# Energy Expenditure Following Oral Glucose Load in Ten Uremic Patients Before and After Three Months on a Ketoacid-Supplemented Very-Low-Protein Diet

Laurence Baillet, Vincent Rigalleau, Michel Aparicio, Nicole Barthe, and Henri Gin

**We have previously shown that a ketoacid-supplemented very-low-protein diet (KSVLPD), which has been proposed to slow down the rate of progression of chronic renal failure (CRF), improves tissue insulin sensitivity and decreases hyperinsulinemia in predialytic uremic patients. However, this diet may interfere with nutritional status. The aim of this study was to study basal energy expenditure (EE) and EE after an oral glucose load in patients with CRF before and during a KSVLPD (0.3 cal · kg $wt^{-1}$ · $d^{-1}$ supplemented with aminoacid and ketoanalogs) using oral glucose loading in combination with indirect calorimetry. We also monitored body weight and analyzed body composition by dual-energy x-ray (DEXA) during KSVLPD. In the third month of KSVLPD, no significant change in total body weight was observed, but DEXA showed a decrease in lean tissue mass (LTM; 46.2 ± 3.6 kg before *v* 44 ± 3.4 kg in the third month; *P* < .01) and an increase in body fat mass (20.1 ± 2.4 kg before *v* 21.3 ± 2.4 kg on KSVLPD; *P* < .05). Postabsorptive plasma glucose level was significantly lower, and glucose oxidation and energy expenditure per LTM were significantly increased (EE, 20 ± 0.8 cal · kg $LTM^{-1}$ · $min^{-1}$ before diet *v* 21.9 ± 1.1 cal · kg $LTM^{-1}$ · $min^{-1}$ after 3 months on KSVLPD; *P* < .01). Plasma glucose and serum insulin levels were significantly lower after glucose loading, and glucose oxidation increased. EE values were significantly higher after the oral glucose load, and cumulative EE after oral load increased from 20.7 ± 0.7 cal · kg $LTM^{-1}$ · $min^{-1}$ before the diet to 22.9 ± 1.1 cal · kg $LTM^{-1}$ · $min^{-1}$ in the third month of KSVLPD; *P* < .001). Glucose oxidation was higher and cumulative glucose storage was decreased after diet (29.6 ± 4.2 g *v* 20.9 ± 3.4 g on KSVLPD; *P* < .01). We conclude that KSVLPD increases EE in the postabsorptive state and after an oral glucose load with an adaptation of lean tissue mass in the third month of the diet. Therefore, during KSVLPD, strict monitoring of dietetic management is necessary to maintain energy requirements at high levels appropriate to the new EE.**

***Copyright © 2001 by W.B. Saunders Company***

INDIVIDUALS WITH chronic renal failure (CRF) frequently develop metabolic disorders. Abnormalities in glucose metabolism have long been known to occur during the course of CRF. Most uremic patients have mild fasting hyperglycemia, reduced glucose tolerance, hyperinsulinemia, and insulin resistance,[1] all of which are associated with increased cardiovascular risk.[2] Diets with protein restriction are commonly prescribed to slow the decline in renal function.[3,4] In previous studies, we found that ketoacid-supplemented very-low-protein diet (KSVLPD) also improved disorders of carbohydrate metabolism. Using the clamp technique and indirect calorimetry, we showed that tissue insulin sensitivity improves during KSVLPD and that the suppression of hepatic glucose production by insulin is enhanced.[5-7] Consequently, the glucose intolerance and hyperinsulinemia typically observed in patients with CRF are improved during KSVLPD. However, metabolic acidosis and secondary hyperparathyroidism, which also occur frequently in patients with advanced CRF, accelerate the body's rate of catabolism, posing the threat of secondary malnutrition.[8-10] Uremia per se does not induce hypercatabolism, and the physiological adaptive response to protein restriction is preserved in uremic patients. Patients in the Modification of Diet in Renal Disease (MDRD) study (very low protein diet plus ketoacid) did not exhibit malnutrition, even through body weight and antropometric parameter decreased during the first 4 months of the diet.[11] Nonetheless, the risk of malnutrition is genuine in patients on KSVLPD, particularly if their energy intake is low.[12]

Cases of decline in muscle mass among elderly patients[13] and patients who have type 1 diabetes mellitus and early nephropathy[14] have been reported following institution of dietary protein restriction. Using the glucose clamp technique and indirect calorimetry in a preliminary study involving six CRF patients treated by KSVLPD, we found that the beneficial effect of the diet on metabolic disorders was accompanied by a slight increase in the fasting energy production rate.[7]

The purpose of the present study was to follow body fat mass and lean mass tissue in nondiabetic CRF patients after KSVLPD using dual-energy x-ray absorptiometry (DEXA) and to measure energy expenditure (EE) in patients with CRF in the fasting state and after an oral glucose load. In CRF patients on KSVLPD, diet-mediated thermogenesis is predominantly represented by carbohydrate-induced thermogenesis because carbohydrates account for 67% of the dietary caloric intake. For this reason we used oral glucose loading in combination with indirect calorimetry to measure fasting and postloading EE, glucose oxidation, glucose storage, and fat oxidation before and in the third month of KSVLPD in 10 patients with CRF.

