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Insulin resistance and hyperinsulinemia are already present in patients with incipient renal disease

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Insulin resistance and hyperinsulinemia are already present in patients with incipient renal disease. In uremic patients resistance to the action of insulin has been documented, but it is not known at what stage of renal disease it appears. We therefore examined 29 patients with IgA glomerulonephritis (IgAGN) and 21 patients with adult polycystic kidney disease (ADPKD) in different stages of renal failure, and in addition, healthy age-matched subjects. Insulin sensitivity and other variables of glucose metabolism were assessed using a frequent sampling intravenous glucose tolerance test (minimal-model technique). Glomerular filtration rate (GFR) was assessed in renal patients using the inulin-clearance technique. Mean insulin sensitivity index (SI), that is, insulin sensitivity, was significantly lower ($P < 0.001$) in all patients combined than in matched healthy subjects ($N = 16$; 14 males, mean age 42 ± 3 years; mean SI 8.6 ± 0.8 min^{-1} μU/ml). The mean SI was not significantly different in patients with renal disease of immune (IgAGN) or non-immune (ADPKD) origin, and it was not correlated with GFR ($r = 0.01$, $P < 0.52$), intact PTH ($r = -0.23$, $P < 0.11$) or calcitriol concentration ($r = -0.03$, $P < 0.82$). Consequently, the mean SI was similar in renal patients with GFR within the normal range ($N = 19$; 17 males, mean age 41 ± 2 years; mean GFR 119 ± 5 ml/min/1.73 m^2; mean SI 5.1 ± 0.7 min^{-1} μU/ml), in patients with mild to moderate renal failure ($N = 16$; 15 males, 46 ± 3 years; 67 ± 4 ml/min/1.73 m^2; 5.1 ± 0.7 min^{-1} μU/ml) and in patients with advanced renal failure ($N = 15$; 13 males, 46 ± 3 years; 25 ± 2 ml/min/1.73 m^2; 4.7 ± 0.6 min^{-1} μU/ml). Mean fasted plasma insulin concentration, the area under the curve for plasma insulin concentration (AUC) and total insulin delivery (TID) during the glucose tolerance test were significantly higher in patients than in healthy subjects, reflecting hyperinsulinemia in renal patients. Further, fasted plasma insulin concentration ($r = -0.32$, $P < 0.009$), AUC ($r = -0.62$, $P < 0.0001$) and TID ($r = -0.34$, $P < 0.004$) in patients were significantly correlated with insulin sensitivity (SI). The present data document that insulin resistance and concomitant hyperinsulinemia are present early in the course of renal disease, that is, even in patients with GFR within the normal range, irrespective of the type of renal disease. This observation may have potential implications with respect to the high cardiovascular morbidity and mortality in patients with renal disease.

Uremia is characterized by resistance to the action of insulin and this is accompanied by hyperinsulinemia, glucose intolerance and dyslipidemia [1–5]. An impaired glucose tolerance in patients with renal failure has been recognized decades ago [6], but only after the euglycemic clamp technique had become available, diminished insulin-stimulated glucose uptake, that is, insulin resistance, could be documented [7]. Alvestrand et al showed that glucose uptake by extrahepatic tissues is universally reduced in uremic patients, that is, that insulin resistance is present [8]. It is only in some patients with more severe reduction of glucose-induced insulin secretion by β-cells, however, that hyperglycemia and frankly abnormal glucose tolerance are present [9–12].

The incidence of atherosclerotic cardiovascular complications is increased in patients with terminal renal failure as compared with healthy subjects [13]. Frequent presence of lipoprotein abnormalities, atherosclerosis and high cardiovascular death rate have been noted even in patients with modest renal failure, however [14, 15]. Since insulin resistance and consecutive hyperinsulinemia are thought to be involved in the development of atherosclerosis [16], it is of interest at which stage of renal disease the derangements of glucose metabolism, specifically insulin resistance, develop.

