Cross-sectional assessment of nutritional and immune status in renal patients undergoing continuous ambulatory peritoneal dialysis 1-3

Leocadia Palop and J Alfredo Martínez

ABSTRACT Malnutrition prevalence and immunocompetence were assessed in uremic patients undergoing continuous ambulatory peritoneal dialysis (CAPD). Forty-two males and twenty-four females with kidney disease undergoing CAPD were distributed into three groups according to the length of time they had been undergoing dialysis. Group 0 included patients beginning dialysis; group 1, patients undergoing CAPD for < 30 mo; and group 2, patients undergoing CAPD for > 30 mo. Body weight and body mass index were greater in patients who had been undergoing CAPD for longer periods of time (≈11% in males and 14% in females), which was accompanied by higher fat stores and muscle mass when assessed through triceps skinfold thickness and arm muscle measurements. These differences were more apparent in females than in males. Immunoglobulin M values were lower in patients in groups 1 and 2 than in group 0, whereas retinol binding protein, fibronectin, and C4 were higher. Estimated protein intake was higher in predialysis patients (1.31 g·d⁻¹·kg⁻¹) than in the other groups (≈0.95 g·d⁻¹·kg⁻¹). The percentage of B cells decreased with time on dialysis. Although no changes in total or helper T cells were found, a significant rise was noted for the T cell subpopulation with assumed suppressor and cytotoxic activities and for natural killer cells in those patients undergoing longer periods of CAPD treatment. Alterations in immune cell numbers in immunoglobulins and complement proteins might be responsible for immunologic disturbances and infectious processes occurring in patients with chronic renal failure and undergoing CAPD. Am J Clin Nutr 1997;66:4985-503S.

KEY WORDS CAPD, continuous ambulatory peritoneal dialysis, chronic renal failure, immunity, nutrition, nutritional status, peritoneal dialysis, uremia, complement, T cell

INTRODUCTION The mutual interactions among nutrition, immune function, and the pathologic condition are multidirectional (1). Thus, first, nutritional intake and status influence host immunocompetence and the body’s response to illness or infection (2-4); second, immune impairments bring about detrimental effects on nutrient utilization and affect the outcome of disease and infectious challenges (5, 6); and third, some pathogenic microorganisms or sicknesses may induce malnutrition and immunodeficiency (7-9). Hence, anthropometric, biochemical, and immunologic determinations have been studied in different groups of patients and have been correlated with dietary intakes and clinical examinations (10-13).

The interactions between nutrition and morbidity in patients with renal failure are well documented; these patients frequently suffer from wasting and malnutrition (3, 14-17). Thus, when renal failure appears, uremia as well as several nutritional problems related to the kidney’s inability to excrete waste products, conserve nutrients, regulate fluid and electrolyte balance, produce hormones, and perform other metabolic functions may develop (18). The cause of malnutrition in maintenance dialysis patients has been attributed to unbalanced nutrient intake, infections or underlying illnesses, metabolic and endocrine disorders accompanying uremia, blood and nutrient losses into dialysate, and the impairment of renal metabolism (3, 14).

The treatment of chronic renal failure may require dialysis therapy to remove undesirable substances by diffusion, which may involve the semipermeable membrane of the artificial kidney (hemodialysis) or the patient’s peritoneum (peritoneal dialysis). Continuous ambulatory peritoneal dialysis (CAPD) is a type of dialysis (19) in which the dialysate is left in the peritoneum and exchanged manually four to five times daily with increased selective applications in cardiac and diabetic patients (20). The present investigation, an 8-y cross-sectional study, was performed to further define the disturbances in anthropometric and biochemical status in different cohorts of CAPD maintenance patients and also to characterize the long-term evolution of immune function in a population with chronic renal failure, in which nutrition, dialysis adequacy, and infection (peritonitis) are involved in the risk of morbidity and mortality.

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SUBJECTS AND METHODS

Subjects

The survey was conducted in the nephrology unit of a tertiary care hospital (Nuestra Señora del Pino, Las Palmas, Spain). Sixty-six patients with chronic renal failure undergoing CAPD, and who gave their informed consent according to national regulations, participated in the study.