## SUBJECTS AND METHODS

### *Patients*

Ten undialyzed patients with advanced CRF (glomerular filtration rate [GFR] was 13.2 ± 4.8 mL/min) were studied before and in the third month on KSVLPD. Mean serum creatinine was 401 ± 35 μmol · $L^{-1}$ and mean serum urea was 23.6 ± 1.8 mmol · $L^{-1}$ (serum creatinine and serum urea were measured using semiautomated methods). There were 6 men and 4 women (mean age, 56.4 ± 3 years; range, 39

*From the Service de diabétologie, Hôpital du Haut Lévêque, Pessac; and the Service de néphrologie and Service de biophysique, Hôpital Pellegrin, Bordeaux, France.*

*Submitted May 23, 2000; accepted August 29, 2000.*

*Address reprint requests to Henri Gin, MD, Service de diabétologie, Hôpital du Haut Lévêque, 5 Avenue Magellan, 33600 Pessac, France.*

*Copyright © 2001 by W.B. Saunders Company*

*0026-0495/01/5003-0031$35.00/0*
*doi:10.1053/meta.2001.20203*

to 69 years). The underlying renal diseases were as follows: chronic glomerulonephritis (n = 5), interstitial nephropathy (n = 1), polycystic kidney disease (n = 1), nephroangiosclerosis (n = 2), and sequelae of dissecting aortic aneurysm (n = 1). None had diabetes mellitus or a family history of diabetes mellitus. No patient was being treated with beta blockers. No drug regimen was modified during the study.

The experimental protocol was approved by the ethics committee of our institution, and informed consent was obtained from each patient before starting the KSVLPD diet.

### *KSVLPD*

The subjects were taught how to follow a ketoacid-supplemented very-low-protein, low-phosphorus diet (0.3 g protein and 5 to 7 mg inorganic phosphorus per kg of body weight per day). Only protein of vegetable origin was used. However, each gram of urinary protein loss (proteinuria) was replaced by an additional 1.25 g protein of high biological value of animal origin. The KSVLPD was supplemented daily with essential amino acids and ketoanalogs in the form of one tablet (Ketosteril, Fresenius-Germany) per 5 kg body weight administered daily in divided doses with meals, 1 to 2 g of calcium carbonate to maintain normal serum calcium concentration, iron, and a multivitamin preparation. The energy ration (theoretically 35 kcal · kg body $wt^{-1} \cdot d^{-1}$) was furnished mainly by carbohydrate and fat (67% and 30% of the total dietary energy intake, respectively).

### *Follow-up*

Compliance with the diet was verified monthly by dietary interview and by urinary urea and phosphorus excretion measurements and was encouraged by the nurse, the dietetician, and the physician. Monthly adjustments in caloric intake based on dietary interviews were made to maintain initial weight.

### *Nutritional Status*

Body weight was determined monthly. Arm muscle circumference and triceps skinfold thickness were measured at the beginning of the diet and after 3 months on KSVLPD, according to the antropometric standards for the assessment of nutritional status.[15]

DEXA was performed before and in the third month of KSVLPD using the Hologic QRD-2000. The technique consists of scanning the body with x-rays at two energy levels and separating bone from soft tissue by measurement of differential attenuation. Fat tissue mass (FTM) is differentiated from lean tissue mass (LTM) by the ratio of low-energy to high-energy attenuation in soft tissue.[16] The reproductibility of the technique was prealably tested for CRF patients, and the coefficient of variation of the measure of LTM was 0.7%.[17]

### *Metabolic Parameters and EE*

*Oral glucose load.* The study was performed at 8 AM after 12 hours' overnight fasting. Patients were given 1 g · kg body $wt^{-1}$ glucose in solution in 300 mL of water as described by Ferrannini et al.[18] After ingestion of the carbohydrate load, a transparent ventilated Plexiglass canopy was placed over the head of the patient to measure gas exchanges.

*Gas exchange measurements and metabolic oxidation calculations.* Indirect calorimetry measurements were made using an open-circuit ventilated hood system (Delatrac Metabolic Monitor; Datex, Helsinki, Finland). Gas exchange measurements were performed 30 minutes before oral load (postabsorptive state) and over 5 hours after the oral load (25 minutes of measurement, 5 minutes free, and so on). Blood samples were collected in the fasting state and every 30 minutes after the oral glucose load to measure plasma glucose, serum insulin, plasma free fatty acid (FFA), and plasma triacylglycerol levels. Urine was collected at the end of each monitoring session for determination of urinary excretion rates of urea (mmol · $min^{-1}$), creatinine (mmol · $min^{-1}$), and uric acid (mmol · $min^{-1}$) using semiautomated methods and Mitch's formula.[19] We did not use Kjeldahl nitrogen measurement because the patients were proteinuric. Urinary glucose concentration was also measured.

Urinary nitrogen ($U_N$) was defined as $U_N = (2 \cdot U_{urea}) + (3 \cdot U_{creatinine}) + (4 \cdot U_{uric\ acid})$. Total nitrogen excretion can be estimated as $U_N$ + 31 mg N/kg/d.

Glucose (G), lipid (L), and protein (P) oxidation rates and EE were approximated according to formulas proposed by Ferrannini[20]:

$$G(g \cdot min^{-1}) = 4.55V_{CO_2} - 3.21V_{O_2} - 2.87U_N,$$

$$L(g \cdot min^{-1}) = 1.67(V_{O_2} - V_{CO_2}) - 1.92U_N,$$

$$P(g \cdot min^{-1}) = 6.25U_N, \quad \text{and}$$

$$EE(kcal \cdot min^{-1}) = 3.91V_{O_2} + 1.1V_{CO_2} - 3.34U_N,$$

where $V_{O_2}$ represents oxygen consumption, $V_{CO_2}$ carbon dioxide production, and $U_N$ the number of grams of total urinary nitrogen excretion per minute. The gas exchange measurements and these formulas yielded oxygen consumption, carbon dioxide production, and EE values.

