Diastolic blood pressure (mmHg)	78 ± 12	101 ± 13	<0.001
BMI (kg/m^2)	26.2 ± 3.3	26.8 ± 3.6	0.152
Waist-to-hip ratio	0.91 ± 0.09	0.91 ± 0.10	1.000
Serum creatinine (μmol/l)	90 ± 31	98 ± 28	0.019
Total cholesterol (mmol/l)	5.30 ± 1.03	5.45 ± 1.84	0.455
LDL cholesterol (mmol/l)	3.34 ± 0.96	3.48 ± 1.02	0.240
HDL cholesterol (mmol/l)	1.42 ± 0.41	1.2 ± 0.38	0.029
Triglycerides (mmol/l)	1.26 ± 0.55	1.43 ± 0.77	0.049
Fasting glucose (mmol/l)	4.8 ± 0.8	5.0 ± 1.2	0.133
Fasting insulin (pmol/l)	60.2 ± 17.4	77.3 ± 38.7	<0.001
Fasting C-peptide (nmol/l)	0.55 ± 0.21	0.76 ± 0.39	<0.001
Fasting glucose-to-insulin ratio × 100	8.00 ± 2.15	6.46 ± 2.71	<0.001
AUC blood glucose (mmol · l^{-1} · min)	22.0 ± 6.1	24.3 ± 7.7	0.009
AUC plasma insulin (pmol · l^{-1} · min)	864 ± 446	1,062 ± 632	0.005

Data are means ± SD. Comparisons are by Student's *t* test or Pearson χ^2 test. To convert to conventional units, multiply creatinine by 0.0113 (mg/dl), cholesterol by 38.6 (mg/dl), and triglycerides by 88.5 (mg/dl); glucose by 0.05551 (mg/dl), insulin by 7.175 (μU/ml), and C-peptide by 3.021 (ng/ml). AUC for blood glucose and serum insulin concentration 180 min after oral glucose load.

urine protein excretion, and microalbuminuria. The cardiovascular status was assessed in all patients by a complete history, physical examination, electrocardiogram, echocardiography, and ultrasound examination of abdominal aorta, carotid, iliac, and femoral arteries. Additional laboratory tests, including treadmill exercise stress testing, myocardial perfusion scan, and coronary arteriography were performed following specific indications (17). The retrospective diagnosis of myocardial infarction was confirmed by documented history, electrocardiographic changes, and greater than twofold elevation of the serum creatine kinase with positive MB-fraction. The neurological diagnosis of transient ischemic attack, prolonged reversible neurological deficits, and atherothrombotic stroke was confirmed by documented history, clinical signs, and computerized cerebral axial tomography. The assessment of cardiovascular status was done without prior knowledge of patients' glucose metabolism parameters.

Ninety-two normotensive individuals (aged 52 ± 18 years; 48 men, 44 women) served as control subjects. These subjects were selected from the general population of the same geographic area as the hypertensive patients by frequency matching after specification of inclusion criteria to avoid age and sex as potential confounding variables.

Impairment of renal function in hypertensive patients was considered to be present when the 24-h creatinine clearance was <90 ml · min^{-1} · 1.73 m^{-2} body surface area. This limit was selected a priori, as performed in earlier studies (6). History, review of medical records, urinalysis, repeated urine cultures, and renal ultrasound examination were used to establish the etiology of renal failure. Other tests, such as specific blood biochemistries, pyelography, renal scintigraphy, renal arteriography, computerized tomography, and renal biopsy, were performed when needed. Patients with decreased creatinine clearance were subdivided into three groups according to their renal function: *1*) patients with creatinine clearance between 70 and 89 ml · min^{-1} · 1.73 m^{-2}; *2*) patients with creatinine clearance between 50 and 69 ml · min^{-1} · 1.73 m^{-2}; and *3*) patients with creatinine clearance between 30 and 49 ml · min^{-1} · 1.73 m^{-2}. All patients had stable renal function for at least 6 months before the study, and none of them were treated with erithropoietin or vitamin D. A total of 212 (66%) of the hypertensive patients included in the study were treated with antihypertensive drugs (monotherapy 44%, multiple drug therapy 56%, calcium antagonists 46%, ACE inhibitors 39%, diuretics 36%, β-blockers 29%, angiotensin II receptor antagonists 13%, and α-blockers 6%) and were withdrawn from treatment a minimum of 1 week before measurement of blood parameters. At the time of the study, patients were allowed to maintain their usual unrestricted diet. The study was approved by the Ethical Committee of the University of Udine. A sample of venous blood was obtained without venous stasis after fasting for 12–14 h and after the patients were in the sitting position for 10 min for analysis of glucose, insulin, C-peptide, lipids, Hb, pH, bicarbonate, potassium, magnesium, glucagon, and growth hormone. The fasting glucose-to-insulin ratio was calculated as an index of insulin sensitivity, as previously reported (16,18,19).

Glucose tolerance was evaluated with the use of a 180-min OGTT as previously described (18). Briefly, a solution of 75 g glucose in 200 ml water was given orally, and blood for determination of plasma glucose, insulin, and C-peptide was drawn at baseline and after 30, 60, 90, 120, and 180 min. The area under the curve (AUC) for blood glucose and plasma insulin concentration during the glucose tolerance test (>180 min) was calculated by the trapezoidal rule (18).

