Nutritional status in patients with diabetes and chronic kidney disease: a prospective study\textsuperscript{1–3}

Christelle Raffaitin, Catherine Lasseur, Philippe Chauveau, Nicole Barthe, Henri Gin, Christian Combe, and Vincent Rigalleau

ABSTRACT

Background: A poor nutritional status reduces the life expectancy of diabetes patients undergoing hemodialysis.

Objective: The study objective was to specify the nutritional outcome in patients with chronic kidney disease (CKD) and well-controlled diabetes.

Design: Forty-five diabetes patients with CKD were enrolled in a cooperative-care program designed to control glucose, blood pressure, LDL cholesterol, and the albumin excretion rate (AER). Their glomerular filtration rate (GFR), body composition, serum albumin (SA), and resting energy expenditure were assessed and compared at baseline and 2 y later.

Results: Thirty-five patients did not start dialysis. Their glycated hemoglobin, blood pressure, LDL cholesterol, and AER improved; their GFR declined slowly (\(-3.3 \text{ mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2} \cdot \text{y}^{-1}\)). Their body mass index (BMI), lean body mass, and SA increased. The GFR decline was correlated negatively with the initial BMI \((r = -0.37, P < 0.05)\) and positively with the initial GFR \((r = 0.34, P < 0.05)\). Ten patients started hemodialysis: except for higher total body water \((P < 0.05)\) and extracellular volume \((P < 0.01)\), their initial nutritional status did not differ significantly from that of 10 patients with comparable baseline severe CKD but without dialysis. At the second evaluation, patients on hemodialysis lost lean body mass, and their SA was lower than that of the patients with severe CKD \((P = 0.05)\); lean body mass was unchanged and SA was higher \((P = 0.01)\) in the patients with severe CKD. No significant difference was detected for resting energy expenditure.

Conclusions: Nutritional status improved in CKD patients with well-controlled diabetes without dialysis, and it deteriorated in patients who started dialysis. A high initial BMI was associated with a slower decline in GFR. Am J Clin Nutr 2007;85:96–101.

KEY WORDS Nutritional status, diabetes mellitus, chronic kidney disease, prospective study, body composition, resting energy expenditure

INTRODUCTION

A poor nutritional status is a well-documented consequence of chronic kidney disease (CKD; 1), even before dialysis became widely available (2). It is now recognized as an important predictor of the prognosis for patients starting dialysis. An alteration in anthropometric parameters is found in 70% and severe malnutrition in 25% of dialysis patients (3). A prospective study showed that the independent factors of mortality in such patients were age, low serum albumin and prealbumin concentrations, and diabetes mellitus (DM; 4).

Diabetes is the most common cause (in some populations) of end-stage renal disease (ESRD). The proportion of patients with both DM and ESRD is increasing, and this increase is described as a real epidemic (5) with an abysmal prognosis (6). Many factors are involved—in particular, poor glycemic control (7). To improve this prognosis and to avoid delayed referral to the nephrologist and the detrimental effects of that delay, cooperative follow-up involving both diabetologists and nephrologists is recommended (8, 9).

A poor nutritional status plays a role in the poor outcome of uremic diabetes patients. The prevalence of malnutrition is noticeably higher in diabetes patients undergoing dialysis than in nondiabetic patients undergoing dialysis (10). Many factors, including higher resting energy expenditure (REE), can contribute to this deterioration in nutritional status (11), insulin deprivation [the anabolic effects of insulin on protein homeostasis appear to be impaired in patients with type 1 DM (12)], increased muscle protein breakdown [as reported in patients with type 2 DM undergoing hemodialysis (13)], and, in some cases, restrictive dietary advice (14). However, malnutrition is not easy to identify with precision because many of these patients are still overweight (10), and that difficulty led to the interest of this prospective study in the body composition of the patients. In particular, it is not known whether nutritional status deteriorates before dialysis even with a cooperative follow-up. It is also not known whether nutritional status is linked to the decline in glomerular filtration rate (GFR).

