Kidney International, Vol. 51 (1997), pp. 1222–1227

Low protein diet in uremia: Effects on glucose metabolism and energy production rate

VINCENT RIGALLEAU, CHRISTIAN COMBE, VALÉRIE BLANCHETIER, JEAN AUBERTIN, MICHEL APARICIO, and HENRI GIN

Clinique Médicale and Service de Néphrologie, Hôpital Pellegrin-Tripode, Bordeaux, France

Low protein diet in uremia: Effects on glucose metabolism and energy production rate. Low-protein diets (LPD) increase insulin-mediated glucose disposal in chronic renal failure (CRF), but the fate of the better utilized glucose and the effect on energy production rate are unknown. Using a two-step (1 and 5 $mU \cdot kg^{-1} \cdot min^{-1}$) euglycemic hyperinsulinemic clamp combined with indirect calorimetry, we studied the effects of a LPD (0.3 $g \cdot kg^{-1} \cdot day^{-1}$, supplemented with essential amino acids and ketoanalogs) in six patients suffering from chronic renal failure. After three months of diet, no significant change was observed concerning glomerular filtration rate, body wt, or arterial pH. In the postabsorptive state, plasma glucose and insulin levels were significantly lower, and energy production rose from 15.72 ± 0.48 to 17.16 ± 0.67 $Cal \cdot kg^{-1} \cdot min^{-1}$ ($P < 0.05$). Insulin-stimulated glucose oxidation (2.36 ± 0.29 vs. 3.37 ± 0.35 $mg \cdot kg^{-1} \cdot min^{-1}$; $P < 0.05$ at first clamp step) and nonoxidative disposal ($P < 0.05$ at both clamp steps) increased after LPD. This confirms that LPD ameliorates insulin sensitivity in CRF, even for low plasma insulin concentrations. Since energy production rate is increased by LPD, the caloric intake should be increased when protein intake is restricted.

Insulin resistance and hyperinsulinemia are well-known features of chronic renal failure (CRF) [1, 2], and may play a role in the increased cardiovascular morbidity in chronically uremic patients. We previously showed that a low-protein diet (LPD) improved insulin sensitivity [3] and increased insulin metabolic clearance rate [4] in such patients.

The glucose that is more efficiently taken up by tissues during a hyperinsulinemic euglycemic clamp is essentially removed by muscle, and can have two metabolic fates: oxidative, or nonoxidative disposal (mainly glycogen synthesis). We do not yet know which of these two metabolic pathways is more responsive to insulin in patients on LPD.

An improvement in glucose storage, which is preferentially affected by insulin resistance in CRF [5], is the most likely explanation of the beneficial effect of LPD on glucose metabolism in CRF. However, Eidemak et al have demonstrated a positive correlation between insulin sensitivity and aerobic work capacity in CRF [6], suggesting that the oxidative metabolism of glucose might also be important. Moreover, the mechanism of the improvement by LPD is not necessarily related to the pathophysiology of the defect in CRF, as beneficial effects of LPD on glucose metabolism have been reported in nonuremic diabetic patients [7]. Finally, as recently underlined by H. Yki-Järvinen, it is much more unlikely to detect a defect in glucose oxidation than storage, because a notable part is not insulin dependent (oxidation by brain, and heart) and oxidation is quantitatively less important than storage at high insulin concentrations [8]. In contrast, at a moderate (physiological) insulin level, both metabolic pathways contribute to the utilization of glucose in almost similar proportions. Therefore, an LPD-induced improvement in insulin sensitivity of oxidative glucose metabolism should not be excluded, and use of a moderate insulin infusion rate should permit its detection.

The major potential adverse effect of LPD is malnutrition, which has been attributed in uremic patients to several factors such as uremia itself, metabolic acidosis, a decrease in energy and protein intake, hypercatabolic status, and secondary hyperparathyroidism [9]. The protein-sparing effect of a sufficient caloric intake is well established [10], but, to our knowledge, the possibility that protein restriction may in itself modify energy production rate in uremic patients has not been examined.

Using the glucose-clamp technique with moderate (1 $mU \cdot kg^{-1} \cdot min^{-1}$) and high (5 $mU \cdot kg^{-1} \cdot min^{-1}$) insulin infusion rates in combination with indirect calorimetry, we measured insulin-stimulated glucose oxidation, nonoxidative glucose disposal and energy production rate in six patients with advanced renal failure before and after three months of LPD.