Insulin sensitivity was further evaluated in a subgroup of 104 patients by a hyperinsulinemic-euglycemic clamp that was performed according to De Fronzo et al. (20) as previously described (21). In brief, a priming insulin (Humulin R; Eli Lilly, Sesto Fiorentino, Italy) dose of 100 mU/kg body wt was administered intravenously over a period of 10 min, and then a sustained infusion of insulin (dissolved in 0.9% NaCl), at a rate of 2 mU · kg body wt^{-1} · min^{-1}, was started to maintain serum insulin concentrations at ~700 pmol/l. Concomitantly, an intravenous infusion of a 20% glucose solution was started to stabilize blood glucose values at 5.0 mmol/l. To this purpose, plasma glucose was determined every 10 min during the clamp. Sensitivity to insulin was assessed as the glucose metabolic clearance rate (MCR) (milliliters per kilogram per minute) during 60 min of the clamp.

Plasma glucose was assayed using the glucose oxidase method with an oxygen electrode. Total cholesterol and triglycerides were assayed enzymatically by an automated method (International Laboratory, Milan, Italy). HDL cholesterol was assayed enzymatically after magnesium chloride–dextran sulfate precipitation of apolipoprotein-B–containing lipoproteins. The concentration of LDL cholesterol was calculated with the formula of Friedewald et al. (22). Plasma insulin, C-peptide, glucagon, growth hormone, and microalbuminuria were measured by radioimmunoassay as previously described (6,16,18,23), and intact parathyroid hormone (i-PTH) by IRMA (immunoradiometric test with monoclonal antibody).

All values are expressed as means ± SD. The Student's *t* test was used for comparisons between two groups, and ANOVA (two-way) was used for comparisons of more than two groups. The Pearson χ^2 test was used to compare frequency distributions. The relationship between different parameters was examined by linear regression analysis, and the correlation was expressed by the correlation coefficient.

RESULTS

Clinical, lipid, and glucose metabolism parameters of hypertensive and control subjects are presented in Table 1. In addition to greater triglyceride and lower HDL cholesterol levels, hypertensive patients had greater fasting plasma insulin and C-peptide levels, greater AUC for blood glucose and plasma insulin, and lower fasting glucose-to-insulin ratio than control subjects. Creatinine clearance <90 ml · min^{-1} · 1.73 m^{-2} was found in 116 of 321

TABLE 2
Clinical, lipid, and renal parameters of the hypertensive patients according to creatinine clearance values

	Creatinine clearance (ml · min^{-1} · 1.73 m^{-2})			
	≥90	70–89	50–69	30–49
n	205	69	29	18
Age (years)	52 ± 11	54 ± 12	56 ± 14	60 ± 14*
Sex (M/F)	120/85	38/31	16/13	10/8
Systolic blood pressure (mmHg)	164 ± 25	172 ± 22	178 ± 22*	179 ± 24*
Diastolic blood pressure (mmHg)	101 ± 13	102 ± 12	101 ± 12	102 ± 10
Duration of hypertension (months)	52 ± 69	66 ± 52	89 ± 73†	105 ± 71‡
BMI (kg/m^2)	26.8 ± 3.3	26.7 ± 4.1	26.4 ± 2.8	26.6 ± 3.9
Waist-to-hip ratio	0.92 ± 0.08	0.91 ± 0.09	0.92 ± 0.07	0.91 ± 1.10
Current smokers (%)	36	41	38	39
Total cholesterol (mmol/l)	5.44 ± 1.14	5.48 ± 0.99	5.47 ± 1.04	5.50 ± 1.13
LDL cholesterol (mmol/l)	3.47 ± 1.04	3.52 ± 0.88	3.48 ± 0.91	3.52 ± 1.09
HDL cholesterol (mmol/l)	1.32 ± 0.39	1.32 ± 0.39	1.33 ± 0.28	1.31 ± 0.43
Triglycerides (mmol/l)	1.31 ± 0.76	1.43 ± 0.79	1.51 ± 0.82	1.79 ± 0.81*
Free fatty acids (mg/l)	176 ± 23	174 ± 21	180 ± 27	181 ± 26
Serum creatinine (μmol/l)	86.7 ± 12.4	102.7 ± 17.7‡	114.2 ± 29.2‡	198.2 ± 79.6‡
Creatinine clearance (ml · min^{-1} · 1.73 m^{-2})	117.2 ± 23.1	79.3 ± 5.6‡	61.2 ± 4.2‡	34.6 ± 4.3‡
Urinary protein excretion (mg/day)	220 ± 172	219 ± 203	329 ± 332	538 ± 529‡
Microalbuminuria (mg/day)	22 ± 27	34 ± 92	118 ± 314‡	187 ± 302‡

Data are means ± SD. Comparisons are by two-way ANOVA or Pearson χ^2 test. *$P < 0.05$ vs. patients with creatinine clearance ≥90 ml · min^{-1} · 1.73 m^{-2}; †$P < 0.01$ vs. patients with creatinine clearance ≥90 ml · min^{-1} · 1.73 m^{-2}; ‡$P < 0.001$ vs. patients with creatinine clearance ≥90 ml · min^{-1} · 1.73 m^{-2}. To convert to conventional units, multiply creatinine by 0.0113 (mg/dl), cholesterol by 38.6 (mg/dl), and triglycerides by 88.5 (mg/dl).