To address this issue, we carried out a cross sectional study to examine insulin sensitivity (and other variables of glucose metabolism) in patients with different degrees of renal function. Patients with renal disease of immune origin, that is, IgA glomerulonephritis (IgAGN), and patients with renal disease of non-immune origin, that is, adult polycystic kidney disease (ADPKD) were included. The technique of the frequent sampling intravenous glucose tolerance test and analysis using the minimal-model technique were exploited.

METHODS

Participants and protocol

The protocol was approved by the Ethics Committee of the University of Heidelberg. All participants gave their informed consent. Fifty Caucasian patients with chronic renal disease between 20 and 60 years of age were examined; 29 had biopsy confirmed IgAGN and 21 had ADPKD. Patients with known diabetes mellitus of any type were excluded from the study. Patients were allocated into three groups with respect to their renal function: (*i*) normal plasma creatinine concentration, that is, below 1.3 mg/dl, (*ii*) mild to moderate impairment of renal function, that is, plasma creatinine concentration between 1.3 and

Key words: ADPKD, insulin resistance, glucose metabolism, IgA glomerulonephritis, renal disease, uremia.

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Table 1. Clinical data of healthy subjects and of renal patients

	Healthy subjects	Patients plasma creatinine concentration *mg/dl*		
		< 1.3	> 1.3 < 3.0	> 3.0
IgAGN/ADPKD	—	12/7	9/7	8/7
Age *years*	42 ± 3[a]	41 ± 2[a]	46 ± 3[a]	46 ± 3[a]
Gender (m/f)	14/2[a]	17/2[a]	15/1[a]	13/2[a]
BMI kg/m^2	25.2 ± 0.8[a]	25.7 ± 1.3[a]	25.9 ± 0.7[a]	25.4 ± 1.1[a]
Serum creatinine *mg/dl*	1.0 ± 0.1[a]	1.0 ± 0.1[a]	1.7 ± 0.1	4.2 ± 0.3
C_{In} *ml/min/1.73* m^2	—	119 ± 5	67 ± 4	25 ± 2
Serum cholesterol *mg/dl*	180 ± 6[a]	192 ± 6[a]	206 ± 6[a]	212 ± 7[a]
Serum triglycerides *mg/dl*	87 ± 4[a]	118 ± 5[ab]	142 ± 7[b]	154 ± 6[b]
PTH *pmol/liter*	—	4.7 ± 0.4	8.4 ± 1.6	39.6 ± 7.9
Calcitriol *pg/ml*	—	53 ± 3	40 ± 3	24 ± 2
HCO_3 *mmol/liter*	—	25.3 ± 0.4[a]	24.0 ± 0.2[a]	20.2 ± 0.6

Abbreviations are: IgAGN, IgA glomerulonephritis; ADPKD, adult polycystic kidneay disease; BMI, body mass index; C_{In}, glomerular filtration rate by inulin clearance; PTH, intact plasma parathyroid hormone concentration; HCO_3, plasma bicarbonate concentration. The statistical differences are given at a *P* level of 0.05 only; shared superscripts are not significantly different.

3.0 mg/dl, and (*iii*) advanced renal failure, that is, plasma creatinine concentration above 3.0 mg/dl. The three groups of patients were matched with respect to age, gender, body mass index (BMI) and type of renal disease (Table 1). All patients studied had stable renal function for at least six months before the study and none of them was treated with vitamin D, erythropoietin, fish oil or immunosuppresive agents. Higher grade proteinuria (that is, above 1 g/day) was present in 1 of 19 patients with normal renal function, in 5 of 16 patients with mild to moderate renal failure and in 11/15 patients with advanced renal failure. Anemia [defined as hemoglobin (Hb) concentration below 12 g/liter] was present in 9 of 15 patients with advanced renal failure (mean Hb concentration 10.9 ± 0.5 g/liter), but in none of the patients with normal renal function (15.4 ± 0.4 g/liter) or patients with mild to moderate renal impairment (14.8 ± 0.5 g/liter). Drugs with the potential of confounding the assessment of insulin sensitivity (such as β-receptor blockers, diuretics, etc.) were washed out for time periods depending on their half-life of action, that is, short-acting drugs were withdrawn for at least three days preceding examination, whereas long-acting drugs were washed out for at least one week prior to examination. Hypertension according to WHO criteria (that is, above 140/90 mm Hg) was present in 11 of 19 patients with normal renal function, in 13 of 16 patients with mild to moderate renal failure and in all patients with advanced renal failure. Mean arterial blood pressure (MAP) after washout of the antihypertensive drugs was not significantly different in all three groups of patients, that is, 103 ± 3, 107 ± 3 and 110 ± 3 mm Hg. For comparison, 16 healthy normotensive subjects between 20 and 60 years of age were also examined. They were matched with respect to age, gender and BMI to the patients (Table 1).