Methods

Patients

Six patients (5 men, 1 postmenopausal woman) were studied. Their mean age was 46.5 ± 5.7 years. Mean body wt was 73.5 ± 3.8 kg and height 174 ± 3 cm. The underlying renal diseases were as follows: chronic glomerulonephritis ($N = 2$), interstitial nephropathy ($N = 2$), polycystic kidney disease ($N = 1$), and sequellae of Moschowitz's syndrome ($N = 1$). All were nondialyzed patients with advanced renal failure. Serum creatinine was 455 ± 43 $\mu mol \cdot liter^{-1}$ and glomerular filtration rate (GFR), assessed by urinary clearance of ^{51}Cr-EDTA as previously described [11], was 13.6 ± 3.1 $ml \cdot min^{-1}$. They presented no other major organ system disease, and none was taking any medication known to interfere with carbohydrate metabolism. Exclusion criteria were hepatic failure, diabetes mellitus, a family history of

Received for publication August 5, 1996
and in revised form November 8, 1996
Accepted for publication November 11, 1996

© 1997 by the International Society of Nephrology

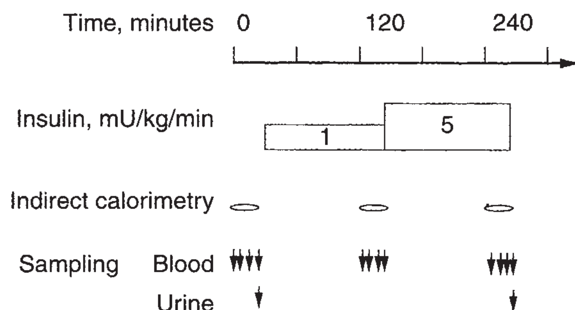


Fig. 1. *Study design.*

diabetes mellitus, and metabolic acidosis (because its correction might interfere with interpretation of indirect calorimetry results [12]). Nutritional status was assessed by body wt, mid-arm circumference, triceps skinfold thickness, serum protein and albumin levels. Plasma sodium, chloride and potassium concentrations were within the normal range. The experimental protocol was approved by the ethics committee of our institution. All patients gave informed consent to the procedures of the study.

Low-protein diet

Patients were first studied while on their usual unrestricted diet, providing in every case at least 0.8 g protein and 10 to 13 mg inorganic phosphorus per kg body wt daily. Patients were prescribed a LPD providing, per kg body wt, 0.3 g protein of vegetable origin and 5 to 7 mg inorganic phosphorus. The energy supplied (35 kCal $\cdot$ kg^{-1} $\cdot$ day^{-1}) was furnished mainly by carbohydrates (67%), with lipids accounting for 30% of the energy intake. Monthly adjustments in the caloric intake based on dietary interviews were made for weight maintenance. In patients with heavy proteinuria, each gram of urinary protein loss was replaced by an additional 1.25 g protein of high biological value of animal origin. The LPD was supplemented with essential amino acids and ketoanalogs (to minimize nitrogen intake) in tablet form (Cetolog; Clintec Laboratory, Amilly, France; the composition of tablets is provided in the **Appendix**), one tablet per 5 kg body wt given daily in divided doses with meals, calcium carbonate at a dose of 1 to 2 g in order to maintain normal serum calcium concentration, iron and a multivitamin preparation providing 25 μg (1000 IU) ergocalciferol per day. Compliance was verified monthly by dietary interview and by measurements of urinary urea and phosphorus excretion. Antihypertensive medication was not modified during the study (no subject was on betablockers or angiotensin converting enzyme inhibitors).

Materials

Common human insulin was obtained from Novo Nordisk (Copenhagen, Denmark). Respiratory exchange measurements were performed with a computerized flow-through canopy gas analyzer system (Deltatrac metabolic monitor; Datex, Helsinki, Finland).

Study design

All subjects were studied twice, before and after three months of LPD (Fig. 1). Studies were performed in the postabsorptive (PA) state after overnight fasting. Tests began at 9:30 a.m. with a 30-minute basal period to measure postabsorptive substrate oxidation rates. Then a two-step hyperinsulinemic-euglycemic clamp was performed, each step lasting 120 minutes, with two successive insulin infusion rate determinations (1 and 5 mU $\cdot$ kg^{-1} $\cdot$ min^{-1}).

Study procedures

Patients were admitted in the metabolic ward the evening before the test, and allowed to rest in the supine position. Intravenous catheters were inserted into veins of one forearm for different infusions. To obtain arterialized blood samples, another catheter was inserted in a retrograde manner into a vein of the contralateral hand kept at 55°C in an electric blanket. Initial blood samples were obtained, and then respiratory exchange measurements began. At 30 minutes, the clamp was started and primed-continuous insulin infusion began. Insulin was dissolved in 48 ml of saline (154 mmol $\cdot$ liter^{-1}) mixed with 2 ml of blood taken from the patient. Each insulin infusion was primed according to Rizza, Mandarino and Gerich [13], and the continuous infusion rates were 1.0 and 5.0 mU $\cdot$ kg^{-1} $\cdot$ min^{-1} for 120 minutes each, delivered by an electric syringe (Havard Apparatus, Les Ulis, France). Euglycemia was maintained according to the clamp technique, automatically by an artificial pancreas (Biostator GCIIS; Laboratoire Miles, Epernon, France) working in a 9:1 mode (no human intervention) as previously described [3]. Exogenous glucose infusion rates necessary to maintain euglycemia (M value) were measured during the last 30 minutes of each step of the clamp. During the basal period and the last 30 minutes of the two clamp steps, arterialized blood samples were withdrawn every 10 minutes and a plastic ventilation hood was placed over the head of the subject and made airtight around the neck, allowing measurement of respiratory exchanges with the Deltatrac Metabolic Monitor. Urine samples were collected at the beginning and end of each test.