hypertensive patients. Decreased creatinine clearance was caused by hypertensive nephrosclerosis in all patients, a diagnosis that was made after exclusion of other renal diseases. As shown in Table 2, age, systolic blood pressure, and duration of hypertension were significantly and inversely related to creatinine clearance. Sex distribution, anthropometric indexes, current smoking status, and plasma lipids, with the exception of triglycerides, were comparable among the four creatinine clearance groups. Among patients with early renal failure, those with creatinine clearance <50 ml · min^{-1} · 1.73 m^{-2} had significantly greater fasting plasma insulin and C-peptide levels, greater AUC for blood glucose and plasma insulin, and lower fasting glucose-to-insulin ratio than patients with normal renal function (Table 3 and Fig. 1). These differences remained significant after correction of values for age. All measures of glucose metabolism were comparable among patients groups with creatinine clearance of ≥50 ml · min^{-1} · 1.73 m^{-2}. During the hyperinsulinemic clamp, comparable steady-state plasma glucose and plasma insulin levels were maintained in the four creatinine clearance groups. Consistent with the results of the OGTT, lower glucose MCR was observed in patients with creatinine clearance <50 ml · min^{-1} · 1.73 m^{-2}, indicating reduced peripheral sensitivity to insulin in this group (Table 3). No differences in glucose MCR were found among patient groups with creatinine clearance of ≥50 ml · min^{-1} · 1.73 m^{-2}. Patients with creatinine clearance <50 ml · min^{-1} · 1.73 m^{-2} had significantly lower levels of Hb and serum bicarbonate and greater levels of serum potassium than patients with creatinine clearance of ≥50 ml · min^{-1} · 1.73 m^{-2}, whereas no significant differences were found in plasma magnesium, calcium, phosphorus, parathyroid hormone, glucagon, and growth hormone levels (Table 4).

Comparison of hypertensive patients with and without microalbuminuria showed significantly greater systolic

TABLE 3
Glucose metabolism parameters of the study patients

	Creatinine clearance (ml · min^{-1} · 1.73 m^{-2})			
	≥90	70–89	50–69	30–49
n	205	69	29	18
Fasting glucose (mmol/l)	5.05 ± 0.94	5.10 ± 1.44	4.77 ± 1.17	4.76 ± 1.33
Fasting insulin (pmol/l)	73.2 ± 19.5	78.2 ± 20.9	73.9 ± 27.3	90.3 ± 28.0*
Fasting C-peptide (nmol/l)	0.73 ± 0.29	0.72 ± 0.39	0.73 ± 0.36	1.47 ± 1.04†
Fasting glucose-to-insulin ratio × 100	6.90 ± 2.75	6.52 ± 2.90	7.46 ± 4.35	5.25 ± 2.07*
AUC blood glucose (mmol · l^{-1} · min)	23.8 ± 6.7	24.1 ± 8.6	25.1 ± 10.6	33.1 ± 5.3†
AUC plasma insulin (pmol · l^{-1} · min)	1,054 ± 603	1,033 ± 581	954 ± 674	1,722 ± 1,011†
Glucose MCR (ml · kg^{-1} · min)	15.6 ± 2.2	14.8 ± 3.4	15.1 ± 3.1	11.2 ± 2.9*

Data are means ± SD. Comparisons are by one-way ANOVA. *$P < 0.05$ vs. patients with creatinine clearance ≥90 ml · min^{-1} · 1.73 m^{-2}; †$P < 0.001$ vs. patients with creatinine clearance ≥90 ml · min^{-1} · 1.73 m^{-2}. AUC for blood glucose and serum insulin concentration 180 min after oral glucose load. Glucose MCR was assessed by a hyperinsulinemic-euglycemic clamp in a subgroup of 104 patients (creatinine clearance ≥90 ml · min^{-1} · 1.73 m^{-2}, $n = 42$; 70–89 ml · min^{-1} · 1.73 m^{-2}, $n = 32$; 50–69 ml · min^{-1} · 1.73 m^{-2}, $n = 19$; 30–49 ml · min^{-1} · 1.73 m^{-2}, $n = 11$). To convert to conventional units, multiply glucose by 0.05551 (mg/dl), insulin by 7.175 (μU/ml), and C-peptide by 3.021 (ng/ml).