Glucose oxidation (mg · kg $LTM^{-1}$ · $min^{-1}$) and lipid oxidation (mg · kg $LTM^{-1}$ · $min^{-1}$) were calculated in postabsorptive state and over a 300-minute period after oral glucose loading. The total amount of nonoxidative glucose metabolism (glucose storage) was calculated by subtracting the total quantity of glucose oxidized from the amount of glucose ingested minus urinary loss. Lean tissue oxidation was calculated by dividing total glucose oxidation by lean tissue mass. EE was calculated in the postabsorptive state (kcal · kg $LTM^{-1}$ · $min^{-1}$) and after oral glucose leading (kcal · kg $LTM^{-1}$ · $min^{-1}$). Values before and after 3 months on KSVLPD were compared using Student's *t* test.

The plasma glucose concentration was determined by the glucose oxidase method. Serum total urea, phosphorus, bicarbonate, and uric acid were determined by routine, semiautomatic methods. Serum insulin was measured by radioimmunoassay (Pharmacia kit) and total triacylglycerol and FFA by an enzymatic method. Triiodothyronine ($T_3$) and thyroxine ($T_4$) were measured by radioimmunoassay.

### *Presentation of Results and Statistical Analysis*

Resting EE and EE during oral glucose load were expressed per kilogram LTM as proposed by Ravussin and Zadwadki[21] because lean tissue mass is the major contributor of EE.

Glucose and lipid oxidation were also calculated as a function of LTM as advocated by Groop et al[22] and Zurlo et al[23] (muscle is the specific tissue that oxidizes glucose). LTM was calculated by DEXA.

All data are presented as means ± SEM. Values before and after KSVLPD were compared by Student's *t* test. $P < .05$ was considered statistically significant.

## RESULTS

### *Diet*

Compliance with KSVLPD and ketoanalogs was good in this group of highly motivated patients. Actually patient diets did not differ from the prescribed diet by more than 20%. The mean total caloric intake had to be increased from 27.8 ± 2.7 kcal · kg body $wt^{-1} \cdot d^{-1}$ before to 31 ± 2.9 kcal · kg body $wt^{-1} \cdot d^{-1}$ after KSVLPD, but this increase was not significant (Table 1). Plasma urea decreased dramatically from 23.1 ± 1.8 mmol · $L^{-1}$ to 6.8 ± 1.22 mmol · $L^{-1}$ ($P < .001$). Urinary urea decreased from 244 ± 15.6 mmol · $d^{-1}$ before diet to 57.8 ± 8.6 mmol · $d^{-1}$ after 3 months of KSVLPD ($P < .001$). The

**Table 1. Dietary Inquiry and Nutritional Parameters Before and After KSVLPD**

| | Before Diet | After Diet | *P* |
|---|---|---|---|
| Total caloric intake (kcal · kg body $wt^{-1} \cdot d^{-1}$) | 27.85 ± 2.7 | 31 ± 2.9 | NS |
| Protein intake (g · kg body $wt^{-1} \cdot d^{-1}$) (calculated from urinary urea excretion) | 0.8 ± 0.08 | 0.3 ± 0.02 | <.001 |
| Body weight (kg) | 68.8 ± 5 | 68.1 ± 4.5 | NS |
| Midarm circumference (cm) | 31 ± 0.8 | 30.9 ± 1 | NS |
| Triceps skinfold thickness (mm) | 14.5 ± 2.6 | 14.7 ± 2.7 | NS |
| Lean tissue mass (kg) DEXA | 46.2 ± 3.6 | 44 ± 3.4 | <.01 |
| Fat tissue mass (kg) DEXA | 20.1 ± 2.4 | 21.3 ± 2.4 | <.05 |

mean calculated protein intake (results obtained from urinary urea excretion) decreased with dietary recommendations from 0.8 ± 0.08 g · kg body $wt^{-1} \cdot d^{-1}$ to 0.3 ± 0.02 g · kg body $wt^{-1} \cdot d^{-1}$ ($P < .001$). Urinary creatinine decreased from 9.7 ± 0.8 mmol · $d^{-1}$ before diet to 6.9 ± 0.7 mmol · $d^{-1}$ after 3 months of KSVLPD ($P < .001$). Plasma bicarbonate concentration was 24.1 ± 1.4 mmol · $L^{-1}$ before the diet and 26.1 ± 1.2 mmol · $L^{-1}$ after 3 months of KSVLPD ($P < .02$). Urinary proteinuria was 1.86 ± 1.45 g/24 h before the diet and 0.97 ± 0.81 g/24 h in the third month of KSVLPD ($P < .01$).

*Anthropometric Measurements*

Total body weight remained unchanged after diet (68.8 ± 5 kg before diet *v* 68.1 ± 4.5 kg after 3 months of KSVLPD). Midarm circumference was 31 ± 0.8 cm before and 30.9 ± 1 cm after diet, and mean triceps skinfold thickness was 14.5 ± 2.6 mm before and 14.7 ± 2.7 mm after diet (differences not statistically significant; Table 1).

DEXA measurements showed a decrease in lean tissue mass from 46.2 ± 3.6 kg to 44 ± 3.4 kg after 3 months of KSVLPD. This reduction was statistically significant ($P < .01$), as was the increase in body fat mass (20.1 ± 2.4 kg before *v* 21.3 ± 2.4 kg on KSVLPD; $P < .05$; Table 1).

*Carbohydrate Metabolism After Glucose Load*

*Plasma glucose and serum insulin.* Figure 1 shows oral glucose test results before and after 3 months on KSVLPD. Compared with initial values, blood glucose was significantly reduced from T0 to T180, and serum insulin was significantly reduced at T60, T90, and T120.

At T0, plasma glucose was 5.3 ± 0.2 mmol · $L^{-1}$ before *v* 5 ± 0.2 mmol · $L^{-1}$ on KSVLPD ($P < .02$). Serum insulin values at T0 were not different.