In the current study, nutritionist-diabetologists and nephrologists followed 45 diabetic patients with CKD who at inclusion had not started dialysis. This 2-y prospective study included the measurement of GFR by \(^{51}\text{Cr}-\text{EDTA}\) clearance, the main variables known to influence the course of diabetes—glycated hemoglobin \((\text{HbA}_{1c})\), blood pressure, LDL cholesterol, albumin...
Diabetes, Kidney Disease, and Nutritional Status

Subjects and Methods

Subjects

Subjects were recruited from the Departments of Nutrition-Diabetology and Nephrology at the Bordeaux University Hospital (Bordeaux, France). Inclusion criteria included type 1 or type 2 DM with a GFR ≤ 60 mL · min⁻¹ · 1.73 m⁻². Patients who were < 18 y old or who were pregnant also were excluded from the study.

Written informed consent was obtained from all the patients. The local ethics committee approved the study protocol.

Study design

This prospective study began in June 2001. It was based on a cooperative follow-up between nutritionists and nephrologists that involved the establishment of a joint medical file for each patient. This cooperative follow-up had nutritional-diabetologic and nephrologic components. The nutritional-diabetologic follow-up included one visit every 4 mo and one short (24-h) hospitalization every 2 y that included a nutritional assessment (as described below). The nephrologic follow-up included one visit every year if 40 < GFR ≤ 60 mL · min⁻¹ · 1.73 m⁻², one visit every 4 mo if 20 < GFR ≤ 40 mL · min⁻¹ · 1.73 m⁻², one visit every 1 or 2 mo if GFR is ≤ 20 mL · min⁻¹ · 1.73 m⁻², and one short (24-h) hospitalization every 2 y that included an isotopic estimation of GFR (as described below).

Thus, after 2-y follow-up, patients not on hemodialysis had had a short hospitalization for the assessment of nutritional status, GFR, and metabolic control. The patients on hemodialysis were admitted to hospital on a nondialysis day for this short stay on average 6.5 mo after the start of their dialysis.

Cooperative follow-up

Care of type 2 DM patients with microalbuminuria was described by Gaede et al (15) in the Steno 2 prospective study. That care includes glycemic control and also control of associated factors such as hypertension and dyslipidemia.

To maintain HbA₁c within the ranges recommended for type 2 DM patients (16)—ie, HbA₁c < 8.0%—and HbA₁c < 7.0% for type 1 DM patients (17)—and, if possible, HbA₁c of 6.5% without severe hypoglycemia, we adopted the following strategy. If HbA₁c was ≥ 8.0% on 2 consecutive occasions, treatment was reinforced; and if HbA₁c was ≤ 6.5%, treatment was reduced; if HbA₁c was > 6.5% but < 8.0%, reinforcement of treatment was determined from a comparison of advantages and disadvantages.

Control of blood pressure and blood lipids and dietary advice

Our objective was to maintain blood pressure at < 130/80 mm Hg in accordance with the recommendations of the American Diabetes Association (18) and the French Agence Nationale d’Accréditation des Etablissements de Santé (19). With respect to blood lipids, in high-risk DM patients, LDL cholesterol should be ≤ 1.3 g/L, according to American Diabetes Association recommendations (20).

For most patients, we prescribed 0.8 g protein · kg⁻¹ · d⁻¹ according to the recommendations of the National Kidney Foundation (21). The exceptions were patients with clinical signs of malnutrition or those aged ≥ 65 y. For these patients, we recommended ≥ 1.0 g protein · kg⁻¹ · d⁻¹.

Biochemical data

Blood samples were drawn after an overnight fast. Serum creatinine, albumin, plasma bicarbonates, and urinary urea were measured on a multiparameter analyzer (Olympus AU 640: Olympus Optical, Tokyo, Japan). HbA₁c was measured by using HPLC. C-reactive protein (CRP) was measured by using the Olympus analyzer. AER was measured on an immunonephelometric analyzer (Nephelometer 2; Dade Behring, Marburg, Germany) by using an appropriate kit (Nanisme VO human albumin, Dade Behring). The formula proposed by Masud et al (22) and validated by Masud et al (23) was used to estimate protein intake on the basis of the measurement of urinary urea (24).