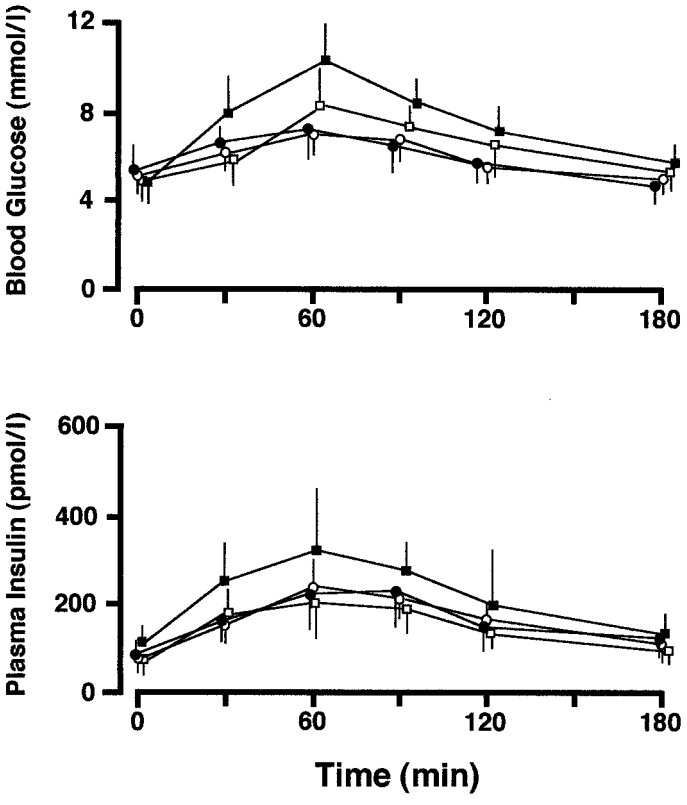

FIG. 1. Plasma glucose and plasma insulin response to a 75-g OGTT in patients with various creatinine clearance rates (≥90 ml · min^{-1} · 1.73 m^{-2}, n = 205, ○; 70–89 ml · min^{-1} · 1.73 m^{-2}, n = 69, ●; 50–69 ml · min^{-1} · 1.73 m^{-2}, n = 29, □; 30–49 ml · min^{-1} · 1.73 m^{-2}, n = 18, ■). Plasma glucose and insulin responses were significantly increased in patients with creatinine clearance <50 ml · min^{-1} · 1.73 m^{-2}.

blood pressure and duration of hypertension in patients with microalbuminuria (Table 5); no significant difference was found in glucose metabolism parameters with the exception of C-peptide levels. Analysis of correlations showed that creatinine clearance was significantly and inversely correlated with age ($r = -0.276$, $P < 0.001$), plasma C-peptide ($r = -0.183$, $P < 0.01$), systolic blood pressure ($r = -0.177$, $P < 0.01$), and microalbuminuria ($r = -0.177$, $P < 0.01$). No correlations were found between the other parameters of glucose metabolism and creatinine clearance or microalbuminuria.

Clinical and instrumental evidence of one or more events attributed to atherosclerosis was found in 10.7% of patients with creatinine clearance of ≥90 ml · min^{-1} · 1.73 m^{-2} and in 14.5, 31.0, and 38.9% of patients with creatinine clearance between 70 and 89, 50 and 69, and 30 and 49 ml · min^{-1} · 1.73 m^{-2}, respectively ($P < 0.001$) (Table 6). Most of these events (97%) occurred in the 5 years before the study. Significant difference in prevalence of atherosclerotic complications was also observed between patients with normal and impaired renal function when coronary artery, cerebrovascular, and peripheral vascular disease were considered separately. Among patients with decreased creatinine clearance, those with evidence of atherosclerotic complications were older, had significantly greater levels of systolic blood pressure, total and LDL cholesterol, cigarette consumption, and microalbuminuria and significantly lower HDL cholesterol than patients without such evidence (Table 7). All parameters of glucose metabolism were comparable in renal failure patients, with and without evidence of atherosclerotic complications.

DISCUSSION

The present study was performed in a large group of patients with hypertensive nephrosclerosis to investigate at which stage of renal failure abnormalities of glucose metabolism develop. The results demonstrate that fasting hyperinsulinemia, abnormal glucose and insulin response to an OGTT, and decreased sensitivity to insulin were not detectable at the earliest stages of renal failure, whereas they are present when creatinine clearance is <50 ml · min^{-1} · 1.73 m^{-2}. These abnormalities do not appear to be related to glomerular damage as evaluated by measurement of microalbuminuria. Although patients with early renal failure have increased prevalence of atherosclerotic complications, these are not associated with significant changes in the parameters of glucose metabolism.

Many studies have shown that the sensitivity to the action of insulin with respect to carbohydrate metabolism is markedly impaired in patients with end-stage renal failure who are undergoing conservative or dialytic treatment (10–13). Because hyperglycemia and hyperinsulinemia may contribute to development of atherosclerosis (8,9) and accumulation of glycosylation end products in various tissues and because they have adverse effects on

TABLE 4
Biochemical and hormonal parameters in the study patients

	Creatinine clearance (ml · min^{-1} · 1.73 m^{-2})			
	≥90	70–89	50–69	30–49
n	205	69	29	18
Hb (mmol/l)	8.9 ± 1.1	8.7 ± 1.3	8.4 ± 1.0	8.0 ± 0.9*
Bicarbonate (mmol/l)	24 ± 2	24 ± 3	22 ± 2†	20 ± 2‡
Potassium (mmol/l)	4.1 ± 0.5	4.0 ± 0.6	4.2 ± 0.5	4.5 ± 0.7†
Magnesium (mmol/l)	0.92 ± 0.12	0.93 ± 0.14	0.90 ± 0.13	0.88 ± 0.09
Calcium (mmol/l)	2.4 ± 0.3	2.4 ± 0.2	2.3 ± 0.3	2.2 ± 0.3
Phosphorus (mmol/l)	1.22 ± 0.20	1.20 ± 0.18	1.27 ± 0.21	1.31 ± 0.23
Parathyroid hormone (ng/l)	59 ± 35	64 ± 32	65 ± 31	81 ± 37
Glucagon (ng/l)	74 ± 31	70 ± 25	81 ± 30	77 ± 27
Growth hormone (μg/l)	4.5 ± 1.9	4.7 ± 2.0	4.7 ± 1.7	4.3 ± 1.6

Data are means ± SD. Comparisons are by one-way ANOVA. *$P < 0.05$ vs. patients with creatinine clearance ≥90 ml · min^{-1} · 1.73 m^{-2}; †$P <$ 0.01 vs. patients with creatinine clearance ≥90 ml · min^{-1} · 1.73 m^{-2}; ‡$P < 0.001$ vs. patients with creatinine clearance ≥90 ml · min^{-1} · 1.73 m^{-2}. To convert to conventional units, multiply Hb by 1.611 (mg/dl).