The forty-two males and twenty-four females (mean age: 52.9 ± 12.6 y) were distributed into three groups according to the length of time they had been undergoing dialysis. Thus, group 0 (n = 16) included predialysis uremic patients; group 1 (n = 26), patients undergoing CAPD for < 30 mo (x: 16.3 ± 7.4 mo; range: 7–30 mo); and group 2 (n = 24), patients undergoing CAPD for > 30 mo (x: 51.0 ± 19.7 mo; range: 31–94 mo).

The cause of renal disease before the start of the dialysis procedure was glomerulonephritis (9.1%), polycystic kidney (7.6%), diabetes (39.4%), tubular and interstitial disorders (12.1%), or other unidentified processes (31.8%). Exclusion criteria were age < 18 y or > 75 y, malignant disease, unsuccessful hemodialysis, intestinal disease, or terminal heart disease. Patients were also excluded if they had contracted peritonitis within the past 2 mo. Four dialysis exchanges were performed daily with commercial dextrose solutions with a volume of 1500 mL (n = 54) and 2000 mL (n = 12) according to needs and peritoneal capacity (21). Diabetic patients were administered insulin to maintain glycemia within physiologic levels.

Methods

Height was measured to the nearest 5 mm with a wall-mounted anthropometer and weight was measured to the nearest 0.1 kg with a calibrated beam balance. The heights and weights of the patients were measured while the patients were dressed in indoor clothes and no shoes. Body mass index (Quetelet index) was calculated as weight (in kg) divided by the square of the height (in m). Triceps skinfold thickness was assessed twice with a caliper (Holtaan Ltd, Crymch, United Kingdom) over the left triceps muscle, midway between the acromion and olecran processes and the mean value was recorded. Midarm muscle circumference was derived from triceps skinfold thickness and midarm circumference, which was obtained by encircling the upper arm at the midpoint mark with flexible, nonstretchable tape (22). Anthropometric measurements were compared with adequate geographic norms of reference (23).

Blood samples were collected to quantify serum total protein, albumin, prealbumin, retinol binding protein, and plasma fibronectin, which were measured with a conventional autoanalyzer and nephelometric methods (10, 24). Immunoglobulins and complement factors were determined by radial immunodiffusion (25).

Protein catabolic rate was calculated from four direct measurements (urea and protein in dialysate and urine) and two estimates (amino acids in dialysate and losses of nonurea nitrogen) according to an accepted formula for CAPD patients (26), which has been correlated with daily protein intake (27) and was also normalized per kilogram of body weight as described previously (21). The glucose absorbed per day was obtained once the peritoneal pattern was established (28). Plasma amino acids were quantitatively assessed by HPLC through a standardized protocol (29).

Lymphocytes were counted by routine automated analytic procedures (Coulter STKR, Hialeah, FL). Percentages of lymphocyte subsets were determined by flow cytometry with use of the following commercially available monoclonal antibodies (Coulter Scientific and Becton Dickinson, Orangeburg, NY) as follows: antibody to CD3 (pan T cells), antibody to CD4 (helper T cells), antibody to CD8 (cytotoxic-suppressor T cells), antibody to CD19 (B cells), and antibody to CD57 (natural killer cells). Fluorescence from fluorescein isothiocyanate-labeled immunoglobulins was analyzed with a fluorescence-activated cell sorter (EPICS profile II; Coulter Electronics Inc). Forward and perpendicular light-scatter signals were gated by using appropriate software (25). Data were analyzed with statistical comparisons widely used in nutritional research: analysis of variance and the Dunnett t test.

RESULTS

Body weight and body mass index were greater in patients of both sexes who had been undergoing CAPD for longer periods of time (≈11% greater in males and 14% in females). This was accompanied by higher fat stores and muscle mass when assessed through triceps skinfold thickness and muscle arm measurements, these compositional changes being more apparent in female than in male patients (Table 1).