GFR

Clearance of the radionuclide marker was measured after intravenous injection of ⁵¹Cr-EDTA (Cis Industries, Gif/Yvette, France). All patients were studied in the morning (0900), after a light breakfast. After a single 100-μCi (3.7 MBq) bolus of ⁵¹Cr-EDTA, 4 venous blood samples were drawn at 75, 105, 135 and 165 min, and urinary samples were collected at 90, 120, 150 and 180 min, as previously described (25). ⁵¹Cr-EDTA radioactivity was measured in a gamma counter (COBRA 2, model 05003; Packard Instruments, Meriden, CT). The results were indexed to the body surface area of the subjects, calculated from the formula of DuBois and DuBois (26).

Body composition

Body weight and height were measured in the morning by the same observer. Body mass index (BMI; in kg/m²) was calculated. Body composition was analyzed by using 2 different methods. First, biphotonic absorptiometry (DXA) was used (27). A whole-body scan was performed by using a fan-beam densitometer (model QDR-4500A-DXA and software version 8.19; Hologic Inc, Waltham, MA). The scan time was 3 min, and the radiation dose was ≈ 2 μSv per scan. Total analyses were performed by using the manufacturer’s standard protocol. All the DXA scans were completed with the use of the same device and software and on the same day as the GFR measurements. Second, bioelectrical impedance analysis (BIA) with a Thomasset and Boulier apparatus (L’Impulsion, Hérouville, France) was used (28). Subcutaneous stainless steel needles were placed on the opposite hand and foot to define total body water and extracellular volume.

Resting energy expenditure measurement

REE was measured by using indirect calorimetry. Respiratory exchanges were monitored during 45-min sessions in all subjects, who were at rest in the postabsorptive state at 0800 before...
breakfast after an overnight fast, by using a Deltatrac monitor (Datex, Paris, France) that was calibrated with the use of a reference gas before each session. The usual diet, physical activity, and medications of the patients were not modified before or during the study. REE was derived from respiratory exchange measurements with conventional equations (29).

STATISTICAL ANALYSIS

Data are expressed as means ± SDs. Pearson’s correlation analysis was used to determine relations between the different variables and the decline in GFR. Measurements at the first (inclusion) and second evaluations within each group were compared by using two-tailed paired Student t tests. Linear regressions were used for between-group comparisons by comparing differences between the first and second evaluations after adjustment for initial value. Chi-square tests were used to compare the noncontinuous variables. Significance was fixed at \( P < 0.05 \). The statistical analyses were performed by using SPSS software (version 10.0; SPSS Inc, Chicago, IL).

RESULT

Subjects

The 45 subjects were 65 ± 11 y old; most of them had type 2 DM (71.1%) and were men (66.7%). The mean duration of DM was 23.6 ± 11.6 y (33.8 ± 13.6 y in type 1 DM and 19.5 ± 7.7 y in type 2 DM). Eighty percent of the patients required insulin either alone or with oral antihyperglycemic agents (13.3%), 17.8% were treated with oral antihyperglycemic agents alone, and 1 patient was maintained with diet alone (2.2%). Their mean GFR was 35.9 ± 21.4 mL · min\(^{-1} \cdot 1.73 \text{m}^2\), and their serum creatinine was 92 ± 81 μmol/L.

Outcome of subjects not undergoing hemodialysis

Thirty-five subjects (23 men; \( \bar{x} \) age: 66.5 ± 10.8 y; 67.0% type 2 DM) did not require hemodialysis during the follow-up. The comparison between the first evaluation at inclusion and the second evaluation 2 y later is shown in Table 1. The GFR declined by \(-6.5 ± 16.7 \text{mL} · \text{min}^{-1} · 1.73 \text{m}^2\), which is a rate of \(-3.3 \text{mL} · \text{min}^{-1} · 1.73 \text{m}^2\) per year. The \( \mathrm{HbA}_{1c} \), blood pressure, LDL cholesterol, and AER improved during the follow-up period. They gained weight, BMI, and lean body mass to a significant extent.