TABLE 5
Clinical and glucose metabolism parameters in patients with and without microalbuminuria

	Microalbuminuria ≤30 mg/day	Microalbuminuria >30 mg/day
n	208	113
Age (years)	53 ± 11	54 ± 12
Systolic blood pressure (mmHg)	164 ± 23	171 ± 22*
Diastolic blood pressure (mmHg)	101 ± 13	102 ± 10
Duration of hypertension (months)	50 ± 61	89 ± 94*
BMI (kg/m^2)	26.8 ± 3.2	27.1 ± 3.6
Serum creatinine (μmol/l)	89.4 ± 17.7	96.5 ± 36.3†
Creatinine clearance (ml · min^{-1} · 1.73 m^{-2})	100.9 ± 28.7	92.9 ± 31.8†
Microalbuminuria (mg/day)	8.1 ± 4.9	91.7 ± 191.0*
Fasting glucose (mmol/l)	4.94 ± 0.89	4.99 ± 1.44
Fasting insulin (pmol/l)	78.2 ± 35.9	75.3 ± 40.2
Fasting C-peptide (nmol/l)	0.71 ± 0.31	0.81 ± 0.49†
Fasting glucose-to-insulin ratio × 100	6.32 ± 3.86	6.63 ± 3.49
AUC blood glucose (mmol · l^{-1} · min)	24.1 ± 7.1	23.8 ± 7.7
AUC plasma insulin (pmol · l^{-1} · min)	1,134 ± 667	971 ± 610
Glucose MCR (ml · kg^{-1} · min)	15.2 ± 2.6	15.0 ± 2.9

Data are means ± SD. Comparisons are by Student *t* test. *$P < 0.001$ vs. patients without microalbuminuria; †$P < 0.05$ vs. patients without microalbuminuria. AUC for blood glucose and serum insulin concentration 180 min after oral glucose load. MCR was assessed during the hyperinsulinemic-euglycemic clamp. Glucose MCR was assessed by a hyperinsulinemic-euglycemic clamp in a subgroup of 104 patients (56 without microalbuminuria and 48 with microalbuminuria). To convert to conventional units, multiply creatinine by 0.0113 (mg/dl), glucose by 0.05551 (mg/dl), insulin by 7.175 (μU/ml), and C-peptide by 3.021 (ng/ml).

protein metabolism, it is important to define the stage in which renal failure abnormalities of glucose metabolism develop. Only a few studies have addressed this question in patients with mild impairment of renal function. Eidemak et al. (24) studied 29 patients with renal failure of mixed etiology and a median glomerular filtration rate (GFR) of 25 ml · min^{-1} · 1.73 m^{-2} and observed normal blood glucose response to the OGTT, hyperinsulinemia during both fasting and the OGTT, and decreased sensitivity to insulin as compared with 15 healthy control subjects. The major limitation of this study was that it included patients with obesity and patients treated with β-blockers, thiazides, or ACE inhibitors, drugs that are known to affect glucose metabolism and insulin sensitivity (25–27). Insulin resistance and hyperinsulinemia were also observed by Stenvinkel et al. (28) early in the course of renal insufficiency in patients with nephrotic syndrome (GFR 64 ± 6 ml/min) and in renal transplant recipients (GFR 44 ± 6 ml/min). However, in these categories of patients, factors other than renal insufficiency per se, such as dyslipidemia and immunosuppressive drugs, are likely to contribute to the derangement of glucose metabolism. More recently, Fliser et al. (29) evaluated 50 renal patients with IgA glomerulonephritis or adult polycystic kidney disease in different stages of renal failure. These authors observed hyperinsulinemia and insulin resistance of the same degree throughout the range of renal function considered (~20–130 ml/min), including renal patients with GFR in the normal range, suggesting that abnormal glucose metabolism may be part of the phenotype of these two

TABLE 6
Cardiovascular disease status of the study patients

	Creatinine clearance (ml · min^{-1} · 1.73 m^{-2})			
	≥90	70–89	50–69	30–49
n	205	69	29	18
Coronary artery disease*	14 (6.8)	5 (7.3)	5 (17.2)	4 (22.2)
Angina pectoris	10	4	4	2
Myocardial infarction	4	1	1	2
Cerebrovascular disease*	6 (2.9)	3 (4.3)	4 (5.8)	2 (11.1)
Atherosclerotic plaques	4	2	—	—
TIA or PRIND	1	—	1	1
Atherothrombotic stroke	1	1	3	1
Peripheral vascular disease*	8 (3.9)	3 (4.3)	3 (10.3)	4 (22.2)
Atherosclerotic plaques	5	2	1	1
Symptomatic arterial occlusive disease	3	1	2	2
Aortic aneurysm	—	—	—	1
Total number of events	28	11	12	10
Number of subjects with events†	22 (10.7)	10 (14.5)	9 (31.0)	7 (38.9)

*$P < 0.05$ by Pearson χ^2 test; †$P < 0.001$ by Perason χ^2 test. Carotid arteries, abdominal aorta, and iliac and femoral arteries were evaluated with a B-mode ultrasound system equipped with a 7.5-MHz transducer. Examination was performed in the supine position, and multiple projections were used. Atherosclerotic lesions were defined by the presence of plaques at least 50% greater than the surrounding wall. PRIND, prolonged reversible ischemic neurologic deficit; TIA, transitory ischemic attack.