All participants were examined using a frequently sampled intravenous glucose tolerance test (FSIGT) with plasma glucose and insulin measurements. For three days before the test they adhered to a diet with normal carbohydrate content. They were examined while in recumbent position in a quiet environment after an overnight fast of at least 12 hours. After a cannula was placed in both forearms, blood samples for the measurement of basal (fasted) plasma glucose and insulin concentrations were withdrawn. Immediately thereafter an i.v. bolus injection of a 40% glucose solution was given over three minutes. The glucose load was 0.3 g/kg body wt in healthy normotensive and normoresponsive subjects. It was 0.5 g/kg body wt in patients, in whom lower responsiveness to a glucose load was expected [9–12, 17]. Blood samples for measurement of plasma glucose and insulin concentrations were withdrawn before and at 1, 2, 3, 5, 8, 10, 15, 20, 25, 30, 40, 50, 60, 75, 90, 120 and 150 minutes after the glucose load.

In addition to the above protocol, glomerular filtration rate (GFR) was assessed in patients on a separate day using the steady-state inulin (C_{In}) infusion clearance technique as described elsewhere (normal range, 90 to 150 ml/min/1.73 m^2) [18]. Further, blood samples for measurement of plasma intact parathyroid hormone (PTH), 1,25(OH)D_3 (calcitriol) and standard bicarbonate concentrations were drawn in all patients.

Measurements and calculations

Plasma glucose concentrations were measured with the Glucoanalyzer II® (Beckmann Instruments GmbH, Munich, Germany) and plasma insulin concentrations immuno-enzymatically using an ELISA with monoclonal insulin antibodies (ES 22®; Boehringer Mannheim, Mannheim, Germany; normal range, 4 to 16 μU/ml). The cross reactivity with proinsulin was less than 10% (as compared with a double sandwich RIA) and less than 1% for C-peptide. The intraassay and interassay coefficient of variation in healthy subjects is 5.2% and 7.5%, respectively, as assessed by 20 measurements of pooled random samples of healthy volunteers ($N = 10$). Parathyroid hormone (PTH) was measured with an immuno-radiometric assay (normal range, 1.2 to 6.0 pmol/liter), calcitriol was measured with an immuno-radiometric assay as well (normal range, 30 to 70 pg/ml), and inulin enzymatically using inulinase as described by Kühnle, von Dahl and Schmidt [19].