At T60, plasma glucose was 11.7 ± 0.45 mmol · $L^{-1}$ before *v* 9.5 ± 0.6 mmol · $L^{-1}$ on KSVLPD ($P < .01$), and serum insulin was 77 ± 15 IU/mL before *v* 65 ± 15.6 IU/mL on KSVLPD ($P < .02$).

At T180, plasma glucose was 5.4 ± 0.5 mmol · $L^{-1}$ before *v* 4.7 ± 0.4 mmol · $L^{-1}$ on KSVLPD ($P < .05$), and serum insulin values were not significantly different.

*Glucose, lipid, and protein oxidation and glucose storage.* In the fasting state, glucose oxidation per lean tissue mass was higher after 3 months on KSVLPD (2 ± 0.2 mg · kg $LTM^{-1}$ · $min^{-1}$ before the diet *v* 2.9 ± 0.3 mg · kg $LTM^{-1}$ · $min^{-1}$ after 3 months on KSVLPD; $P < .01$). After 3 months of KSVLPD, a significantly higher glucose oxidation rate was observed at T180 (Fig 2). Cumulative glucose storage was significantly lower after oral glucose loading after 3 months on KSVLPD, decreasing from 29.6 ± 4.2 g to 20.9 ± 3.4 g ($P < .01$).

Postabsorptive lipid oxidation was not modified by the diet. After 3 months on KSVLPD, lipid oxidation was only significantly higher only at 240 minutes after oral glucose loading, at which time the value of lipid oxidation was 0.8 ± 0.1 mg · kg $LTM^{-1}$ · $min^{-1}$ before KSVLPD and 1.0 ± 0.1 mg · kg $LTM^{-1}$ · $min^{-1}$ after 3 months of KSVLPD ($P < .05$). Prediet values of plasma FFA and plasma triacylglycerol after oral glucose loading were not different from those after dieting.

Results of cumulative glucose oxidation, lipid oxidation, glucose storage, and energy expenditure are shown in Table 2. Protein oxidation was estimated at the start of the study and

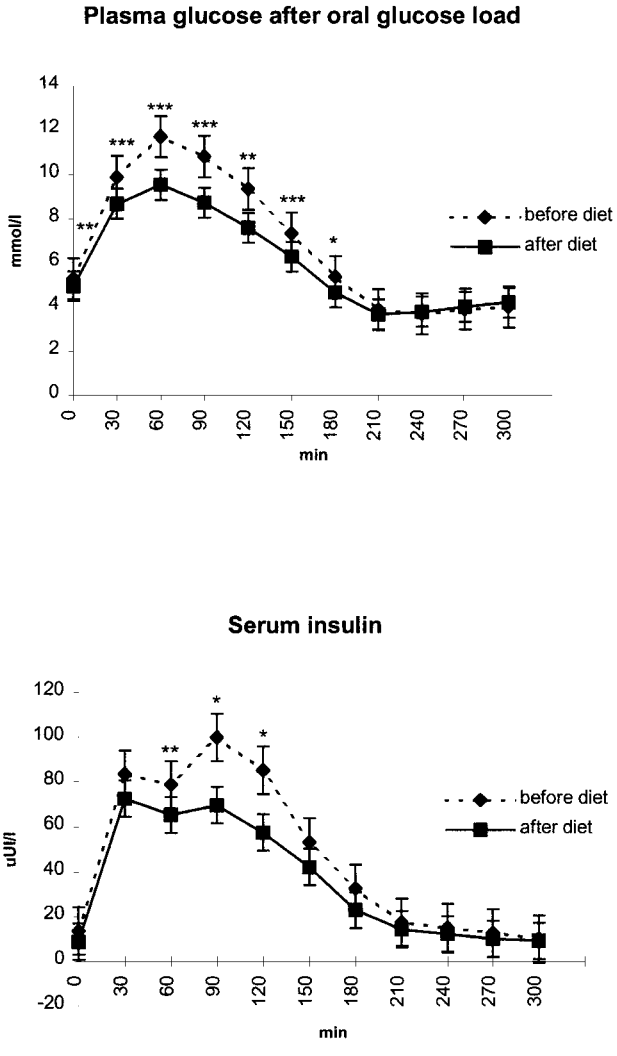


**Fig 1. Plasma glucose (mmol/L) and serum insulin (μIU/L) were measured every 30 minutes during an oral glucose load before and after the beginning of a KSVLPD diet. Values before and after KSVLPD were compared using Student's *t* test. **P* < .05; ***P* < .02; ****P* < .01.**

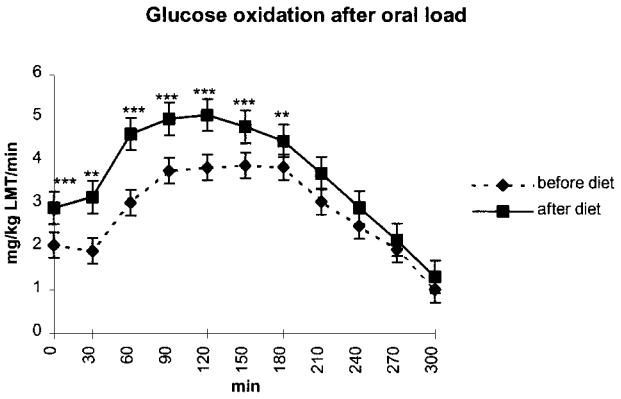


**Fig 2. Glucose oxidation (mg · kg LTM$^{-1}$ · min$^{-1}$). After oral loading, we calculated glucose oxidation using indirect calorimetry measurements; glucose oxidation by LTM (mg · kg LTM$^{-1}$ · min$^{-1}$) was calculated by dividing total glucose oxidation by LTM. Values before and after KSVLPD were compared using Student's *t* test. *$P$ < .05; **$P$ < .02; ***$P$ < .01.**