TABLE 7
Clinical and metabolic parameters in patients with early renal failure with and without evidence of cardiovascular disease

	Patients without cardiovascular disease	Patients with cardiovascular disease
n	90	26
Age (years)	54 ± 12	64 ± 12*
Systolic blood pressure (mmHg)	171 ± 21	185 ± 27*
Diastolic blood pressure (mmHg)	101 ± 12	101 ± 14
BMI (kg/m^2)	26.7 ± 3.8	26.5 ± 3.3
Current smokers (%)	34	57†
Total cholesterol (mmol/l)	5.37 ± 0.98	5.83 ± 0.91†
LDL cholesterol (mmol/l)	3.39 ± 0.84	3.90 ± 0.86*
HDL cholesterol (mmol/l)	1.36 ± 0.37	1.18 ± 0.34†
Triglycerides (mmol/l)	1.33 ± 0.93	1.61 ± 0.90
Creatinine clearance (ml · min^{-1} · 1.73 m^{-2})	72.6 ± 13.7	60.2 ± 19.7*
Urinary protein excretion (mg/day)	233 ± 198	479 ± 216*
Microalbuminuria (mg/day)	50 ± 90	144 ± 223*
Fasting glucose (mmol/l)	5.00 ± 1.44	4.88 ± 1.22
Fasting insulin (pmol/l)	75.3 ± 35.9	76.1 ± 42.3
Fasting C-peptide (pmol/l)	0.85 ± 0.52	1.02 ± 0.55
Fasting glucose-to-insulin ratio × 100	6.64 ± 2.65	6.41 ± 4.48
AUC blood glucose (mmol · l^{-1} · min)	24.9 ± 9.3	27.5 ± 9.4
AUC plasma insulin (pmol · l^{-1} · min)	1,148 ± 732	990 ± 524
Glucose MCR (ml · kg^{-1} · min)	14.5 ± 3.0	13.8 ± 3.4

Data are means ± SD. Comparison by Student *t* test or Pearson χ^2 test. *$P < 0.01$ vs. patients with creatinine clearance ≥90 ml · min^{-1} · 1.73 m^{-2}; †$P < 0.05$ vs. patients with creatinine clearance ≥90 ml · min^{-1} · 1.73 m^{-2}. AUC for blood glucose and serum insulin concentration 180 min after oral glucose load. MCR was assessed during the hyperinsulinemic-euglycemic clamp. To convert to conventional units, multiply cholesterol by 38.6 (mg/dl), triglycerides by 88.5 (mg/dl), glucose by 0.05551 (mg/dl), insulin by 7.175 (μU/ml), and C-peptide by 3.021 (ng/ml).

specific pathological conditions, independent of renal function. This possibility was supported by another study by Vareesangthip et al. (30), who observed insulin resistance and hyperinsulinemia in 15 patients with adult polycystic kidney disease and GFR in the normal range. The present study examined the largest sample of renal patients and was devoid of potential confounders, such as different etiology of the renal failure, inclusion of patients with obesity or family history of diabetes, and treatments with drugs that might affect glucose metabolism. Moreover, in addition to calculation of the fasting glucose-to-insulin ratio (16,19), in order to better define the sensitivity to insulin of peripheral tissues, we performed a hyperinsulinemic-euglycemic clamp in a subgroup of patients. Our study demonstrates that abnormal plasma glucose response to an oral glucose load, hyperinsulinemia, and insulin resistance develop when the GFR is <50 ml · min^{-1} · 1.73 m^{-2} but are not present at earlier stages of renal failure.

Different mechanisms may contribute to the abnormal glucose metabolism in chronic renal failure, including decreased sensitivity to insulin, inadequate insulin secretion, and increased hepatic gluconeogenesis (13,31). In addition to some conditions intrinsically related to renal failure (such as anemia [32] and metabolic acidosis [33]), accumulation of some toxic substance(s), including free fatty acids (31), hormones with antagonistic actions to insulin (31), "middle molecules" (34), pseudouridine (35), nitrogenous substances derived from protein metabolism (36), and acute phase reactants (37), may contribute to the impaired insulin-mediated glucose metabolism occurring after a certain degree of renal function loss. Some of these potential contributors were evaluated in our study. In patients with creatinine clearance <50 ml · min^{-1} · 1.73 m^{-2} and altered glucose metabolism, we found significant differences in Hb, bicarbonate, and potassium concentrations but not in plasma magnesium, free fatty acid, glucagon, and growth hormone concentrations as compared with patients with GFR ≥50 ml · min^{-1} · 1.73 m^{-2}. Moreover, because insulin resistance and hyperinsulinemia of uremia may be related to secondary hyperparathyroidism (38), we evaluated plasma calcium, phosphorus, and i-PTH levels and found a trend, though not significant, for increased i-PTH in patients with decreased creatinine clearance, suggesting a possible contributor to the impairment of glucose metabolism in these patients.