Serum albumin and REE increased, but REE normalized to lean body mass was stable. CRP improved significantly during follow-up. Plasma bicarbonate did not deteriorate. The protein intake estimated from urinary urea remained \( \approx 0.8 \text{g} · \text{kg}^{-1} · \text{d}^{-1} \). The loss of GFR was not significantly correlated with blood pressure or the concentrations of \( \mathrm{HbA}_{1c} \), LDL cholesterol, and AER, but it was correlated with the initial GFR (\( r = 0.37, P = 0.031 \)).

Outcome of patients who started hemodialysis

Ten patients had to start hemodialysis 15 ± 7 mo after inclusion in the study. The comparison between their first and second evaluations—the latter occurred 6 ± 3 mo after they began dialysis—is shown in Table 2. We also compared their results with those of 10 patients with SCKD at inclusion (initial GFR ≤ 30 mL · min\(^{-1} · 1.73 \text{m}^2\)) who did not start hemodialysis during the course of the study, despite a follow-up comparable with that of patients who did start hemodialysis.

At inclusion (\( t_0 \)), no differences were seen in sex (hemodialysis: 6 men; SCKD without hemodialysis: 5 men), age (hemodialysis: 59.1 ± 3.9 y; SCKD without hemodialysis: 65.6 ± 9.6 y), type of DM (80.0% type 2 in both groups), or GFR. The groups
also did not differ significantly in weight, LBMI, serum albumin, and REE, but patients on hemodialysis were more hydrated than those not on hemodialysis, as shown by higher extracellular volume and total body water.

At the second evaluation (ie, after beginning dialysis), the patients on hemodialysis had lost weight because of a significant loss of LBMI (4.2 ± 5.7 kg; \( P = 0.046 \) compared with \( t_0 \) 0.008 compared with SCKD patients not on hemodialysis), and their serum albumin concentrations became significantly lower than those of SCKD patients not on hemodialysis. In contrast, in the SCKD patients not on hemodialysis, weight and LBMI were unchanged, and serum albumin improved significantly (\( P = 0.010 \) compared with \( t_0 \)). CRP tended to increase in the hemodialysis patients and to decrease in those without hemodialysis (\( P = 0.064 \) between groups).

**DISCUSSION**

Our subjects were patients who were enrolled in a structured cooperative-care program: their HbA1c, blood pressure, LDL cholesterol, and AER improved during the follow-up. These variables are predictive of GFR decline in DM, and GFR fell by 3.3 mL·min\(^{-1}\)·1.73 m\(^{-2}\) per year compared with a decrease of 4 mL·min\(^{-1}\)·1.73 m\(^{-2}\) per year in the Steno prospective study (30). Our main objective was to describe the evolution of the nutritional status of diabetic uremic patients in such controlled conditions. The nutritional status of the patients not on dialysis did not deteriorate. In contrast, their BMI, weight, LBMI, and serum albumin increased. These increases could be considered a benefit, despite the fact that they occurred in patients who mostly had type 2 DM and were slightly overweight: the greater weight was not associated with any deterioration in control of blood glucose, blood pressure, or cholesterol. The higher albumin concentration was notable because it suggested that the gain in lean body mass was not due to increased hydration, as confirmed by the BIA results. A low albumin concentration is associated with a poor prognosis for patients starting dialysis (4). The relation between BMI and GFR decline in our patients also supported the possibility of a benefit.

Several mechanisms may have contributed to this good nutritional outcome. The reduction in AER (\( \approx 300 \) mg/d), if cumulated over 2 y, represents the retention of 220 g protein and may account for a gain of \( \approx 1 \) kg in lean body mass. The reduction in HbA1c (0.7%) that results from the optimized insulin therapy of most of the patients is associated with a mean weight gain of 2 kg per 1% loss of HbA1c (31), which may involve both fat and fat-free mass (32, 33). REE is increased in diabetes (34), especially when glucose control is poor (35), whereas low REE has been reported in chronic renal insufficiency (36). Because the diabetic uremic patients were submitted to the combined influences of diabetes and uremia on REE (37), the better glucose control and declining renal function during the follow-up could have contributed to the weight gain by reducing REE. The preservation of REE when referred to lean body mass showed that this was not the case. Our cautious dietary advice was 0.8 g protein · kg\(^{-1} \)·d\(^{-1}\) except for undernourished or older patients (\( \geq 65 \) y): such advice did not represent “protein restriction,” whose indication is a matter of debate with benefits in type 1 (38) but not in type 2 (39) DM. We are not suggesting, however, that a more restrictive diet would have precluded the favorable nutritional outcome of our patients, because protein restriction is compatible with the preservation of nutritional status before (40) or after (41) a patient begins dialysis. Moreover, protein

