Effects of a low-protein, low-phosphorus diet on metabolic insulin clearance in patients with chronic renal failure[1–3]

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ABSTRACT The metabolic clearance rate (MCR) of insulin was studied in 17 nondiabetic patients with advanced chronic renal failure (creatinine 479 ± 15 μmol/L, glomerular filtration rate 14.6 ± 2.9 mL/min) before and after 3 mo of a low-protein, low-phosphorus diet (LPD) providing daily per kilogram 0.3 protein of vegetal origin and 3–5 mg inorganic phosphorus. The energy supply (146 $kJ \cdot kg^{-1} \cdot d^{-1}$) was furnished mainly by carbohydrates. The diet was supplemented with a mixture of essential amino acids and ketoanalogues. The MCR of insulin was determined by using the euglycemic clamp technique. Before the diet the MCR of insulin was low (450 ± 127 $mL \cdot min^{-1} \cdot m^{-2}$) but increased significantly at the third month (568.8 ± 148 $mL \cdot min^{-1} \cdot m^{-2}$), reaching values close to the MCR of control subjects (630 ± 135 $mL \cdot min^{-1} \cdot m^{-2}$). Identical results have been described during hemodialysis of anephric patients, leading us to hypothesize that an LPD reduces the production of dialyzable factors that interfere with peripheral insulin metabolism. *Am J Clin Nutr* 1994;59:663–6.

KEY WORDS Metabolic insulin clearance rate, chronic renal failure, low-protein diet

Introduction

The mechanisms of progressive glucose intolerance during chronic renal failure (CRF) have not been clearly established. The possibility of a decrease in insulin released under the influence of the high parathormone concentrations of the secondary hyperparathyroid state is well known in CRF (1). Also, considerable attention has been focused on insulin resistance, which is now clearly demonstrated (2). The consequence of this insulin resistant state is a high plasma insulin concentration and at a later stage glucose intolerance, as demonstrated in other states of insulin resistance (non-insulin-dependent diabetes mellitus and extreme insulin resistance syndrome) (3, 4). Insulin resistance seems to be the predominant mechanism of hyperinsulinism in CRF (5) but a decrease in insulin removal (by the kidney and otherwise) could also contribute to the high insulin concentration. The direct role of peripheral tissues (3) and the possibility of uremic toxins that interfere with insulin action at peripheral sites seem to be considered (6). The improvement of insulin resistance by dialysis, which clears some of these toxins (7), and by a low-protein diet that diminishes toxin production (8) has been demonstrated.

In a previous study on insulin resistance in uremic patients, we observed that the plateau insulin concentration of the clamp period was lower after a low-protein diet (8); an influence of the diet on metabolic insulin clearance in CRF patients was hypothesized. In the present study we used the euglycemic glucose clamp technique to determine the clearance rate of insulin in uremic patients compared with control subjects and the influence of a low-protein, low-phosphorus diet (LPD) in such patients. Low-protein diets are now recommended to uremic patients in the hope of slowing down the progression of renal failure.

Subjects and methods

Insulin clearance was studied in 10 healthy control subjects aged 24–68 y ($\bar{x}$ 46.8 y) eating a usual Western diet and in 17 patients suffering from CRF, before and after 3 mo on an LPD. The healthy subjects had a normal oral glucose-tolerance test and their carbohydrate intake was maintained stable at a daily amount ≥ 180 g carbohydrates for 3 d before the study; their body mass index (BMI; in kg/m^2) was 22.8 ± 2.6.

Over the 4-y period beginning in January 1988, 17 patients with CRF (12 men and 5 women aged (26–71 y, $\bar{x}$ 55.6 y) were recruited. The etiology of their underlying renal disease is as follows: chronic glomerular nephritis (n = 6), nephroangiosclerosis (n = 3), polycystic kidney disease (n = 3), uropathy (n = 1), interstitial nephropathy (n = 2), and unknown (n = 2). Their BMI was 22.6 ± 1.8. All patients presented with advanced renal failure; their creatinine concentration was 479 ± 152 mmol/L and their glomerular filtration rate (GFR) assessed by the urinary clearance of ^{51}Cr-EDTA isotopical measurement was 14.6 ± 2.9 mL/min. The patients were first studied while on their usual diet, which provided daily < 1 g protein/kg body wt and 10–13 mg inorganic phosphorus/kg body wt. They were again studied after 3 mo of an LPD providing daily per kilogram 0.3 g protein of vegetal origin and 5–7 mg inorganic phosphorus. Sodium chloride intake was significantly reduced; the energy supply (≈146 $kJ \cdot kg^{-1} \cdot d^{-1}$) was furnished mainly by carbohydrates