Analytical procedures

Plasma glucose concentration was determined by the glucose oxidase method [14]. Urinary N was defined as the sum of urinary urea (mmol $\cdot$ min^{-1}), creatinine (mmol $\cdot$ min^{-1}) and uric acid (mmol $\cdot$ min^{-1}) N, determined using routine, semiautomated methods:

$$U_N\,(\text{mmol} \cdot \text{min}^{-1}) = (2 \times U_{Urea}) + (3 \times U_{Cr}) + (4 \times U_{Uric\ acid})$$

As reported by Thorburn et al [15], this gives results comparable to the Kjeldahl method, with comparable trends during euglycemic hyperinsulinemic clamp studies. We did not measure global urinary N by a classical Kjeldhal method to avoid the inclusion of N from proteinuria that was present in some of our patients.As proposed by Thorburn et al, we calculated the corrected values for urinary N during the clamp, to take into account the insulin-induced changes in urea clearance rate [15]. Serum total calcium, phosphorus, uric acid, urea and bicarbonates, arterial pH, hemoglobin and hematocrit were measured by routine, semiautomated methods. Plasma insulin and intact PTH were determined by radioimmunoassay (Pharmacia kit for insulin and Sorin kit for PTH).

Calculations

Protein oxidation (POx) was estimated as [16]:

$$\text{POx}\,(\text{mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}) = 6.25 \times U_N\,(\text{mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1})$$

Table 1. Nephrologic parameters before and after LPD

	Before	After
Basal/*clamp* plasma urea *mmol · liter^{-1}*	25.0 ± 3.8/*23.8 ± 3.9*	8.3 ± 2.4[a]/*8.0 ± 2.2*[a]
Basal/*clamp* urinary urea *μmol · min^{-1}*	105 ± 17/*133 ± 31*	27 ± 4[a]/*63 ± 12*[a]
Basal/*clamp* urea clearance *ml · min^{-1}*	4.2 ± 0.6/*5.6 ± 1.3*	3.2 ± 0.3/*7.7 ± 1.8*

[a] $P < 0.001$

Table 2. Nutritional parameters before and after LPD

	Before	After
Body weight *kg*	73.5 ± 3.8	72.0 ± 2.8
Triceps skinfold thickness *mm*	11.1 ± 0.18	10.6 ± 0.16
Mid-arm circumference *mm*	308 ± 9	301 ± 6
Serum protein *g · liter^{-1}*	68 ± 3.2	69 ± 3.0
Serum albumin *g · liter^{-1}*	39.9 ± 1.8	39.7 ± 1.9

Table 3. Substrate oxidation rates in the postabsorptive state before and after LPD

	Before	After
Glucose oxidation *mg · kg^{-1} · min^{-1}*	1.46 ± 0.31	1.71 ± 0.28
Lipid oxidation *mg · kg^{-1} · min^{-1}*	0.79 ± 0.08	1.02 ± 0.12
Protein oxidation *mg · kg^{-1} · min^{-1}*	0.29 ± 0.06	0.07 ± 0.01[a]
Energy production rate *Cal · kg^{-1} · min^{-1}*	15.72 ± 0.48	17.16 ± 0.67[a]

[a] $P < 0.05$

Total glucose and lipid oxidation rates were calculated from gas exchange measurements during the postabsorptive period and last 30 minutes of each clamp step using the equations proposed by Ferrannini [16]. During the clamp, total suppression of endogenous glucose production was assumed and glucose utilization was considered as equal to exogenous glucose infusion rate. Nonoxidative glucose disposal was calculated as the difference between glucose utilization and glucose oxidation.

Statistical analysis

Data are expressed as mean ± SEM. Parameters were compared before and after LPD by one-way ANOVA for repeated measurements. P values <0.05 were considered statistically significant.

Results

Renal parameters

After three months on LPD, plasma creatinine levels (455 ± 43 vs. 448 ± 72 μmol · liter^{-1}), isotopically determined GFR (13.6 ± 3.1 vs. 11.6 ± 2.1 ml · min^{-1}), and urea clearance rate (4.2 ± 0.6 vs. 3.2 ± 0.3 ml · min^{-1}) were not significantly modified (Table 1). Plasma urea and urinary urea dramatically declined from 25.0 ± 3.8 to 8.3 ± 2.4 mmol · liter^{-1} ($P < 0.001$) and 105 ± 17 to 27 ± 4 μmol · min^{-1} ($P < 0.001$), respectively, confirming a satisfactory compliance with the diet. Before and after LPD, urea clearance rate increased during the euglycemic clamp, this increment reaching significance only after LPD (from 4.2 ± 0.6 to 5.6 ± 1.3 ml · min^{-1} ($P = 0.13$) at the start of the study and from 3.2 ± 0.3 to 7.7 ± 1.8 ml · min^{-1} ($P < 0.05$ after 3 months on LPD).