FSIGT data were analyzed using a computer program (MINMOD), which calculates the characteristic metabolic parameters by fitting glucose and insulin data to the minimal models that describe the time courses of plasma glucose and insulin concentrations [20]. The models assume a first order linear kinetic for insulin and a glucose-controlled biphasic release from the β-cell. Both have previously been described in detail [20–22]. The glucose disappearance model, by accounting for the effect of insulin and glucose on glucose disappearance, provides two parameters: SI ($min^{-1}/(\mu U/ml)$) is the insulin sensitivity index and SG the glucose effectiveness (min^{-1}), that is, the ability of glucose *per se*, independent of changes in insulin, to enhance glucose uptake [22]. The minimal model of insulin appearance in plasma accounts for the effect of glucose on insulin concentration during an FSIGT by describing the kinetics of insulin after its entry into the peripheral circulation. These models provide the time course of post-hepatic insulin delivery, that is, IDR(t) (μU/ml/min), and Φ_1 [(μU/ml)min^{-1}/(mg/dl)]. The latter describes the dynamic (supra-basal) glucose-controlled first phase post-hepatic insulin delivery and represents a sensitivity index of early insulin response to a glucose load. The integral over 150 minutes of IDR(t) gives TID (μU/ml in 150 min), which is the total amount of insulin per unit volume entering the peripheral circulation during the test. The area under the curve (AUC) for plasma insulin concentration during the glucose tolerance test (over 150 min) was calculated using the trapezoidal rule.

Table 2. Analysis of glucose metabolism using the minimal model (MINMOD) in healthy subjects and renal patients

	Healthy subjects	Patients plasma creatinine concentration *mg/dl*		
		< 1.3	> 1.3 < 3.0	> 3.0
SI *[min^{-1}/(μU/ml)]*	8.6 ± 0.8	5.1 ± 0.7[a]	5.1 ± 0.7[a]	4.7 ± 0.6[a]
SG $min^{-1} \times 100$	2.9 ± 0.3	1.7 ± 0.2[a]	1.9 ± 0.3[a]	1.8 ± 0.3[a]
Ib μU/ml	6.1 ± 0.8	11.9 ± 1.3[a]	12.1 ± 1.5[a]	10.8 ± 1.3[a]
AUC $mU \times min$/ml	2.1 ± 0.3[a]	3.8 ± 0.4[b]	4.1 ± 0.6[b]	3.4 ± 0.4[ab]
TID μU/ml	279 ± 27[a]	497 ± 92[b]	492 ± 84[b]	390 ± 56[ab]
Φ_1 (μU/ml) min^{-1}/(mg/dl)	5.4 ± 0.9	2.4 ± 0.5[a]	2.3 ± 0.5[a]	2.0 ± 0.4[a]
Gb *mmol/liter*	5.0 ± 0.1[a]	4.9 ± 0.2[a]	5.0 ± 0.2[a]	5.0 ± 0.2[a]
DV *% body weight*	17.7 ± 1.2[a]	18.8 ± 0.8[a]	18.2 ± 0.8[a]	19.2 ± 0.8[a]

Abbreviations are: SI, insulin sensitivity index; SG, glucose effectiveness; Ib, basal (fasted) plasma insulin concentration; AUC, area under the curve for plasma insulin concentration in 150 minutes; TID, total insulin delivery in 150 minutes; Φ_1, dynamic first phase insulin response to glucose; Gb, basal plasma glucose concentration; DV, distribution volume for glucose. The statistical differences are given at a P level of 0.05 only; shared superscripts are not significantly different.

Statistics

The SPSS package was used for statistical analysis. After testing for normality of data distribution, the data of healthy subjects and the three groups of patients were compared using a two-tailed analysis of variance (ANOVA). Bonferroni correction was applied. Pearson's correlation analysis between SI on the one hand and age, BMI, basal (fasted) plasma insulin concentration, AUC, TID, GFR, PTH, calcitriol, cholesterol and triglyceride concentration on the other hand was done in pooled patient data only. All data are presented as mean ± SEM. Differences were considered as significant at a P level of 0.05.

RESULTS

Table 2 shows the results of the intravenous glucose tolerance test (minimal model). Insulin sensitivity (mean SI), was markedly lower in all groups of patients than in healthy subjects. The difference between the combined results of all patients and healthy subjects was highly significant ($P < 0.001$; Fig. 1). In parallel, mean fasted plasma inulin concentration, AUC and TID were higher in patients as compared with healthy subjects, reflecting concomitant hyperinsulinemia. There was a trend for insulin secretion to be less in patients with most advanced renal failure, however.