### TABLE 2
An anthropometric and biochemical characteristics during follow-up of patients with severe chronic kidney disease (SCKD) who did or did not start hemodialysis

<table>
<thead>
<tr>
<th></th>
<th>At inclusion</th>
<th>Second evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hemodialysis</td>
<td>SCKD†</td>
</tr>
<tr>
<td></td>
<td>((n = 10))</td>
<td>((n = 10))</td>
</tr>
<tr>
<td>Glomerular filtration rate</td>
<td>16.2 ± 5.3(^{\dagger})</td>
<td>19.7 ± 6.2</td>
</tr>
<tr>
<td>(mL·min(^{-1})·1.73 m(^{-2}))</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>73.9 ± 16.8</td>
<td>73.7 ± 12.4</td>
</tr>
<tr>
<td>Serum albumin (g/L)</td>
<td>49.9 ± 10.4</td>
<td>51.2 ± 11.0</td>
</tr>
<tr>
<td>Extracellular volume (L)</td>
<td>18.6 ± 4.1</td>
<td>13.4 ± 3.0</td>
</tr>
<tr>
<td>Total body water (L)</td>
<td>36.0 ± 7.2</td>
<td>27.0 ± 6.3</td>
</tr>
<tr>
<td>Resting energy expenditure (kcal/d)</td>
<td>1577 ± 264</td>
<td>1416 ± 200</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>7.2 ± 0.6</td>
<td>8.2 ± 1.2</td>
</tr>
<tr>
<td>Blood pressure (mm Hg)</td>
<td>151/83</td>
<td>141/81</td>
</tr>
<tr>
<td>LDL cholesterol (g/L)</td>
<td>1.2 ± 0.6</td>
<td>1.3 ± 0.4</td>
</tr>
<tr>
<td>Albumin excretion rate (mg/d)</td>
<td>2068 ± 1357</td>
<td>953 ± 992</td>
</tr>
<tr>
<td>C-reactive protein (mg/L)</td>
<td>9.0 ± 9.7</td>
<td>9.2 ± 11.4</td>
</tr>
<tr>
<td>Plasma bicarbonate (mmol/L)</td>
<td>23.2 ± 1.6</td>
<td>23.4 ± 6.1</td>
</tr>
<tr>
<td>Urinary urea (mmol/d)</td>
<td>230 ± 100</td>
<td>321 ± 93</td>
</tr>
<tr>
<td>Protein intake (g·kg(^{-1} )·d(^{-1}))</td>
<td>0.65 ± 0.3</td>
<td>0.87 ± 0.2</td>
</tr>
</tbody>
</table>

\(\dagger\) HbA1c = glycated hemoglobin.

† These 10 SCKD patients had the lowest baseline glomerular filtration rates of the 35 SCKD patients who did not start hemodialysis.

\(^4\) Means between groups were compared by using linear regressions comparing changes between inclusion and second evaluation after adjustment for inclusion value.

\(\bar{x} \pm SD\) (all such values).
restriction has been shown to improve insulin response (42). The reduction in CRP may have played a role: in patients with CKD, inflammation contributes to hypoalbuminemia and enhanced catabolic state (1).