Nutritional parameters

Weight did not significantly change (Table 2). All patients reported a general feeling of well being, and did not change their lifestyle during the three months of the study. No significant change was observed concerning mid-arm circumference, triceps skinfold thickness, serum protein or albumin levels.

Metabolic parameters at postabsorptive state

Postabsorptive plasma glucose (5.0 ± 0.1 vs. 4.7 ± 0.1 mmol · liter^{-1}; $P < 0.05$) and insulin (14.0 ± 3.7 vs. 8.1 ± 1.5 μU · ml^{-1}; $P < 0.05$) levels were lower after LPD. Protein oxidation was lower after LPD (0.37 ± 0.09 vs. 0.07 ± 0.01 mg · kg^{-1} · min^{-1}; $P < 0.01$; Table 3). Nonproteic substrate oxidation rates did not significantly differ before and after the diet, although they slightly increased: glucose oxidation, 1.46 ± 0.31 vs. 1.71 ± 0.28 mg · kg^{-1} · min^{-1}; lipid oxidation, 0.79 ± 0.08 vs. 1.02 ± 0.12 mg · kg^{-1} · min^{-1}). Resting energetic production rate was increased on LPD from 15.72 ± 0.48 to 17.16 ± 0.67 Cal · kg^{-1} · min^{-1} ($P < 0.05$); changes in individual values are shown in Figure 2. Uric acid level decreased under LPD from 580 ± 33 to 380 ± 23 μmol · liter^{-1} ($P < 0.01$). Arterial pH (7.39 ± 0.01 vs. 7.40 ± 0.01; NS) and bicarbonates (24.2 ± 1.2 vs. 24.5 ± 1.3 mmol · liter^{-1}; NS) did not change. Total calcium (2.31 ± 0.09 vs. 2.42 ± 0.08 mmol · liter^{-1}), phosphorus (1.44 ± 0.21 vs. 1.35 ± 0.09 mmol · liter^{-1}), and PTH (280 ± 139 vs. 177 ± 86 pg · ml^{-1}) varied without reaching significance. Hemoglobin (11.5 ± 0.7 vs. 11.1 ± 0.5 g · dl^{-1}) and hematocrit (34.0 ± 2.1 vs. 33.4 ± 1.5%) did not change significantly.

Clamp study

All subjects were clamped at the same glycemic level (4.8 mmol · liter^{-1}) maintained constant (mean CV = 3.5%) (Table 4 and Fig. 3). Identical insulin infusion rates resulted in lower insulin levels after LPD (1st step, from 80.0 ± 10.6 to 69.0 ± 6.7 μU · ml^{-1}; 2nd step, from 582 ± 88 to 481 ± 63 mU · ml^{-1}), but the differences did not reach significance. The glucose infusion rates to maintain euglycemia were higher on LPD (1st step, 3.65 ± 0.65 vs. 5.95 ± 0.86 mg · kg^{-1} · min^{-1}, $P < 0.05$; 2nd step, 7.32 ± 0.93 vs. 9.37 ± 0.56 mg · kg^{-1} · min^{-1}, $P < 0.05$), indicating improved insulin sensitivity. After three months of LPD, glucose oxidation rate was more efficiently stimulated at the first step (2.36 ± 0.29 vs. 3.37 ± 0.35 mg · kg^{-1} · min^{-1}; $P < 0.05$). Glucose nonoxidative disposal also increased (1st step, from 1.29 ± 0.51 to 2.58 ± 0.68 mg · kg^{-1} · min^{-1}, $P < 0.05$; 2nd step, from 3.74 ± 0.74 to 5.31 ± 0.41 mg · kg^{-1} · min^{-1}, $P < 0.05$). Energetic production rates were higher after LPD (1st step, from 15.78 ± 0.64 to 17.51 ± 0.56 Cal · kg^{-1} · min^{-1}, $P < 0.01$; 2nd step, from 16.67 ± 0.65 to 18.24 ± 0.47, $P < 0.05$). LPD did not produce any change concerning the inhibition of lipid oxidation during the clamp.