There was no significant difference in SI between the three groups of patients, that is, in patients with GFR values within the normal range, patients with mild to moderate renal failure and patients with advanced renal failure. As is known in the normal population the dispersion of SI values was wide. Accordingly, some patients had a SI within the range observed in healthy subjects, whereas others were severely insulin resistant (Fig. 1). The SI in patients was not correlated with GFR ($r = 0.01$, $P < 0.52$; Fig. 2), PTH ($r = -0.23$, $P < 0.11$) or calcitriol ($r = -0.03$, $P < 0.82$) concentration, but was significantly correlated with age ($r = -0.32$, $P < 0.011$), BMI ($r = -0.25$, $P < 0.042$), fasted plasma insulin concentration ($r = -0.32$, $P < 0.009$), AUC ($r = -0.62$, $P < 0.0001$), TID ($r = -0.34$, $P < 0.004$) and serum triglyceride ($r = -0.29$, $P < 0.04$) or cholesterol concentrations ($r = -0.36$, $P < 0.007$). In addition, glucose effectiveness (SG) and the early phase insulin secretion (Φ_1) were also found to be disturbed even in patients when GFR values were within the normal range. These parameters were similarly reduced in all patient groups as compared with healthy subjects (Table 2). The separate analysis of patients with immune origin of renal disease (IgAGN) and patients with non-immune renal disease (ADPKD) showed no significant differences between the groups (Table 3).

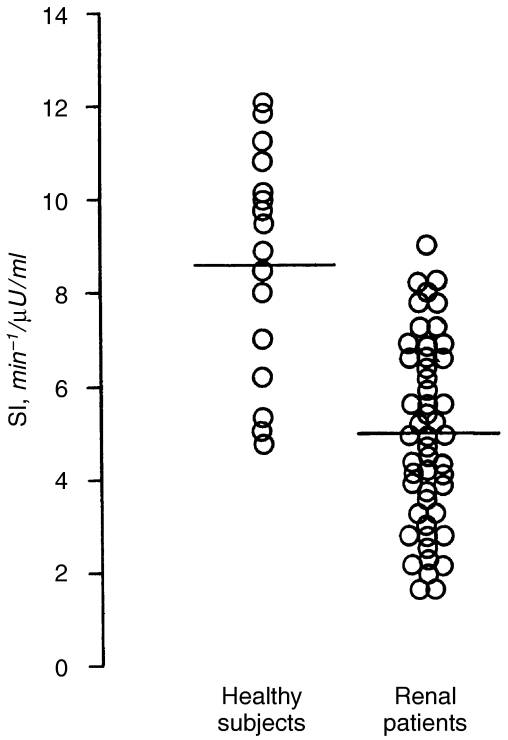

Fig. 1. Insulin sensitivity index (SI), that is, insulin sensitivity, in healthy subjects ($N = 16$) and in renal patients ($N = 50$). The statistical difference between groups was highly significant ($P < 0.001$).

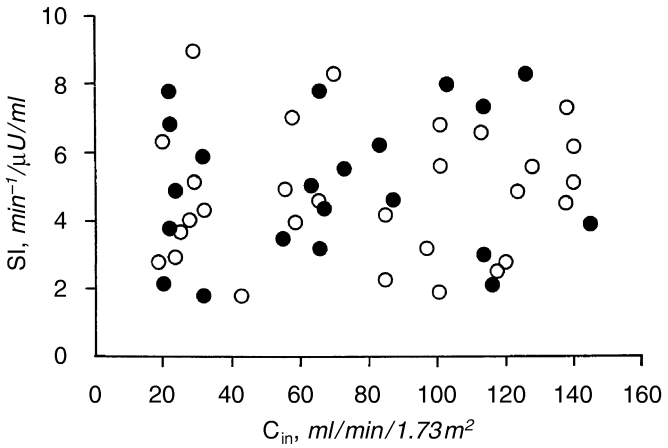

Fig. 2. Correlation between insulin sensitivity (insulin sensitivity index, SI) and glomerular filtration rate (inulin clearance, C_{In}) in 29 patients with IgA glomerulonephritis (○) and 21 patients with adult polycystic kidney disease (●). There was no correlation between both variables ($r = 0.01$, $P < 0.52$).