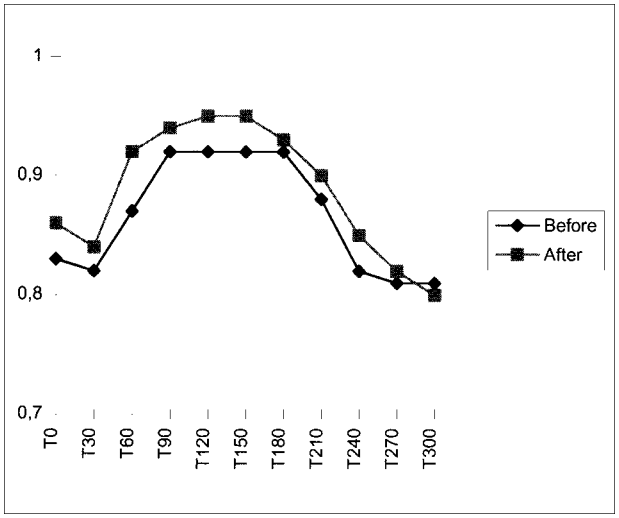


**Fig 3. Variation with time of respiratory quotient during oral glucose loading before and after the beginning of KSVLPD.**

after 3 months on KSVLPD. On KSVLPD, patients had significantly lower protein oxidation values. In the fasting state, protein oxidation was 0.53 ± 0.1 mg · kg$^{-1}$ · min$^{-1}$ before the diet and 0.17 ± 0.02 mg · kg$^{-1}$ · min$^{-1}$ after KSVLPD ($P <$ .01). After glucose loading, protein oxidation was 0.48 ± 0.07 mg · kg$^{-1}$ · min$^{-1}$ before the diet and 0.1 ± 0.02 mg · kg$^{-1}$ · min$^{-1}$ after KSVLPD ($P <$ .001).

*Energy expenditure.* Postabsorptive EE expressed per lean tissue mass was significantly higher after 3 months on KSVLPD (20.0 ± 0.8 cal · kg LTM$^{-1}$ · min$^{-1}$ before diet *v* 21.9 ± 1.1 cal · kg LTM$^{-1}$ · min$^{-1}$; $P <$ .01). EE per LTM values increased during oral glucose load, and cumulative EE after oral glucose was 20.7 ± 0.7 cal · kg LTM$^{-1}$ · min$^{-1}$ before the diet and 22.9 ± 1.1 cal · kg LTM$^{-1}$ · min$^{-1}$ after 3 months on KSVLPD ($P <$ .01; Table 2).

## DISCUSSION

We studied 10 CRF patients before and after 3 months on a KSVLPD (0.3 g · kg wt$^{-1}$ · d$^{-1}$). At the third month of the diet, body weight remained unchanged but DEXA measurements showed a decrease in lean tissue mass and an increase in fat mass. The use of indirect calorimetry showed an increase in glucose oxidation and a decrease in glucose storage after 3 months on KSVLPD. As previously reported, we observed an improvement in insulin sensitivity (decrease in serum insulin and plasma glucose levels and increase in glucose oxidation). We also observed an increase in postabsorptive EE. Moreover, energy production rates were significantly higher after oral glucose loading in patients on KSVLPD. To our knowledge, this is the first evidence that postabsorptive and post–oral glucose load EE are increased in patients on KSVLPD.

**Table 2. Cumulative Glucose and Lipid Oxidation, Cumulated Glucose Storage, and Cumulative EE Before and After 3 Months on KSVLPD**

| | Before Diet | After Diet | *P* |
|---|---|---|---|
| Postabsorptive state | | | |
| Gox (mg · kg LTM$^{-1}$ · min$^{-1}$) | 2 ± 0.2 | 2.9 ± 0.3 | <.01 |
| Lox (mg · kg LTM$^{-1}$ · min$^{-1}$) | 0.9 ± 0.1 | 0.9 ± 0.1 | NS |
| EE (kcal · kg LTM$^{-1}$ · min$^{-1}$) | 20.0 ± 0.8 | 21.9 ± 1.1 | <.01 |
| After oral glucose load | | | |
| Cumulative Gox (g) | 39.2 ± 2.8 | 47.2 ± 8.3 | <.02 |
| Cumulative glucose storage (g) | 29.6 ± 4.2 | 20.9 ± 3.4 | <.01 |
| Cumulative Lox (g) | 9.3 ± 1.5 | 10.1 ± 1.5 | NS |
| Cumulative EE (kcal · kg LTM$^{-1}$ · min$^{-1}$) | 20.7 ± 0.8 | 22.9 ± 1.1 | <.01 |

Abbreviations: Gox, glucose oxidation; Lox, lipid oxidation.

In healthy controls on low-protein diets (0.6 g protein · kg body wt$^{-1}$ · d$^{-1}$ and 0.1 g protein · kg body wt$^{-1}$ · d$^{-1}$ for 7 days) (Motil et al[24]) and in CRF patients on a diet of 0.8 g protein · kg body wt$^{-1}$ · d$^{-1}$ for 10 days (Maroni et al[25]), whole-body leucine, lysine metabolism, and serum albumin remained unchanged. Long-term adaptive responses to KSVLPD are related to reduction in amino acid oxidation and decreases in proteolysis and proteinuria.[25-27] Proteinuria spontaneously activates nitrogen conservation by decreasing amino acid oxidation and urea production.[25,26] In spite of these protein-preserving adaptations, the risk of modification of nutritional status merits consideration in patients managed by low protein intake.[25,26]