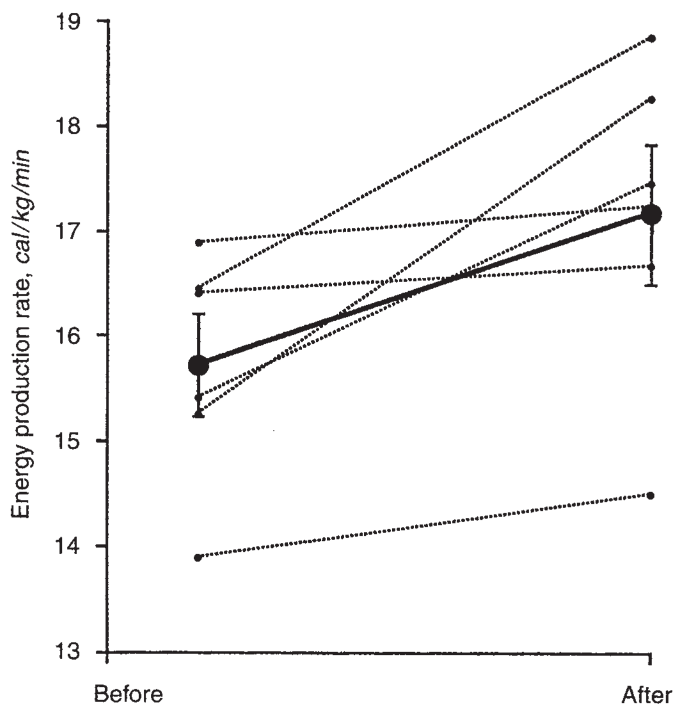
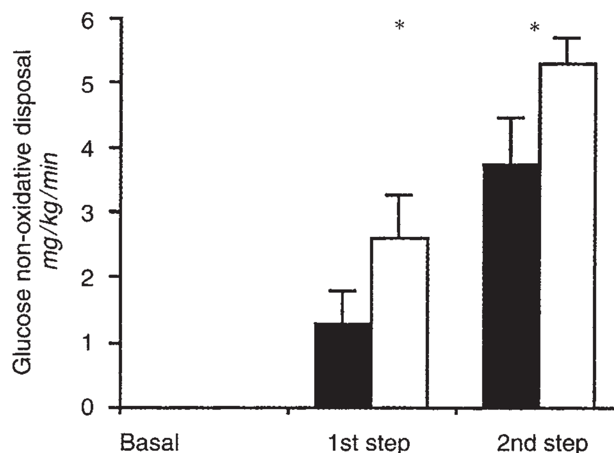


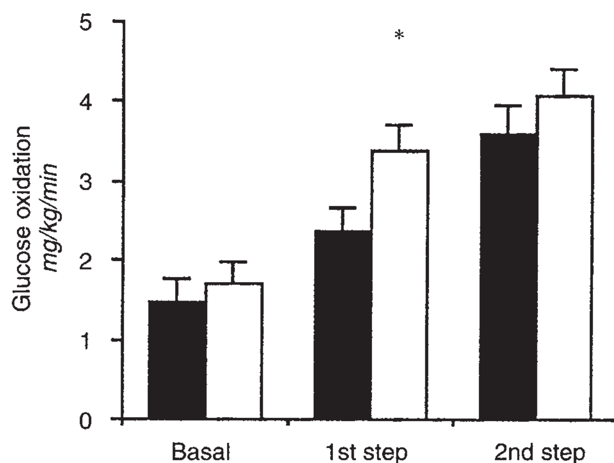
Fig. 2. *Individual resting energy production rates before and after LPD.*

Table 4. Insulin-stimulated substrate oxidation rates and nonoxidative glucose disposal before and after LPD

	First step		Second step	
	Before	After	Before	After
Plasma insulin *μU · ml⁻¹*	80.0 ± 10.6	69 ± 6.7	582.8 ± 88.2	481 ± 63.7
Glucose oxidation *mg · kg⁻¹ · min⁻¹*	2.36 ± 0.29	3.37 ± 0.35[a]	3.58 ± 0.36	4.06 ± 0.35
Glucose nonoxidative disposal *mg · kg⁻¹ · min⁻¹*	1.29 ± 0.50	2.58 ± 0.68[a]	3.74 ± 0.74	5.31 ± 0.41[a]
Energy production rate *Cal · kg⁻¹ · min⁻¹*	15.78 ± 0.64	17.51 ± 0.56[b]	16.67 ± 0.65	18.24 ± 0.47[a]
Lipid oxidation *mg · kg⁻¹ · min⁻¹*	0.46 ± 0.10	0.60 ± 0.09	0.30 ± 0.10	0.27 ± 0.10

[a] $P < 0.05$
[b] $P < 0.01$





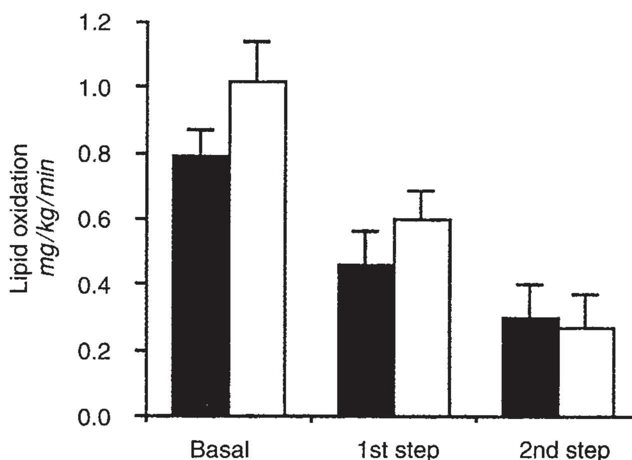


Fig. 3. *Insulin-stimulated substrate oxidation rates and nonoxidative glucose disposal before (■) and after (□) LPD.* *$P < 0.05$.