Table 3. Results in patients with immune (IgAGN) and non-immune renal disease (ADPKD) according to degree of renal function

	Plasma creatinine concentration *mg/dl*		
	< 1.3	> 1.3 < 3.0	> 3.0
Patients with IgAGN			
Age *years*	44 ± 3[a]	46 ± 2[a]	43 ± 3[a]
BMI kg/m^2	25.6 ± 1.3[a]	26.0 ± 0.6[a]	25.7 ± 1.2[a]
SI $min^{-1}/(\mu U/ml)$	4.9 ± 0.6[a]	4.9 ± 0.6[a]	4.7 ± 0.6[a]
TID $\mu U/ml$	530 ± 94[a]	497 ± 76[a]	417 ± 63[a]
Patients with ADPKD			
Age *years*	35 ± 2	47 ± 3[a]	50 ± 3[a]
BMI kg/m^2	25.8 ± 1.3[a]	25.8 ± 0.8[a]	25.2 ± 1.0[a]
SI $min^{-1}/(\mu U/ml)$	5.3 ± 0.7[a]	5.3 ± 0.5[a]	4.8 ± 0.7[a]
TID $\mu U/ml$	477 ± 49[a]	480 ± 73[a]	373 ± 47[a]

Abbreviations are: BMI, body mass index; SI, insulin sensitivity index; TID, total insulin delivery in 150 minutes. The statistical differences are given at a P level of 0.05 only; shared superscripts are not significantly different.

Mean SI was reduced in both groups of patients irrespective of the stage of renal function (Fig. 2), although a trend for less marked SI reduction was noted in patients with ADPKD.

DISCUSSION

The novel finding in the present study is the demonstration that in patients with renal disease insulin sensitivity is diminished early on, even before GFR is below the normal range. A diminished ability of insulin to stimulate glucose uptake by its target organs, as documented by a decreased insulin sensitivity index (SI), was seen even in patients whose GFR values were still within the normal range, and in whom anemia, metabolic acidosis, secondary hyperparahyroidism or vitamin D insufficiency were not present. The SI was significantly lower in renal patients than in matched controls; and it was not correlated with C_{In} across a wide range of GFR values. These findings are in general agreement with observations of other authors in smaller populations using a different methodological approach [23, 24]. Fasted insulin concentration was increased, presumably as a compensatory mechanism to overcome insulin resistance. Total insulin delivery during the test calculated using quantitative modeling analysis was also increased. Furthermore, in patients with renal disease we found not only a reduction of the ability of insulin to stimulate glucose uptake (SI), but also a reduction of the ability of glucose to stimulate glucose uptake (SG). Finally, our patients exhibited a reduced beta cell responsivness to glucose during the first phase, reflected by the decreased sensitivity (Φ_1) to glucose. By delaying delivery of insulin to the liver and the attendent inhibition of liver glucose production, this alteration should promote hyperglycemia as in patients with type 2 (non-insulin dependent) diabetes mellitus [20, 25], althought the reduction of hepatic glucose production by exogenous insulin is not affected in patients with renal failure [2]. In contrast to patients with type 2 diabetes, in whom the metabolic abnormalities become more severe as the disease progresses, in this cross sectional study no clearcut evidence of progression in the severity of insulin resistance was found in renal patients with increasingly lower GFR (C_{In}), although there was a trend for stimulated insulin secretion to be less in patients with most advanced renal failure. Longitudinal studies are required to define the evolution of the disturbances in glucose metabolism with time in patients with progressive renal disease. In this respect it is of interest that higher triglyceride levels were present in patients with normal GFR, and the increase in serum triglyceride concentration was even more marked in patients with advanced renal failure. These data are in good agreement with observations of previous studies [14].