In this small group of highly motivated patients, compliance with the dietary prescription was very good, as demonstrated by reduced urinary urea and phosphorus excretion (data not shown). Mean weight remained stable (68.8 ± 5 kg before the diet *v* 68.1 ± 4.5 kg after the diet), confirming previous results elsewhere.[28] Total caloric intake was increased from 27.8 to 31.0 kcal · kg body wt$^{-1}$ · d$^{-1}$ without attaining the prescribed intake. This result differs from that reported by the French Multicentric Trial IRCCA,[28] in which a decrease in caloric intake was observed in patients on a low-protein diet. In the present study, patients were seen monthly by an experienced dietician, and particular care was taken with the respect to the

low protein intake and the correct energy intake to maintain nitrogen balance.[12] The recommended energy ration of an ill person is typically approximately double the basal EE. In the present study, energy intake was 27.8 ± 2.7 kcal · kg body $wt^{-1} \cdot d^{-1}$ before the diet, with an estimated EE of 13.4 ± 0.6 cal · kg body $wt^{-1}$; after 3 months on KSVLPD, energy intake was 31 ± 2.9 kcal · kg body $wt^{-1} \cdot d^{-1}$ with an estimated basal EE of 14.1 ± 0.6 cal · kg body $wt^{-1}$, ie, energy intake was 1.4 times the basal EE, and total body weight remained stable. These findings indicate that the caloric intake of the present patients was properly adapted to their energy requirements.

Triceps skinfold and midarm circumference did not change significantly, but DEXA showed an increase in fat mass and a decrease in LTM in the third month of the present study. In a previous study,[17] we monitored body composition by DEXA measurement at the initiation and the sixth and twelfth months of the diet with no more change in body composition after the initial decrease in the third month. Brodsky et al, who studied effects of a low-protein diet (0.6 g protein · kg body $wt^{-1} \cdot d^{-1}$ for 12 weeks) on body composition, observed a decrease in muscle strength and an increase in body fat with no change in total body weight, in agreement with the current study.[14] In addition to the modifications of protein metabolism attributable to KSVLPD (including reductions in amino acid oxidation, proteolysis, and proteinuria), other processes such as catabolism of essential amino acids, stimulation of branched-chain amino acid degradation, activation of the ubiquitin-proteasome proteolytic pathway, and obligatory muscle protein turnover might explain the observed decrease in LTM.[8] Acidosis stimulates overall protein degradation and can cause a decrease in LTM.[8] In the present study, acidosis can be ruled out as the cause for LTM reduction because plasma bicarbonate concentration was in the normal range before the diet and increased on KSVLPD ($P < .02$) because of the low amount of acidic ash furnished by such diets.

We observed a diminution in plasma glucose levels that did not result from an increase in insulin concentration, which was also decreased. Improvement in glucose metabolism of uremic patients after protein restriction has been described previously with physiological insulin levels.[5,6] KSVLPD improves the insulin sensitivity of the liver and peripheral tissues, making peripheral glucose intake more efficient.[5] The mechanisms of this improvement in insulin resistance are not clear. A diminution in levels of uremic toxins and correction of hyperuricemia, metabolic acidosis, secondary hyperparathyroidism, and postreceptor defect have been postulated.[29] However, this beneficial effect of protein restriction is not specific to uremic or diabetic patients. It also occurs in normal subjects.[30,31] Lariviere et al[30] reported that postabsorptive glucose production and serum insulin levels of nondiabetic normal-weight young men on a protein-free diet were reduced by 21% and 22%, respectively. This effect should favorably influence morbidity in uremic patients because hyperinsulinemia is known to be a long-term cardiovascular risk factor.[2]

After 3 months on KSVLPD, glucose oxidation was higher during the first 180 minutes after the oral glucose load. This increase may be attributable to the high carbohydrate content of the diet (67% of energy intake). It has been shown that during high carbohydrate intake, whole-body carbohydrate oxidation is markedly stimulated. Moreover, this diet can reduce fasting lipolysis by increasing fasting hepatic glucose production.[32,33] Although the body's regulatory mechanisms are able to efficiently adapt carbohydrate oxidation to intake, the capacity to regulate short-term fat balance is limited. When lipid intake is increased, lipid oxidation is not modified; it can only increase with augmentation of body fat mass over extended periods.[34] In the present study, carbohydrates represented 67% of the total caloric intake. However, the observed increase in glucose oxidation may also have been a means of compensating for the lower protein calorie intake. Branched-chain amino acids (BCAA) represent an important energy source in skeletal muscle, and KSVLPD protein provides only 1.2 kcal · kg $wt^{-1} \cdot d^{-1}$.[14]

After patients had been on KSVLPD for 3 months, we observed a decrease in protein oxidation before and after the oral glucose load, confirming previous reports of such adaptation of protein metabolism.[24,25]

In the present study, there were significant changes in EE after KSVLPD. Fasting EE was significantly increased after 3 months on KSVLPD ($P < .01$). Increased resting energy production rate has been already reported after KSVLPD in animals[35,36] and in a small group of patients.[7] To our knowledge, the present report provides the first analysis of EE before and after oral glucose loading in patients on KSVLPD (postload EE was increased). This phenomenon has been studied in rats and pigs by different investigators: Miller and Payne studied pigs given an ad libitum low-protein diet and found an increase in heat production.[35] These results were confirmed by Gurr et al in pigs[36] and Rothwell et al in rats[37] but not by Mc Cracken and Mc Allister.[38] Monteon et al studied EE in patients with chronic renal failure and did not observe a difference in EE during sitting or exercise or postprandially in 10 nondialyzed chronically uremic patients, 12 normal individuals, and 16 patients undergoing maintenance hemodialysis.[39] Nevertheless, EE figures after a standard meal were lower in undialyzed patients, and results were not expressed per kilogram of lean body mass as proposed by Ravussin and Zawadki.[21] Dulloo and Jacquet reported recently that weight gain during overfeeding in men was much higher when patients were on a low-protein-diet than when they were on a normal-protein diet.[40]