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TABLE 1
Biological data of the 17 patients with chronic renal failure, before and after 3 mo on the low-protein, low-phosphorus diet (LPD)*

	Before LPD	After LPD
Plasma creatinine (μmol/L)	479 ± 152	416 ± 129
Plasma urea (mmol/L)	23.76 ± 6.43	7.42 ± 3.9†
Glomerular filtration rate (mL/min)	14.6 ± 2.9	13.5 ± 3.3
Urinary urea excretion (mmol/d)	212 ± 69	67 ± 36†

* $\bar{x}$ ± SD.
† Significantly different from before LPD, $P < 0.001$.

(67% of energy) whereas lipids accounted for ≈30% of the energy intake. In patients with heavy proteinuria, each gram of urinary protein loss was replaced in the diet by an additional 1.25 g protein of high biological value of animal origin. For 10 patients recruited in the study from January 1988 to October 1990 (period 1), the LPD was supplemented with a mixture of calcium salts of essential amino acids and ketoanalogues in tablet form (Ketosteril; Fresenius Laboratory, Fresenius, Germany). The daily dose was one tablet per 5 kg body wt, each tablet providing 36 mg N and 50 mg Ca. For seven other patients recruited into the study from November 1990 to January 1992 (period 2), the LPD was supplemented with CSW 20-4 tablets (Clintec, Paris). The daily dose was one tablet per 5 kg body wt, each tablet providing 75 mg N and 3–4 mg Ca. Ketosteril and CSW 20-4 tablets were given in divided doses with meals. The composition of both tablets was described in detail elsewhere (9, 10). Calcium carbonate was given at a dose of 1 g (ie, 400 mg elemental Ca) during period 1 and at a dose of 2 g for patients recruited during period 2 to compensate for the lower calcium content of the second mixture of amino acids; no other phosphate binder was prescribed. All patients were also supplemented with iron and a multivitamin preparation providing 25 μg (1000 IU) ergocalciferol/d. Compliance with the prescribed diet was verified monthly by dietary interviews and by measurement of urinary urea and phosphorus excretion. Protein intake was estimated by the equation of Maroni et al (11). All patients gave prior consent to the procedures of the study.

The euglycemic clamp technique was used as previously described, by using an artificial pancreas (Biostator GCIIS; Laboratoire Miles, Epernon, France) working on a 9:1 mode (12). Subjects were awake and supine throughout the clamp procedures. Two basal samples for glucose and insulin dosages were obtained before the start of the clamp study; thereafter samples were obtained at 10-min intervals for insulin dosage between 60 and 120 min during the clamp plateau. Exogenous insulin was infused at a constant rate with an infusion pump (Harvard Apparatus; Ealing, les Ulis, France) and a 1-min prime was followed by 120 min of a constant infusion of human regular insulin (Novo-Nordisk, Paris) (0.5 U/min). Glucose (20%) was administered by the artificial pancreas in a 9:1 mode to maintain glycemia at its basal concentration. The hand on the side of the sampling catheter was maintained at 45 °C by an electric blanket, permitting arterialization of the venous blood.

The experimental protocol was approved by the ethics committee of our institution. Student's paired t test was used for statistical analysis and differences at the $P < 0.05$ level were considered significant.

The MCR of exogenous insulin was calculated according to the dilution principle (13) as the ratio of the insulin infusion rate to the steady-state arterialized plasma exogenous insulin concentration. This was obtained as the difference between the mean arterialized plasma insulin concentration during the last 60 min of the constant insulin infusion and the basal insulin concentration.

Insulin clearance was calculated as follows:

$$\text{Insulin clearance } (\text{mL}\cdot\text{min}^{-1}\cdot\text{m}^{-2}) = \frac{\text{insulin infusion rate } (\mu\text{U/min})}{([\text{mean insulin concentration (60–120 min; in mU/L)} - \text{basal insulin concentration (mU/L)}] \times [\text{body surface area } (\text{m}^2)])}$$

This calculation is based on the assumption that insulin infusion and the resulting hyperinsulinemia do not alter the basal rate of insulin production. In fact basal production is suppressed as attested by C peptide evolution and this calculation of clearance underestimates the clearance rate by 5–10%. The same calculation method was used by other authors with the same probable underestimation (4, 14). Results are expressed as mean ± SD.