Evidence of insulin resistance was found both in patients with immune (IgAGN) and non-immune (ADPKD) renal disease. The finding in the former group excluded the possibility that abnormal glucose metabolism is part of the ADPKD phenotype [24]. It appears paradoxical that in patients with renal disease insulin resistance should be present even though GFR values are still within the normal range. We caution, however, that apparently normal renal function, as documented by GFR values within the normal range, does not necesserily exclude reduction of functional parenchyma by the disease process. Adaptive changes in glomerular filtration dynamics may keep GFR within the normal range despite considerable reduction of tubular cell mass, and this could be causally related to the abnormalities in glucose metabolism. An alternative explanation for the early presence of such abnormalities of the glucose metabolism may be genetic and/or enviromental factors. For instance, a higher frequency of hypertension (and of metabolic syndrome?) is found in families of patients with IgAGN [26]. Another point to consider is abnormal skeletal muscle composition in patients with renal failure [27]; this is reminiscent of findings in patients with the metabolic syndrome, that is, in patients with several derangements of glucose and lipid metabolism, who are prone to develop type 2 diabetes mellitus [28].

In contrast to insulin sensitivity (which is reduced to the same extent in patients with normal GFR values and in patients with reduced GFR) a tendency for less insulin secretion is seen only in patients with severely compromised renal function. Experimental data suggest that PTH and increased intracellular calcium concentration are involved in the impairment of insulin secretion of renal failure [29, 30]. Support for this assumption also comes from studies in uremic patients with secondary hyperparathyroidismus in whom parathyroidectomy ameliorates the abnormalities of insulin secretion [31, 32]. In studies of patients on maintainance hemodialysis a significant correlation was found between increased PTH concentrations (and platelet intracellular calcium) and impaired glucose tolerance, but parathyroidectomy did not affect insulin sensitivity [11, 31, 32]. In our patients PTH concentrations were not significantly correlated with insulin sensitivity, but it must be acknowledged that the sensitivity of this cross-sectional statistical approach is limited. Nevertheless, the absence of an effect of PTH on insulin sensitivity would be in agreement with our own finding in healthy subjects in whom under conditions of euglycemic hyperinsulinemia subacute administration of human 1,34-PTH did not affect insulin sensitivity, despite a significant increase of platelet intracellular calcium concentration and arterial blood pressure [33]. These observations do not definitely exclude a role of PTH, but suggest that any potential role of PTH must be minor compared to other factors that may impact on glucose metabolism. The same consideration applies for the role of calcitriol in the disturbances of glucose metabolism in renal patients. Calcitriol concentrations were within the normal range in patients with normal renal function in whom marked insulin resistance was present. Another factor that might be involved in

derangements of glucose metabolism in renal patients is sympathetic activity, which is increased even in early renal disease, such as in patients with a plasma creatinine concentration below 1.6 mg/dl [34].

In the present study we observed considerable variability of the SI in healthy controls and in renal patients, leading to an overlap of SI values between the group of patients and the group of controls. Such variability of insulin sensitivity was found not only in healthy subjects but also in several conditions with insulin resistance, such as type 2 diabetes mellitus, obesity, etc. [28, 35, 36]. It is thought to reflect interaction of multiple genetic and non-genetic factors determining insulin sensitivity in the general population and by implication also in individuals with impaired insulin sensitivity, such as renal patients.

In conclusion, insulin resistance and hyperinsulinemia are present very early in the course of renal disease, even when GFR values are still within the normal range. These observations may have potential implications for the management of renal patients. The link between insulin resistance, cardiovascular risk factors and cardiac mortality has been documented in patients with the metabolic syndrome. It is reasonable to assume that in renal failure, another example of insulin resistance, a similar link exists. Interventions should presumably be initiated very early on to correct the potentially atherogenic metabolic profile in order to improve survival of patients in the predialytic phase and prevent atherosclerotic disease at the time of entry into dialysis.

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