Although increased cardiovascular morbidity and mortality have been repeatedly reported in patients with end-stage renal failure (1,2,39,40), the incidence of cardiovascular events in patients with early impairment of renal function is still debated. In a prospective cohort study over a 10-year period, Jungers et al. (7) observed a threefold increase in the incidence of cardiovascular events in patients with moderate renal failure as compared with the general population. In addition to other cardiovascular risk factors (3–6), hyperinsulinemia may contribute to increased cardiovascular morbidity in chronic renal failure patients (13). The present study is the first to evaluate the relationship between the prevalence of cardiovascular disease and parameters of glucose metabolism in patients with early impairment of renal function. The results showed that abnormalities of carbohydrate metabolism were not associated with cardiovascular events, suggesting that hyperinsulinemia and altered response to oral glucose load were unlikely contributors to cardiovascular morbidity in these patients. This conclusion requires the support of longitudinal studies.

Some possible limitations of the present study should be discussed. First, the use of a clinic sample might limit the generalizability of the conclusions to the general popula-

tion because of a bias in the referral of patients to the source of care. This might also explain the high incidence of renal failure in hypertensive patients in our patient sample. Second, because the underlying renal disease in patients with decreased creatinine clearance was arteriolar nephrosclerosis, results should be extrapolated to other forms of renal disease with caution.

In conclusion, in patients with hypertensive nephrosclerosis and early impairment of GFR, abnormalities of carbohydrate metabolism and hyperinsulinemia become evident only when creatinine clearance is <50 ml $\cdot$ min^{-1} $\cdot$ 1.73 m^{-2}. These abnormalities are not related to microalbuminuria. Although patients with early renal failure have increased prevalence of cardiovascular events, these events are not associated with abnormal glucose metabolism. Abnormalities of glucose metabolism do not appear to be significant contributors to cardiovascular damage in early renal disease, but this conclusion needs further evaluation in longitudinal studies.

ACKNOWLEDGMENTS

This research was supported by CNR (Consiglio Nazionale delle Ricerche) Grants 92.01096.CT04, 94.084231.CT 04, and 94.02438.CT04; a Fulbright Senior Fellowship; and a Ferrero Foundation grant to L.A.S.