Discussion

In six nondialyzed chronically uremic patients, three months on a very low-protein diet produced significant beneficial effects on glucose metabolism. During the postabsorptive state, plasma glucose and insulin levels were lower, suggesting a better insulin sensitivity, which was confirmed by the hyperinsulinemic euglycemic clamp study. The use of indirect calorimetry showed that the increase of glucose utilization could be attributed to a more efficient stimulation of both glucose oxidation and nonoxidative disposal, at moderate hyperinsulinemia (70 to 80 $\mu U \cdot ml^{-1}$), and predominantly to nonoxidative glucose disposal at a pharmacological level (500 to 600 $\mu U \cdot ml^{-1}$). In the postabsorptive state and under insulin stimulation, energy production rates were significantly higher after LPD. It is noteworthy that during the three month follow-up no other catabolic factor was present. Consequently, the increase in EPR appeared to be related to the change in alimentary protein intake alone.

Insulin resistance is a well-known feature of chronic uremia [1],

and we have previously described its improvement by LPD [3]. The use of a euglycemic clamp combined with indirect calorimetry to localize the defective pathway of glucose utilization in chronically uremic patients is logical, but requires methodological cautiousness. First, metabolic acidosis is a common complication of CRF, that can be ameliorated by LPD, due to the low acidifying activity of the diet [11]. The correction of metabolic acidosis *per se* ameliorates insulin sensitivity [12]. For these reasons, metabolic acidosis was an exclusion criterion for entering the study. Initially close to normal levels, arterial pH and bicarbonates were not significantly modified by three months of diet, and therefore did not influence the results. Second, the hyperinsulinemic euglycemic clamp augments urea clearance in normal subjects, leading to erroneously elevated protein oxidation rates as calculated on the basis of urinary N excretion [17], and an up to 5% underestimation of glucose oxidation [15]. Our results show that this effect is also present in chronically uremic subjects, but more moderately than in healthy subjects, and that it leads to nonsignificant changes in lipid and carbohydrate oxidation rates. However, we corrected the N urinary excretion rate as proposed by Thorburn et al [15], in order to minimize this source of error. Third, in calculating the nonoxidative glucose disposal rate as the difference between exogenous glucose infusion rate to maintain euglycemia and glucose oxidation, we neglected the potential influence of a change in endogenous glucose production insulin sensitivity induced by the diet. However, endogenous glucose production is known to be virtually suppressed in uremic patients at the insulin levels we used [5]. Consequently, modifications it might have undergone would not interfere in our conclusions concerning glucose storage. Finally, it should be noted that insulin infusion produces greater effects on glucose oxidation and storage after LPD, in spite of lower levels of the hyperinsulinemic plateau, in relation with the increase in insulin metabolic clearance rate as we have previously described [4].

The improvement induced by LPD concerns both oxidative and nonoxidative pathways in our patients, at least at the first step of the clamp study. Comparing uremic patients to normal subjects, Castellino showed that their defect of glucose utilization was caused by resistance to insulin of glucose nonoxidative disposal [5]. Our patients presented a more advanced degree of CRF, raising the possibility that glucose oxidation may also resist stimulation by insulin in advanced CRF. In accordance with this hypothesis, using ^{13}C glucose as a tracer, Kalhan et al found that glucose oxidation is reduced in dialyzed uremic patients in the postabsorptive state [18]. However, insulin action was not considered in their report. The improvement in glucose oxidation sensitivity to insulin probably plays a role in the better glucose tolerance after LPD [3], as the improvement is observed at an insulin level that can be attained under physiological conditions.

The mechanism of the effect of LPD on insulin sensitivity is not known. Chronically uremic patients cumulate many factors associated with insulin resistance that may be corrected by the diet. Metabolic acidosis is one of these factors which was not present in our patients. A better control of secondary hyperparathyroidism, as previously reported with LPD in a larger number of patients [19], may interact with glucose metabolism. Diet-induced changes in calcium, phosphorus and PTH levels did not reach significance in this study, because of the small number of patients, but this possible indirect effect may be important. Hyperuricemia is associated with insulin resistance in nondiabetic and nonuremic subjects [20], and three months of LPD significantly lowered uric acid levels in our patients. To our knowledge, no attempt has been made to study modifications of insulin action related to changes in uric acid levels, but it seems probable that this is a marker, rather than a causative factor. The decreased production of a putative factor derived from dietary protein, and able to induce insulin resistance remains a major hypothesis concerning the mechanism of the effect of the diet [21]. Finally, it should be noted that the diet does not necessarily improve insulin sensitivity by acting on a mechanism that produces insulin resistance specifically in CRF. LPD has been shown to improve insulin sensitivity of nonuremic subjects, such as diabetics without renal impairment [7]. The effect on glucose oxidation, that is not known to be resistant to insulin in CRF, may also be nonspecific to renal failure.