The mechanism of the KSVLPD-related increase in EE is not clear. Theoretically, the energy cost of glucose storage (assuming that all of the glucose is stored in the form of glycogen) would account for 45% to 63% of the increase in EE,[41] but in our study calculated glucose storage decreased from 29.6 ± 4.2 g before KSVLPD to 20.9 ± 3.4 g after 3 months on KSVLPD and consequently could not have caused the increase in EE. Nevertheless, this assertion must be tempered by the fact that we did not use a double-tracer approach, which is a more accurate means of qualifying glucose storage. The ketoanalog transamination reaction takes far too little energy[42] to explain the increase noted in EE. The thermic effect of food is known to be a factor of 10% in the regulation of normal body weight in humans.[43] Rothwell et al[44] report that brown adipose tissue, which mediates such thermogenesis by sympathetic activation, is increased by a low-protein-diet in rats. These authors studied low-protein-fed animals before and after subcutaneous injection of propanolol, a β-adrenergic blocker. The intercapsular

brown adipose tissue mass measured after death was higher in rats that had been on a low-protein diet. Moreover, evidence of $\beta$-adrenergic involvement in the increase in EE in intravenously infused glucose and insulin paradigms has been reported.[43,45] Acheson et al showed that after $\beta$-adrenergic blockade with propanolol, EE decreases significantly, accompanied by a decrease in the thermic effect of infused glucose and insulin.[45] We did not investigate the sympathetic pathway and brown adipose tissue in the present series.

A decrease in glucose-induced thermogenesis has been described previously in obesity as well as at the onset of obesity and in type 2 diabetes mellitus without obesity.[46,47] This decrease in glucose-induced thermogenesis can be explained by impairment in insulin action (insulin resistance). In the present study, we observed an improvement in insulin sensitivity that could partially account for the increase in thermogenesis and thus for the increase in EE. An increase in the circulating concentration of thyroid hormones results in elevated thermogenesis.[44] Hepatic mitochondrial glycerol phosphate dehydrogenase activity and shuttle activity are very sensitive to triiodothyronine ($T_3$). In the present patients, $T_3$ remained unchanged by KSVLPD (average, 1.6 $\pm$ 0.2 IU/mL before *v* 1.6 $\pm$ 0.2 IU/mL after diet [data not shown]) and cannot explain the increase in EE.

In summary, the present study of 10 patients with advanced CRF shows that KSVLPD can produce increases in energy expenditure in the postabsorptive state and after oral glucose loading. The mechanism of these increases is not clear. Insulin resistance and plasma glucose levels were reduced, and glucose oxidation increased. These findings suggest that intensified dietary counseling of such patients is necessary to ensure satisfactory compliance with the dietary prescription and to maintain appropriate energy intake. Because CRF patients tend to have loss of appetite and may confound a low-protein diet with a hypocaloric diet, repetitive dietary interviews are essential to maintain sufficient caloric intake adapted to the new EE. Although the supplemented diet induces increased EE, this increase should not be considered unfavorable as long as the diet is strictly monitored.

## REFERENCES


1. De Fronzo RA, Alvestrand A, Smith D: Insulin resistance in uremia. J Clin Invest 67:563-568, 1981
2. Ma KW, Greene EI, Raij L: Cardiovascular risk factors in chronic renal failure and hemodialysis patients. Am J Kidney Dis 19:505-513, 1992
3. Zeller KR: Low-protein diets in renal disease. Diabetes Care 14:856-865, 1991
4. Raal FJ, Kalk WJ, Lawson M, et al: Effect of moderate dietary protein restriction on the progression of overt diabetic nephropathy: A 6-mo prospective study. Am J Clin Nutr 60:579-585, 1994
5. Rigalleau V, Blanchetier V, Combe C, et al: A low-protein diet improves insulin sensitivity of endogenous glucose production in predialytic uremic patients. Am J Clin Nutr 65:1512-1516, 1997
6. Gin H, Aparicio M, Potaux L, et al: 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
7. Rigalleau V, Combe C, Blanchetier V, et al: Low protein diet in uremia: effects on glucose metabolism and energy production rate. Kidney Int 51:1222-1227, 1997
8. Mitch WE: Mechanisms causing loss of lean body mass in kidney disease. Am J Clin Nutr 67:359-366, 1998
9. Gretz N, Lassere J, Strauch M: Caloric supplements for patients on low protein diets? Nephron 50:129-132, 1988
10. Combe C, Morel D, De Precigout V, et al: Long term control of hyperparathyroidism in adversal renal failure by low phosphorus low protein diet supplemented in calcium (without changes in plasma calcitriol). Nephron 70:287-295, 1995
11. Kopple JD, Levey AS, Greene T, et al: Effect of dietary protein restriction on nutritional status in the MDRD study. Kidney Int 52:778-791, 1997
12. Kopple JD, Monteon JF, Shaib JK: Effect of energy intake on nitrogen metabolism in nondialysed patients with chronic renal failure. Kidney Int 29:734-742, 1986
13. Castaneda C, Dolnikowski GG, Dallal GE, et al: Protein turnover and energy metabolism of elderly women fed a low-protein diet. Am J Clin Nutr 62:40-48, 1995
14. Brodsky IG, Robbins DC, Hiser E, et al: Effects of low-protein diets on protein metabolism in insulin-dependent diabetes mellitus patients with early nephropathy. J Clin Endocrinol Metab 75:351-357, 1992
15. Frisancho AR: New standards for assessment of nutritional status of adults and the elderly. Am J Clin Nutr 40:808-819, 1984
16. Georgiou E, Virvidakis K, Douskas G, et al: Body composition changes in chronic hemodialysis patients before and after hemodialysis as assessed by dual-energy x-ray absorptiometry. Metabolism 46:1059-1062, 1997
17. Chauveau P, Barthe N, Rigalleau V, et al: Outcome of nutritional status and body composition of uremic patients on a very low protein diet. Am J Kidney Dis 34:500-567, 1999
18. Ferrannini E, Bjorkman O, Reichard GA, et al: The disposal of an oral glucose load in healthy subjects, a quantitative study. Diabetes 34:580-588, 1985
19. Maroni BJ, Steinman TI, Mitch WE: A method for estimating nitrogen intake of patients with chronic renal failure. Kidney Int 27: 58-65, 1985
20. Ferrannini E: The theoretical basis of indirect calorimetry: A review. Metabolism 37:287-301, 1988
21. Ravussin E, Zawadki JK: Thermic effect of glucose in obese subjects with non insulin-dependent diabetes mellitus. Diabetes 36: 1441-1447, 1987
22. Groop LC, Saloranta C, Shank M, et al: The role of free fatty acid metabolism in the pathogenesis of insulin resistance in obesity and non insulin-dependent diabetes mellitus. J Clin Endocrinol Metab 72: 96-107, 1991
23. Zurlo F, Larson K, Bogardus C, et al: Skeletal muscle metabolism is a major determinant of resting energy expenditure. J Clin Invest 88:1423-1427, 1990
24. Motil KJ, Matthews DE, Bier DM, et al: Whole-body leucine and lysine metabolism: Response to dietary protein intake in young men. Am J Physiol 240:E712-E721, 1981
25. Maroni BJ, Staffeld C, Young VR, et al: Mechanisms permitting nephrotic patients to achieve nitrogen equilibrum with a protein-restricted diet. J Clin Invest 99:2479-2487, 1997
26. Choi EJ, Bailey J, May RC, et al: Metabolic responses to nephrosis: Effect of a low-protein diet. Am J Physiol F432-F438, 1994
27. Tom K, Young VR, Chapman T, et al: Long-term adaptive responses to dietary protein restriction in chronic renal failure. Am J Physiol E668-E677, 1995