REFERENCES

1. Rainer AEG, Margreiter R, Brunner FP, Ehrich JHH, Geelings W, Landais P, Loirat C, Mallik NP, Selwood NH, Tufveson G, Valdebarrano F: Report on the management of renal failure in Europe, XXII, 1991. *Nephrol Dial Transplant* 3:7–35, 1992
2. Lindner A, Charra B, Sherrard DJ, Sribner BH: Accelerated atherosclerosis in prolonged maintenance hemodialysis. *N Engl J Med* 290:697–701, 1974
3. Ma KW, Greene EL, Raij L: Cardiovascular risk factors in chronic renal failure and hemodialysis patients. *Am J Kidney Dis* 19:505–513, 1992
4. Jensen T, Stender S, Deckert T: Abnormalities in plasma concentrations of lipoproteins and fibrinogen in type I (insulin-dependent) diabetic patients with increased urinary albumin excretion. *Diabetologia* 31:142–145, 1988
5. Bostom AG, Gohh RY, Beaulieu AJ, Nadeau MR, Hume AL, Jaques PF, Selhub J, Rosenberg IH: Treatment of hyperhomocysteinemia in renal transplant recipients. *Ann Intern Med* 127:1089–1092, 1997
6. Sechi LA, Zingaro L, De Carli S, Sechi G, Catena C, Falleti E, Dell'Anna E, Bartoli E: Increased serum lipoprotein(a) levels in patients with early renal failure. *Ann Intern Med* 129:457–461, 1998
7. Jungers P, Massy ZA, Nguyen Khoa T, Fumeron C, Labrunie M, Lacour B, Descamps-Latscha B, Man N: Incidence and risk factors of atherosclerotic cardiovascular accidents in predialysis chronic renal failure patients. *Nephrol Dial Transplant* 12:2597–2602, 1997
8. Despres JP, Lamarche B, Mauriege P, Cantin B, Dagenais GR, Moorjani S, Lupien PJ: Hyperinsulinemia as an independent risk factor for ischemic heart disease. *N Engl J Med* 334:952–957, 1996
9. Frayn KN, Coppack SW: Insulin resistance, adipose tissue and coronary heart disease. *Clin Sci* 82:1–8, 1992
10. Horton ES, Johnson C, Lebowitz HE: Carbohydrate metabolism in uremia. *Ann Intern Med* 68:63–74, 1968
11. DeFronzo RA, Tobin JD, Robin JW, Andres R: Glucose intolerance in uremia. *J Clin Invest* 62:425–435, 1978
12. Westrevelt FB: Abnormal carbohydrate metabolism in uraemia. *Am J Clin Nutr* 21:423–425, 1968
13. Alvestrand A: Carbohydrate and insulin metabolism in renal failure. *Kidney Int* 52 (Suppl. 62):S48–S52, 1997
14. Petrie JC, O'Brien ET, Littler WA, de Swiet M: Recommendations on blood pressure measurement. *BMJ* 293:611–615, 1996
15. Grafnetter D, Feruglio GA, Vanuzzo D: Standardization of methods of lipid determination according to WHO in the regional project of prevention of cardiovascular diseases in Friuli-Venezia Giulia. *G Ital Cardiol* 26:287–297, 1996
16. Sechi LA, Melis A, Tedde R: Insulin hypersecretion: a distinctive feature between essential and secondary hypertension. *Metabolism* 11:1261–1266, 1992
17. Sechi LA, Kronenberg F, De Carli S, Falleti E, Zingaro L, Catena C, Utermann G, Bartoli E: Association of lipoprotein(a) levels and apolipoprotein(a) size polymorphism with target-organ damage in arterial hypertension. *JAMA* 277:1689–1695, 1997
18. Sechi LA, Catena C, Zingaro L, De Carli S, Bartoli E: Hypertension and abnormalities of carbohydrate metabolism: possible role of sympathetic nervous system. *Am J Hypertens* 10:678–682, 1997
19. Mbanya JCN, Thomas TH, Wilkinson R, Alberti KGMM, Taylor R: Hypertension and hyperinsulinaemia: a relation in diabetes but not essential hypertension. *Lancet* i:733–734, 1988
20. De Fronzo RA, Tobin JD, Andres R: Glucose clamp technique: a method for quantifying insulin secretion and resistance. *Am J Physiol* 237:E214–E223, 1979
21. Sechi LA, Marigliano A, Tedde R: Evaluation of insulin-induced changes in the renal response to furosemide in normal subjects. *Miner Electrolyte Metab* 17:383–389, 1991
22. Friedewald WT, Levy RI, Friedrickson DS: Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative centrifuge. *Clin Chem* 18:499–502, 1972
23. Christensen CK, Orskov H: Rapid screening PEG radioimmunoassay for quantification of pathological microalbuminuria. *Diabetic Nephrop* 3:92–98, 1984
24. 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
25. Pollare T, Lithell H, Selinus I, Berne C: Sensitivity to insulin during treatment with atenolol and metoprolol: a randomised, double blind study of effects on carbohydrate and lipoprotein metabolism in hypertensive patients. *BMJ* 298:1152–1157, 1989
26. Pollare T, Lithell H, Berne C: A comparison of the effects of hydrochlorothiazide and captopril on glucose and lipid metabolism in patients with hypertension. *N Engl J Med* 321:868–873, 1989
27. Jauch KW, Hartl W, Guenther B, Wicklmayr M, Rett K, Dietze G: Captopril enhances insulin responsiveness of forearm muscle tissue in non-insulin-dependent diabetes mellitus. *Eur J Clin Invest* 17:953–959, 1987
28. 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, 1994
29. Fliser D, Pacini G, Engelleiter R, Kautzky-Willer A, Prager R, Franek A, Ritz E: Insulin resistance and hyperinsulinemia are already present in patients with incipient renal disease. *Kidney Int* 53:1343–1347, 1998
30. Vareesangthip K, Tong P, Wilkinson R, Thomas TH: Insulin resistance in adult polycystic kidney disease. *Kidney Int* 52:503–508, 1997
31. Alvestrand A, Majagic M, Wajngot A, Efendic S: Glucose intolerance in uremic patients: the relative contributions of impaired b-cell function in insulin resistance. *Clin Nephrol* 31:175–183, 1989
32. Mak RHK: Effect of recombinant human erythropoietin on insulin, amino acid, and lipid metabolism in uremia. *J Pediatr* 129:97–104, 1996
33. Reaich D, Channon SM, Scrimgeour CM, Daley SE, Wilkinson R, Goodship THJ: Correction of acidosis in humans with CRF decreases protein degradation and amino acid oxidation. *Am J Physiol* 265:E230–E235, 1993
34. McCaleb ML, Izzo MS, Lockwood DH: Characterization and partial purification of a factor from uremic serum that induces insulin resistance. *J Clin Invest* 75:391–396, 1985
35. Dzuric R, Spustova V, Lajdova I: Inhibition of glucose utilization in isolated rat soleus muscle by pseudouridine: implications for renal failure. *Nephron* 65:108–110, 1993
36. Mak RHK, Turner C, Thompson T, Haycock GB, Chantler C: The effects of low protein diet with amino acid/keto acid supplements on glucose metabolism in children with uremia. *J Clin Endocrinol Metab* 63:985–991, 1986
37. Hotamisligil GS, Arner P, Caro JF, Atkinson RL, Spiegelman BM: Increased adipose tissue expression of tumor necrosis factor-alpha in human obesity and insulin resistance. *J Clin Invest* 95:2409–2415, 1995
38. Fadda GZ, Tanakitcharu P, Smogorzewski M, Massry SG: Parathyroid hormone raises citosolic calcium in pancreatic islets: study on mechanisms. *Kidney Int* 43:554–560, 1993
39. USRDS: Annual Report. *Am J Kidney Dis* 24 (Suppl. 2):S88–S95, 1994
40. Parfrey PS, Harnett JD: Long-term cardiac morbidity and mortality during dialysis therapy. *Adv Nephrol Necker Hosp* 23:311–330, 1994