Our second objective was to determine whether the initiation of hemodialysis had an influence on nutritional status by comparing the 10 patients who required dialysis during the follow-up with the 10 (of 35) patients not on dialysis who had a similar GFR (≤ 30 mL·min⁻¹·1.73m⁻²) at inclusion. Initial anthropometric and nutritional variables were similar in the 2 groups, but BIA showed that the patients on hemodialysis were more hydrated than were those not on hemodialysis. Although the interval before a patient started hemodialysis could not be controlled, the second evaluation was performed after a similar interval in both groups: 15.5 ± 6.5 mo for hemodialysis patients and 24 mo for SCKD patients not on hemodialysis. Hemodialysis patients lost weight because of a significant loss of LBM, whereas the nutritional status of the patients not on hemodialysis was unchanged. As expected, hemodialysis corrected the hyperhydration of the hemodialysis patients. On the other hand, their serum albumin fell below that of the patients not on hemodialysis: loss of LBM could not therefore be accounted for by the correction of hyperhydration by hemodialysis. This was not due to a worse glycemic control: hemodialysis patients had better Hba₁c concentrations at inclusion than did patients not on dialysis. Metabolic acidosis can contribute to the poor nutritional status of patients on dialysis (43), but plasma bicarbonates did not differ between the hemodialysis and no-hemodialysis groups. A higher REE may contribute to the deterioration in nutritional status of the diabetes patients undergoing dialysis in comparison with that of the patients without diabetes (44). REE was not higher at inclusion in the hemodialysis patients in the current study compared with the patients not on hemodialysis, and, at the second evaluation, REE in the former group tended to decrease; the impairment in nutritional status could not thus be attributed to a higher REE. However, hemodialysis is known to stimulate muscle and whole-body protein loss (45), and, in patients with type 2 DM, hemodialysis was recently reported to increase muscle protein breakdown (13). Hemodialysis probably had a negative effect on the nutritional status of our patients. Because we did not evaluate nutritional status immediately before the dialysis, our results do not rule out the possibility that the intrinsic disease course may have led to both the requirement for dialysis and the malnutrition in some patients. In nondiabetic patients, initiation of dialysis is not associated with a decline of nutritional variables; however, the detrimental influence of hemodialysis in diabetic patients is supported by the recent finding of Pupim et al (46) that, during the first year of dialysis, diabetic patients experience a faster loss of LBM than do nondiabetic patients. CRP tended to increase in hemodialysis patients but not in those without hemodialysis. The dialysis technique per se is associated with worsening of inflammatory status and with loss of nutrients (47).

In the patients in the current study, the decline in GFR was negatively correlated with the initial BMI. This finding contrasts with recent reports that a high (48) or previous maximal (49) BMI is a strong risk factor for ESRD and with reports that BMI is increasing in the incident ESRD population (50). These findings are not directly comparable to those of the current study, because GFR was predicted and not measured directly in those large epidemiologic studies. Because nutritional status biases the prediction of GFR according to the formula of Cockcroft and Gault (51) and the Modification of Diet in Renal Disease (MDRD) equation (52), we chose to measure GFR directly by a reference isotopic method. The fact that a high BMI favors the incidence of CKD does not mean that BMI itself is a progression factor: for the renally insufficient subjects of the Swedish prospective study, the risk of starting renal replacement therapy was reduced with increasing BMI (53). This may be of importance for diabetic patients: BMI did not further predict ESRD after adjustment for the presence of diabetes in a study from Okinawa (49). The large (n = 320 252) study of Hsu et al (48) could not assess the deleterious influence of BMI on glucose, lipids, blood pressure, and AER, all of which were well-controlled in our patients. Prospective studies have shown that a high BMI is related to lower incidences of microalbuminuria (54) and renal replacement therapy in type 1 DM patients (55) and of renal function decline (56) and renal replacement therapy in type 2 DM patients (57). BMI may therefore be a risk factor for developing CKD and thereafter become a protective factor. The faster decline in GFR that we found in subjects with higher initial BMI has also been reported by others (58, 59).

In summary, the nutritional status of diabetic patients affected by CKD does not deteriorate —and even improves—before the onset of hemodialysis, when their glucose concentrations, blood pressure, cholesterol and AER are controlled according to recommendations. In contrast, deterioration is detectable in patients who must start hemodialysis.

We thank all 45 patients for their valuable contribution to the study. We also thank all the nurses and technicians involved for their assistance. We thank Simon Jarman for revision of the English manuscript and Luc Letenneur for help with the statistical analysis.

CR, CL, HG, CC, and VR were responsible for the design of the experiment; all authors participated in the collection of data; CR, PC, CC, and VR were responsible for the analysis of data; CR, PC, HG, CC, and VR were responsible for writing the manuscript. None of the authors had a personal or financial conflict of interest.

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