Results

All patients reported a general feeling of well-being without experiencing any change in their normal living habits. Their weight remained stable during the study. Compliance with the prescribed diet was good, as shown by the fall of urinary urea excretion and plasma urea nitrogen at the third month of the diet. Renal function was not influenced by the diet during this short period; plasma creatinine concentration, creatinine clearance rate, and GFR were not significantly changed. Biological data and statistical analysis are shown in **Table 1.**

Similar basal blood glucose concentrations were found before and after dietary treatment and their concentrations were maintained constant during the period of hyperinsulinism (mean CV 3.5%). In all patients the insulin plateau concentration was stable with a variation of only 5%. The concentration of the plateau was different for each patient. This was probably because the insulin infusion rate was the same for each patient regardless of body weight. Postdiet plateau concentrations were lower in all patients.

In the control group the insulin clearance was 630 ± 135 $\text{mL}\cdot\text{min}^{-1}\cdot\text{m}^{-2}$ whereas in patients with CRF metabolic clearance of insulin was lower: 450 ± 127 $\text{mL}\cdot\text{min}^{-1}\cdot\text{m}^{-2}$, but increased significantly after 3 mo on the LPD, reaching 568.8 ± 148 $\text{mL}\cdot\text{min}^{-1}\cdot\text{m}^{-2}$ ($P < 0.01$). The MCR of insulin was close to that of control subjects after 3 mo of the diet but was not totally normalized (**Fig 1**). The amount of glucose infused to maintain the glycemia at the basal concentration was 281 ± 18 $\text{mg}\cdot\text{min}^{-1}\cdot\text{m}^{-2}$ before, and 324 ± 16 $\text{mg}\cdot\text{min}^{-1}\cdot\text{m}^{-2}$ after the diet ($P < 0.01$). There was no difference according to the type of ketoacid supplementation.

Discussion

The euglycemic glucose clamp technique that we performed was essential for the calculation of insulin clearance rate. It necessitates a steady state of hyperinsulinemia achieved by a con-

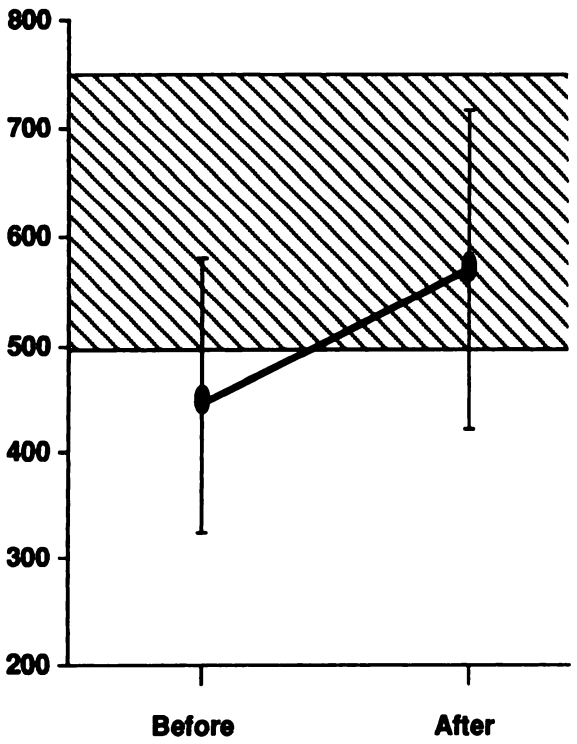

FIG 1. Mean (±SD) metabolic insulin clearance of patients with chronic renal failure before and after 3 mo on a low-protein, low-phosphorus diet. Hatched bars represent control subjects.

stant rate of insulin infusion. During a prolonged insulin infusion even at a low rate, hypoglycemia is a usual consequence and glucose infusion is needed to prevent the fall of the glycemic level. The technique of the euglycemic clamp maintains normoglycemia during the whole study without any excess of glucose infusion, inhibiting secretion of insulin by the endogenous pancreas that would interfere with the insulin plateau concentration, which is essential for the calculation of insulin clearance.