The estimated protein intake obtained from calculations of protein catabolic rate was higher in predialysis patients

| TABLE 1 | Cross-sectional anthropometric measurements in male and female chronic renal failure patients receiving continuous ambulatory peritoneal dialysis1 |
|---------------------------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|
| Variables | Male patients | | | Female patients | | | | |
| | Group 0: admission | Group 1: 7–30 mo | Group 2: 31–94 mo | Group 0: admission | Group 1: 7–30 mo | Group 2: 31–94 mo |
| Weight (kg) | 65.9 ± 77 | 74.5 ± 11.2 | 75.5 ± 15.6 | 54.0 ± 4.3 | 62.5 ± 14.3 | 71.5 ± 15.0 |
| BMI (kg/m²) | 22.6 ± 1.9 | 25.5 ± 3.6 | 25.7 ± 3.6 | 21.9 ± 2.4 | 25.1 ± 4.8 | 28.1 ± 5.1 |
| TSF (mm) | 9.5 ± 3.5 | 11.3 ± 3.8 | 11.3 ± 6.4 | 16.1 ± 8.7 | 16.2 ± 7.9 | 23.7 ± 7.3 |
| MAMC (cm) | 24.1 ± 2.9 | 27.1 ± 3.4 | 26.3 ± 3.1 | 20.9 ± 2.4 | 23.3 ± 3.3 | 25.0 ± 2.5 |

1 ± SD. TSF, triceps skinfold thickness; MAMC, midarm muscle circumference.
2 Significantly different from admission patients. P < 0.05.
TABLE 2
Cross-sectional determinations of amino acid, urea, and glucose utilization in chronic renal failure patients receiving continuous ambulatory peritoneal dialysis

<table>
<thead>
<tr>
<th>Variables</th>
<th>Stages</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group 0:</td>
</tr>
<tr>
<td></td>
<td>(n = 16)</td>
</tr>
<tr>
<td>E:NE</td>
<td>0.64 ± 0.10</td>
</tr>
<tr>
<td>Blood urea (g/L)</td>
<td>1.67 ± 0.46</td>
</tr>
<tr>
<td>PCR (g/d)</td>
<td>78.6 ± 17.5</td>
</tr>
<tr>
<td>NPCR (g · d⁻¹ · kg⁻¹)</td>
<td>1.31 ± 0.3</td>
</tr>
<tr>
<td>GU (g/d)</td>
<td>18.2 ± 4.8</td>
</tr>
<tr>
<td>GAD (g/d)</td>
<td>68.6 ± 20.7</td>
</tr>
</tbody>
</table>

1 (± SD). E:NE, ratio of essential to nonessential amino acids; PCR, protein catabolic rate; NPCR, normalized protein catabolic rate; GU, generation of urea; GAD, glucose absorption per day.
2 Out of the laboratory reference interval.
3 Significantly different from admission patients. P < 0.05.

(1.31 g · d⁻¹ · kg⁻¹) and was reduced (to ∼0.95 g · d⁻¹ · kg⁻¹) in groups 1 and 2. Also, the ratio of essential to nonessential amino acids decreased with time, whereas glucose absorption from the dialysate and blood urea remained stable during the studied periods (Table 2).

Total protein and albumin were similar in all groups but out of the laboratory reference interval, whereas retinol binding protein and fibronectin were higher as a consequence of the stay in dialysis (Table 3). Immunoglobulin M values were lower in male (1.0 ± 0.5 g/L) than in female (1.4 ± 0.6 g/L) patients, whose values were near normal (Table 4).

Additional information concerning immune status was obtained by measuring different lymphocyte subsets (Table 5). The percentage of CD19 cells decreased with time on dialysis. On the other hand, although no significant changes in CD3 or CD4 cell phenotypes or in the ratio of CD4 to CD8 cells was found, significantly higher percentages of CD8 cells, a T cell subpopulation with assumed suppressor and cytotoxic activities, and CD57 cells were found in group 2 compared with group 0.