The elevation of glucose oxidation is not counterbalanced by a reciprocal reduction of lipid oxidation, and the decrease of protein oxidation is not sufficient to equilibrate it. Protein oxidation is a minor component of EPR. As calculated by Ferrannini [16], a 50% misjudgment concerning protein oxidation leads to a 1.2% error in EPR. The energy production rate is therefore increased by LPD in our patients. Resting energy production rate is normal [5, 22] or may be slightly low [23] in CRF, and malnutrition in these patients is thought to be the consequence of inadequate caloric intake [24], that may be aggravated under LPD if the energy supply is not sufficient [9, 25], as observed in normal subjects [10]. Kopple et al have shown that the maintenance of a neutral nitrogen balance in uremic patients on moderately low-protein diet (0.55 to 0.60 g protein $\cdot$ kg^{-1} $\cdot$ day^{-1}) depends on the energy supply [26], and they recommended an energy intake of approximately 35 kCal $\cdot$ kg^{-1} $\cdot$ day^{-1}, the quantity initially proposed to our patients. To our knowledge, the notion that protein-restricted diets may, in fact, raise energy production rate has not yet been reported. This energy-expending effect may be due to the diet itself, or to the ketoanalogs, although the transamination reaction is not known to have a substantial energetic cost [27, 28]. As the energy requirements of normal individuals with moderate physical activity are reported to be about 1.6 to 1.7 times the basal energy expenditure [29], 40 kCal $\cdot$ kg^{-1} $\cdot$ day^{-1} is probably preferable to 35 if protein intake is extremely restricted. Because energy requirements are subject to sizable interindividual variations, the monitoring of body wt and other nutritional parameters remains crucial in patients on such diets, and regular energy production rate determinations may be useful. However, it should be noted that no significant deterioration of nutritional parameters appeared in our patients during the three-month survey. A transient decrease in body wt is frequently observed during the first months on LPD, that is progressively regained later with dietary adjustment as shown by longer (18 months) follow-up [30]. In our study, patients were seen monthly for a dietary interview.

In summary, in six patients with CRF, three months on a LPD produced an improvement of insulin action on glucose oxidation and nonoxidative utilization that was significant at a moderate insulin level. Insulin-stimulated glucose oxidation may be impaired in CRF, at least when GFR is below 20 ml $\cdot$ min^{-1}. The improvement of uremic insulin resistance by a LPD may be explained by several mechanisms: directly by lowering the production of a uremic toxin, indirectly by a reduction in secondary hyperparathyroidism, and nonspecifically in the same way that it improves insulin action in nonuremic patients [7]. The beneficial

effect of the diet was accompanied by a slight increase in energy production rate, that can be considered as an adverse effect and that justifies intensification of nutritional monitoring and surveys of caloric intake. From a practical point of view, this suggests that LPD may be helpful in states of insulin resistance other than CRF as previously proposed [7], and confirms the importance of a sufficient caloric intake for weight maintenance [9, 25, 26].

Acknowledgments

This work was supported by a grant from the Région Aquitaine, and from the Centre Hospitalier et Universitaire Régional de Bordeaux.

Reprint requests to Professeur M. Aparicio, Service de Néphrologie, Hôpital Pellegrin, 33076 Bordeaux, France.

Appendix

The composition of one Cetolog tablet (mg) is:
ketoisoleucine, L-ornithine: 153.24
ketovaline, L-ornithine: 72.67
ketoleucine, L-lysine: 161.78
ketovaline, L-lysine: 76.77
ketoleucine, L-histidine, H_2O: 50.72
DL-hydroxymethioninate Ca^{++}: 28.30
L-tyrosine: 151.54
L-threonine: 74.68