28. Forget D, Caranhac G, Quillot MJ, et al: Compliance with very low protein diet and ketoanalogues in chronic renal failure. Contrib Nephrol 81:79-86, 1990

29. Alvestrand A: Carbohydrate and insulin metabolism in renal failure. Kidney Int 52:548-552, 1997

30. Lariviere F, Chiasson JL, Schiffrin A, et al: Effects of dietary protein restriction on glucose and insulin metabolism in normal and diabetic humans. Metabolism 43:462-467, 1994

31. Fukagawa NK, Anderson JW, Hageman G, et al: High-carbohydrate, high-fiber diets increase peripheral insulin sensitivity in healthy young and old adults. Am J Clin Nutr 52:524-528, 1990

32. Blaack EE, Saris WHM: Postprandial thermogenesis and substrate utilisation after ingestion of different dietary carbohydrates. Metabolism 45:1235-1242, 1996

33. Schwarz JM, Neese RA, Turner S, et al: Short-term alterations in carbohydrate energy intake in humans. Striking effects on hepatic glucose production, de novo lipogenesis, lipolysis, and whole-body fuel selection. J Clin Invest 96:2735-2743, 1995

34. Acheson KJ, Flatt JP, Jequier E: Glycogen synthesis versus lipogenesis after a 500 gram carbohydrate meal in man. Metabolism 31:1234-1240, 1982

35. Miller DS, Payne PR: Weight maintenance and food intake. J Nutr 78:255-262, 1962

36. Gurr MJ, Mawson R, Rothwell NJ, et al: Effects of manipulating dietary protein and energy intake on energy balance and thermogenesis in the pig. J Nutr 110:532-542, 1980

37. Rothwell NJ, Stock MJ, Tyzbir RS: Energy balance and mitochondrial function in liver and brown fat of rats fed "cafeteria" diets of varying protein content. J Nutr 112:1663-1672, 1982

38. Mc Cracken KJ, Mc Allister A: Energy metabolism and body composition of young pigs given low-protein diets. Br J Nutr 51:225-234, 1984

39. Monteon FJ, Laidlan SA, Shaib JK, et al: Energy expenditure in patients with chronic renal failure. Kidney Int 30:741, 1986

40. Dulloo AC, Jacquet J: Low protein overfeeding: A tool to unmask susceptibility to obesity in humans. Int J Obesity 23:1118-1121, 1999

41. Thiebaud D, Schutz Y, Acheson K, et al: Energy cost of glucose storage in human subjects during glucose-insulin infusions. Am J Physiol 244:E216-E221, 1983

42. May RC, Mitch WE: The metabolism and metabolic effects of ketoacids. Diabetes Metab Rev 71-82, 1989

43. Acheson KJ, Ravussin E, Wahren J, et al: Thermic effect of glucose in man. Obligatory and facultative thermogenesis. J Clin Invest 74:1572-1580, 1984

44. Rothwell NJ, Stock MJ, Tyzbir RS: Mechanisms of thermogenesis induced by low protein diets. Metabolism 32:257-261, 1983

45. Acheson KJ, Jequier E, Wahren J: Influence of $\beta$-adrenergic blockade on glucose-induced thermogenesis in man. J Clin Invest 72:981-986, 1983

46. Laville M, Cornu C, Normand S, et al: Decreased glucose-induced thermogenesis at the onset of obesity. Am J Clin Nutr 57:851-856, 1993

47. Gumginer B, Thorburn AW, Henry RR: Reduced glucose-induced thermogenesis is present in noninsulin-dependent diabetes mellitus without obesity. J Clin Endocrinol Metab 72:801-807, 1991