DISCUSSION

Peritoneal dialysis in patients with chronic renal failure is associated with metabolic and nutritional abnormalities due to the combined effects of uremia, underdialysis, glucose absorption from the dialysate, protein and amino acid losses, poor appetite, and recurrent episodes of peritonitis (30). Thus, malnutrition is present 20–40% of the time in different populations of uremic patients receiving CAPD when assessed by using anthropometric and biochemical approaches (14–31). Variables that have been correlated with the degree of malnutrition in dialyzed patients include body mass index, midarm muscle circumference as an index of muscle mass, triceps skinfold thickness as marker of subcutaneous fat, and also serum albumin and other plasma proteins such as retinol binding protein, immunoglobulins, and complement (14–17, 32).

In both male and female subjects with chronic renal failure, weight gains were greater in those who had been receiving CAPD for longer lengths of time. This was significant for the female group with a longer duration of CAPD. Body weight gains could be ascribed in part to the absorption of glucose from the dialysate, which may represent ∼20% of basal energy needs (3).

Because norms for healthy subjects are apparently adequate for individual dialysis patients (33), the reference norms used to compare anthropometric measurements were selected from a geographically suitable population. This comparison indicated that ∼20% of the patients under study were at least moderately malnourished (23). Body composition changes accompanying the CAPD treatment were influenced not only by time on dialysis, but also by sex. Female subjects with renal insufficiency had more evident increases in muscle mass and fat stores as a consequence of the dialytic therapy than did male patients. Previously, sex differences were found for anthropometric measurements in patients on hemodialysis (16): muscle and fat stores were depleted distinctively in male and female patients.

In stable renal cases, the protein catabolic rate (g/d) can be estimated from data of nitrogen losses by using appropriate equations for CAPD (26). Furthermore, the normalized protein catabolic rate by body weight (g · d⁻¹ · kg⁻¹) has been proposed as a useful measure of protein intake, although this value has not consistently predicted nutritional outcome in patients with kidney disease (31). Estimated protein intake (ranging between 1.31 and 0.95 g · d⁻¹ · kg⁻¹) was reduced with time in both male and female chronic renal failure patients, to a value similar to those reported by others (21). The urea generation rate, obtained from data of urinary and dialysate urea losses (34), decreased with length of treatment and was higher in

TABLE 3
Cross-sectional plasma variables in chronic renal failure patients receiving continuous ambulatory peritoneal dialysis

<table>
<thead>
<tr>
<th>Variables</th>
<th>Reference interval</th>
<th>Stages</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group 0:</td>
<td>Group 1:</td>
</tr>
<tr>
<td></td>
<td>(n = 16)</td>
<td>7–30 mo</td>
</tr>
<tr>
<td>Total protein (g/L)</td>
<td>65–85</td>
<td>63.0 ± 7.0²</td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>35–55</td>
<td>34.1 ± 4.5²</td>
</tr>
<tr>
<td>Prealbumin (g/L)</td>
<td>0.25–0.35</td>
<td>0.44 ± 0.10²</td>
</tr>
<tr>
<td>Retinol binding protein (mg/L)</td>
<td>30–60</td>
<td>134 ± 35²</td>
</tr>
<tr>
<td>Fibronectin (mg/L)</td>
<td>250–400</td>
<td>371 ± 130</td>
</tr>
</tbody>
</table>

1 ± SD.
2 Out of the laboratory reference interval.
males than in females, although no changes in blood urea nitrogen associated with duration of CAPD were found.

Serum protein concentrations are often difficult to interpret in renal failure patients because shifts in intravascular volume status affect their measurement (35). However, the assessment of visceral protein through measurement of total plasma protein and albumin revealed that mean values were not within the reference intervals, suggesting some prevalence of malnutrition (10). Hypoalbuminemia has been suggested as a risk factor for peritonitis in CAPD, attributable to insufficient dialysis and protein intake (36). Other indicators of protein metabolism such as prealbumin and retinol binding protein, which are commonly measured to evaluate malnutrition, have been shown to be affected in chronic renal failure patients undergoing CAPD as well as in subjects with uremia (35). Thus, prealbumin and retinol binding protein were markedly elevated in our patients. On the other hand, fibronectin, considered to be an acute indicator of starvation and repletion, also increased in the CAPD patients with time (37).