References

1. EMMANOUEL DS, LINDHEIMER MD, KATZ AL: Endocrine function, in *The Systemic Consequences of Renal Failure*, edited by EKNOYAN G, KNOCHEL JP, New York, Grune & Stratton, 1984, pp 177–232
2. DE FRONZO RA, ALVESTRAND A, SMITH D, HENDLER R, WAHREN J: Insulin resistance in uremia. *J Clin Invest* 67:563–568, 1981
3. GIN H, APARICIO M, POTAUX L, DE PRÉCIGOUT V, BOUCHET JL, AUBERTIN J: Low protein and low phosphorus diet in patients with chronic renal failure: Influence on glucose tolerance and tissue insulin sensitivity. *Metabolism* 36:1080–1085, 1987
4. GIN H, COMBE C, RIGALLEAU V, DELAFAYE C, APARICIO M, AUBERTIN J: Effect of a low-protein, low-phosphorus diet on metabolic insulin clearance in patients with chronic renal failure. *Am J Clin Nutr* 59:663–666, 1994
5. CASTELLINO P, SOLINI A, LUZI L, BARR JG, SMITH DJ, PETRIDES A, GIORDANO M, CARROLL C, DE FRONZO RA: Glucose and amino acid metabolism in chronic renal failure: Effect of insulin and amino acids. *Am J Physiol* 262:F168–F176, 1992
6. EIDEMAK I, FELDT-RASMUSSEN B, KANSTRUP IL, NIELSEN SL, SCHMITZ O, STRANGAARD S: Insulin resistance and hyperinsulinemia in mild to moderate progressive renal failure and its association with aerobic work capacity. *Diabetologia* 38:565–572, 1995
7. LARRIVIERE F, CHIASSON JL, SCHIFFRIN A, TAVEROFF A, HOFFER LJ: Effects of dietary protein restriction on glucose and insulin metabolism in normal and diabetic humans. *Metabolism* 43:462–467, 1994
8. YKI-JÄRVINEN H: Role of insulin resistance in the pathogenesis of NIDDM. *Diabetologia* 38:1378–1388, 1995
9. GRETZ N, LASSERRE J, STRAUCH M: Caloric supplements for patients on low-protein diets? *Nephron* 50:129–132, 1988
10. WATERLOW JC: Metabolic adaptation to low intakes of energy and protein. *Ann Rev Nutr* 6:495–526, 1986
11. COMBE C, DEFORGES-LASSEUR C, CAIX J, POMMEREAU A, MAROT D, APARICIO M: Compliance and effects of treatment on progression and metabolic disorders of chronic renal failure. *Nephrol Dial Transplant* 8:412–418, 1993
12. REAICH D, GRAHAM KA, CHANNON SM HETHERINGTON C, SCRIMGEOUR CM, WILKINSON R, GOODSHIP THJ: Insulin-mediated changes in PD and glucose uptake after correction of acidosis in humans with CRF. *Am J Physiol* 268:E121–E126, 1995
13. RIZZA RA, MANDARINO LJ, GERICH JE: Dose-response characteristics for effects of insulin on production and utilization of glucose in man. *Am J Physiol* 240:E630–E639, 1981
14. BERGMEYER HV: *Methods of Enzymatic Analysis*. New York, Academic Press, 1974, pp 178–185
15. THORBURN AW, GUMBINER B, FLYNN T, HENRY RR: Substrates oxidation errors during combined indirect calorimetry-hyperinsulinemic glucose clamp studies. *Metabolism* 40:391–398, 1991
16. FERRANNINI E: The theorical basis of indirect calorimetry: A review. *Metabolism* 287–301, 1988
17. TAPPY L, OWEN OE, BODEN G: Effect of hyperinsulinemia on urea pool size and substrate oxidation rates. *Diabetes* 37:1212–1216, 1988
18. KALHAN SC, RICANATI ES, TSERNG KY, SAVIN SM: Glucose turnover in chronic uremia: Increased recycling with diminished oxidation of glucose. *Metabolism* 32:1155–1162, 1983
19. COMBE C, MOREL D, DE PRÉCIGOUT V, BLANCHETIER V., BOUCHET J-L, POTAUX L, FOURNIER A, APARICIO M: Long-term control of hyperparathyroidism in advanced renal failure by low-phosphorus low-protein diet supplemented with calcium (without changes in plasma calcitriol). *Nephron* 70:287–295, 1995
20. VUORINEN-MARKKOLA H, YKÏ-JÄRVINEN H: Hyperuricemia and insulin resistance. *J Clin Endocrinol Metab* 78:25–29, 1994
21. MCCALEB ML, IZZO MS, LOCKWOOD DH: Characterization and partial purification of a factor from uremic human serum that induces insulin resistance. *J Clin Invest* 75:391–396, 1985
22. MONTEON JF, LAIDLAW SA, SHAIB JK, KOPPLE JD: Energy expenditure in patients with chronic renal failure. *Kidney Int* 30:741–747, 1986
23. BUCCIANTE G, SENESI G, PIVA M, DONATO D, VELLUTI F, MILITO F, SPISANI C, BERNARD A: Resting metabolic rate by indirect calorimetry in uremic patients. *Contrib Nephrol* 81:214–219, 1990
24. MARONI BJ: Protein, calories and fat in the predialysis patient, in *Nutrition and the Kidney* (2nd ed), edited by MITCH WE, KLAHR S, Boston, Little, Brown, 1993, pp 185–217
25. RAYNER HC, BURTON PR, BENNET S, WALLS J: Changes in nutritional status of patients with chronic renal failure on a low-protein diet. *Nephron* 64:154, 1993
26. KOPPLE JD, MONTEON FJ, SHAIB JK: Effect of energy intake on nitrogen metabolism in nondialyzed patients with chronic renal failure. *Kidney Int* 29:734–742, 1986
27. MAY RC, MITCH WE: The metabolism and metabolic effects of ketoacids. *Diabetes Metabol Rev* 5:71–82, 1989
28. LEHNINGER AL, NELSON DL, COX MM: *Principles of Biochemistry* (2nd ed). New York, Worth Publisher Inc., 1993, p 511
29. COMMITTEE ON DIETARY ALLOWANCES FOOD AND NUTRITION BOARD: *Recommended Dietary Allowances* (9th Ed). Washington DC, National Academy of Sciences, 1980, p 19
30. APARICIO M, GIN H, DE PRÉCIGOUT V, MAROT D, WINNOCK S, MOREL D, BOUCHET J-L, POTAUX L: Compliance with low-protein diet by uremic patients: Three years' experience. *Contrib Nephrol* 81:71–78, 1990