The MCR of insulin in our control subjects was 630 ± 135 $mL \cdot min^{-1} \cdot m^{-2}$. This result agrees with other authors' findings (4, 14). As did others, we found a decrease in insulin clearance in patients with CRF (450 ± 127 $mL \cdot min^{-1} \cdot m^{-2}$) (15). This diminution of the insulin clearance rate has long been attributed to pathological lesions of the kidney (16), but in the present study we demonstrated that it may be improved by a low-protein diet that could not have any effect on anatomical lesions over a 3-mo period (568 ± 148 $mL \cdot min^{-1} \cdot m^{-2}$). The impairment in insulin metabolism in other tissues such as liver or muscle is therefore more likely and the role played by the protein content of the diet and its degradation products is underlined.

In normal humans the liver is responsible for more than half of the total metabolism of insulin (17, 18) and the kidney for approximately one-third (19). Insulin is also metabolized in muscle and adipose tissue. In CRF, the diminution in insulin metabolic clearance could result from different modifications concerning kidney function, liver metabolism, and cellular insulin receptors.

During the early phase of renal insufficiency the impairment in insulin clearance is probably due to reduced renal blood flow. This degradation pathway is, in any case, minor, the liver being the major site of insulin clearance. However, neither acute nor chronic uremic states seem to depress insulin metabolism by the isolated perfused rat liver (20, 21). The effects of uremia on hepatic handling of insulin are complex. Insulin binding to liver plasma membranes isolated from chronically uremic rats has been found impaired in some studies (21) but normal in others (22). So the effect of lower tissue insulin extraction seems to be the major explanation for the fall in insulin MCR. Animal studies confirm that CRF modifies insulin metabolism at several extrarenal sites. For example, insulin metabolism by muscle is impaired in rats with CRF (20, 21). It has also been demonstrated in uremic patients that, when renal function declines, tissue insulin extraction falls from 0.4 (the normal arteriovenous ratio) to 0.1 (23). Similarly, insulin extraction by skeletal muscle isolated from acutely uremic rats is depressed by two-thirds when compared with normal muscle (20, 21). Thus peripheral tissues seem to be the major site for alteration of the MCR of insulin and we can hypothesize that an LPD acts at this level.

In end-stage renal failure, hemodialysis has been found to improve insulin MCR (15). Navalesi et al (15) studied eight patients with CRF and four anephric patients before and after admission in a dialysis program: the MCR was altered at 203 $mL \cdot min^{-1} \cdot m^{-2}$ before hemodialysis and was 424 $mL \cdot min^{-1} \cdot m^{-2}$ after hemodialysis. The marked improvement in the insulin turnover rate in dialyzed uremic patients supports the importance of dialyzable toxic metabolites interfering with insulin degradation by extrarenal tissues. In summary, it seems that whereas kidney insulin metabolism can play a role in the early phase of renal insufficiency, the role of uremic toxins on extrarenal tissue is more important in patients with advanced renal failure, as demonstrated by dialysis treatment. It is likely that an LPD has the same effect as dialysis by lowering production of uremic toxins that probably interfere with mechanisms of insulin clearance at extrarenal peripheral sites. However, insulin clearance still appears depressed compared with healthy subjects. Peripheral tissues and the kidney itself are sites of clearance and the diet may act on the former site.

It is interesting to note that similar beneficial effects of dialysis and a low-protein diet have been previously reported for different metabolisms. We already demonstrated that an LPD improves insulin sensitivity and glucose metabolism (8). The present study confirms this fact: for a lower insulin plateau concentration the amount of glucose needed for maintaining normoglycemia was higher. It can be hypothesized that an LPD may lower the production of some toxins, such as the heat-stable dialyzable factor that has been found able to transfer the insulin-resistant state of patients to cultured cells (6). These same toxins (several toxins) may also interfere with insulin degradation.

The LPD that has been prescribed to our patients has been used by some of them for 5 y, with no malnutrition complications; anthropometric and biological indexes such as albumin, transferrin, and retinol-binding protein were not modified during the diet period.

The present study demonstrates that an LPD exerts other beneficial effects than those, still debated, on the progression of the renal failure. The improvement in the MCR of insulin could lessen morbidity related to a chronic hyperinsulinemic state. The direct role on insulin MCR of uremic toxins originating from a normal-protein diet remains to be confirmed. ■

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