Hypogammaglobulinemia (38) and reduced serum immunoglobulin titers after vaccination (39) have been found in peritoneally dialyzed subjects, accompanying the complement activation associated with uremia (40). However, our determinations showed that immunoglobulin G and immunoglobulin A as well as C3 remained stable during the study whereas C4 was significantly increased after an average of 16 mo on dialysis, which could be associated with the molecular weight of this protein (41). The ratio of essential to nonessential amino acids was also reduced with longer CAPD treatment as described in situations of malnutrition that were ascribed mainly to metabolic and nutritional alterations rather than to amino acid losses in the dialysate (3, 30, 42).

Furthermore, nutritional status and dietary intake have been shown to predict clinical outcome and peritonitis incidence in CAPD patients (19). Thus, peritoneal dialysis provides glucose in the dialysate solution, which may result in an imbalance in the distribution of energy intake (3). Protein supplementation, zinc and vitamin B-6 intakes, and the protein catabolic rate have been associated with nutritional status in uremic patients (21, 43, 44).

Some studies have described controversial alterations in leukocyte and B cell functions, immunoglobulin and lymphokine production, complement activity, T cell activation, and the ratio of CD4 to CD8 cells in CAPD uremic patients (40, 45–48). Other reports showed no marked changes in immuno-phenotypes of peripheral B and T lymphocytes over time (49, 50). The role of peritoneal lymphocytes in host immunity for CAPD patients is just beginning to be understood, although some signs of activation with time have been shown (50), particularly during peritonitis episodes (51).

The distribution of patients into three groups according to duration of CAPD showed that lymphopenia is present in patients receiving CAPD, accompanied by a reduction in the numbers of suppressor-cytotoxic (CD8) and B (CD19) cells with length of time on CAPD, with no apparent changes in the helper T (CD4) subtype.

### TABLE 4

Cross-sectional humoral and innate immunity in chronic renal failure patients receiving continuous ambulatory peritoneal dialysis

<table>
<thead>
<tr>
<th>Variables</th>
<th>Reference interval</th>
<th>Group 0: admission (n = 16)</th>
<th>Group 1: 7–30 mo (n = 26)</th>
<th>Group 2: 31–94 mo (n = 24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C3 (mg/L)</td>
<td>550–1200</td>
<td>646 ± 170^1</td>
<td>692 ± 160</td>
<td>676 ± 159</td>
</tr>
<tr>
<td>C4 (mg/L)</td>
<td>200–500</td>
<td>328 ± 108</td>
<td>376 ± 132</td>
<td>391 ± 95</td>
</tr>
<tr>
<td>Immunoglobulin G (g/L)</td>
<td>8–18</td>
<td>10.8 ± 2.5</td>
<td>12.3 ± 4.8</td>
<td>11.8 ± 2.6</td>
</tr>
<tr>
<td>Immunoglobulin A (g/L)</td>
<td>0.9–4.5</td>
<td>2.6 ± 1.2</td>
<td>2.5 ± 1.2</td>
<td>2.7 ± 1.6</td>
</tr>
<tr>
<td>Immunoglobulin M (g/L)</td>
<td>0.6–2.5</td>
<td>1.4 ± 0.7</td>
<td>1.2 ± 0.7</td>
<td>0.9 ± 0.6</td>
</tr>
</tbody>
</table>

^1 ± SD.

^2 Significantly different from admission patients, P < 0.05.

^3 Out of the laboratory reference interval.

### TABLE 5

Cross-sectional determinations of immune cell subpopulations in chronic renal failure patients receiving continuous ambulatory peritoneal dialysis

<table>
<thead>
<tr>
<th>Variables</th>
<th>Reference interval</th>
<th>Group 0: admission (n = 16)</th>
<th>Group 1: 7–30 mo (n = 26)</th>
<th>Group 2: 31–94 mo (n = 24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphocytes (%)</td>
<td>20–40</td>
<td>28.2 ± 11.3^1</td>
<td>25.5 ± 8.5</td>
<td>23.0 ± 6.7</td>
</tr>
<tr>
<td>CD19 (%)</td>
<td>2–15</td>
<td>8.1 ± 4.8</td>
<td>7.6 ± 3.3</td>
<td>6.2 ± 3.3</td>
</tr>
<tr>
<td>CD2 (%)</td>
<td>65–90</td>
<td>79.5 ± 10</td>
<td>74.0 ± 14</td>
<td>72.1 ± 9.2</td>
</tr>
<tr>
<td>CD4 (%)</td>
<td>35–65</td>
<td>53.5 ± 13.4</td>
<td>54.7 ± 14.4</td>
<td>58.3 ± 8.1</td>
</tr>
<tr>
<td>CD8 (%)</td>
<td>20–35</td>
<td>29.5 ± 12.3</td>
<td>34.2 ± 12.4</td>
<td>45.7 ± 14.3^1</td>
</tr>
<tr>
<td>CD57 (%)</td>
<td>&lt;9</td>
<td>9.6 ± 5.4^1</td>
<td>13.7 ± 7.4^1</td>
<td>18.3 ± 10.7^1</td>
</tr>
<tr>
<td>CD4:CD8</td>
<td>1.1–3</td>
<td>2.0 ± 0.8</td>
<td>1.8 ± 0.9</td>
<td>1.4 ± 0.6</td>
</tr>
</tbody>
</table>

^1 ± SD.

^2 Significantly different from admission patients, P < 0.05.

^3 Out of the laboratory reference interval.
Support indicating the important role of natural killer cells in defense against infection is accumulating (52). Thus, the increase in natural killer cell (CD57) numbers found in our population may suggest that patients are prone to repeated episodes of peritonitis (51). On the other hand, the progressive reduction in B cells may be associated with the plasma concentrations of immunoglobulins. The ratio of T4 to T8, which has been used as an indicator of malnutrition (12), was lower in the final stage of CAPD, although no significant differences were found.

The potential mechanisms involved in immune dysregulation in chronic uremia remain unclear. Several hypotheses have been proposed, such as the participation of uremic toxins and cytokines (53, 54), metabolic and endocrine adaptation to renal failure (3, 30), peritoneal cell involvement (55), and recurrent diseases and infections (56, 57), which may be exacerbated by the biocompatibility of CAPD (52) and in which dietary intake and nutritional status could play a role (58, 59).

Some of the observed immunologic disturbances affecting the balanced cooperation between humoral and cell-mediated responses of the immune system have been found in situations of protein malnutrition (46, 60). Proportions of T lymphocyte subpopulations and lymphokine values have been found to be normal, enhanced, or reduced as has the proliferative response of T cells to mitogens and delayed-type hypersensitivity (2, 61). On the other hand, humoral immune responses remain apparently intact in situations of protein-energy malnutrition, when immunoglobulins and B cell number or function have been measured (4, 6). Dietary intake also affects other immune mechanisms such as natural killer cells, phagocytic activity, secretory immunity, and complement activity, resulting in increased susceptibility to infectious diseases (60–62). In this context, it is difficult to define whether the altered immune response is associated mainly with uremia rather than with the induction of malnutrition or the dialysis therapy. However, it is clear that malnutrition and uremia induce severe alterations in the host defense and specific immune systems if both diseases occur (46, 63), contributing to the high incidence of infection in dialysis patients (3, 56).

In conclusion, altered numbers of immune cells and changes in immunoglobulins and complement proteins might be responsible for the different immunologic abnormalities occurring in patients with chronic renal failure and who are receiving CAPD. Three major factors may be involved in the immunologic abnormalities: low nutrient intake, intercurrent or underlying illnesses, and the dialysis procedure itself.

REFERENCES