Daily nutrient intake represents a modifiable determinant of nutritional status in chronic haemodialysis patients

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Abstract

Background. In maintenance haemodialysis patients, daily food intake is changeable; however, its relationship with nutritional status is unexplored. This study aimed to evaluate the isolated, long-term effect of daily nutrient intake on nutritional status in haemodialysis patients.

Methods. We performed a prospective 1-year controlled study in 27 chronic haemodialysis patients, without recognized risk factors for malnutrition. Each day for 1 week, four times in the year, we measured protein nitrogen appearance, and assessed dietary protein (DPI) and energy (DEI) intake from dietary diaries. We compared the nutritional outcome of patients spontaneously reducing nutrient intake below the threshold of 0.8g/kg body weight/day for DPI and 25kcal/kg body weight/day for DEI during the week (LOW, n = 8), with controls at adequate nutrient intake (CON, n = 19). An interventional 6-month study was then carried out in LOW to verify the cause–effect relationship.

Results. All patients showed a day-by-day reduction of whole nutrient intake during interdialytic period, which was mostly relevant in the third interdialytic day (L3). During the 1-year study, even in the presence of adequate dialysis dose and normal inflammatory indexes, body weight (68.0 ± 5.5 to 65.8 ± 5.9 kg), serum albumin (3.96 ± 0.07 to 3.66 ± 0.06 g/dl) and creatinine (9.2 ± 1.1 to 8.1 ± 0.7 mg/dl) significantly decreased in LOW but not in CON. Diaries evidenced in LOW a reduced number of meals at L3 that was explained by the fear of excessive interdialytic weight gain. During the interventional study, daily DPI and DEI increased at L3; this was associated with a significant increment of body weight, and serum albumin and creatinine levels.

Conclusions. In maintenance haemodialysis patients the persistent, marked reduction of daily nutrient intake, even if limited to a single day of the week, is an independent determinant of reversible impairment of nutritional status.

Keywords: daily nutrient intake; energy intake haemodialysis; nutrition; nutritional status; protein intake; protein nitrogen appearance

Introduction

The minimal protein intake required to maintain a neutral nitrogen balance in patients on chronic haemodialysis is almost two-thirds higher than that required in pre-dialysis patients and in those without renal impairment [1,2]. Catabolic factors strictly related to haemodialysis treatment, such as loss of proteins and amino acids in the dialysate, bio-incompatible membranes, inflammation and metabolic acidosis, account for the higher need of nutrient [3]. In spite of the greater nutrient requirement, in these patients the protein-energy intake is often inadequate [4]. An important cause is anorexia, due to inadequate dialysis dose and/or secondary factors, such as underlying illness, anaemia, psychosocial conditions, loss of dentures and depression [4,5].

Lower nutrient intake in the face of higher requirements leads to malnutrition even in well-nourished and adequately dialysed patients [3]. In this regard, recent cross-sectional studies have suggested that the recommendation to minimize interdialytic weight gain, which is aimed at avoiding excessive sodium and fluid intake, can lead to a concurrent decrease of nutrient intake [6,7]; however, its potential impact on nutritional status remains unexplored. On the other hand, daily nutrient intake is variable, possibly decreasing either in the dialysis day or during the interdialysis period [8,9];
nevertheless, whether a decrease of daily food intake can per se impair nutritional status is unknown. These are critical items as most cases of malnutrition in haemodialysis are of mild to moderate degree and not revealed by the common markers of nutrition [10].

To gain insights into the isolated effect of daily food intake on the nutritional status in maintenance haemodialysis, we prospectively studied for 1-year protein-energy intake and markers of nutritional status in 27 patients on maintenance haemodialysis with no risk factor for malnutrition. To verify the results obtained in the observational study, we subsequently carried out an interventional 6-month study in patients showing a reduced daily nutrient intake.

**Subjects and methods**

**Patients**

Inclusion criteria into the study were the following: adult age (> 18 years), anuria (urinary output < 200 ml during the long interdialytic interval), treatment with bicarbonate haemodialysis from at least 12 months, ability to prepare meals by themselves or by family members and affordability of food, presence during the previous 3 months of adequate dose of dialysis (estimated by urea kinetic model, $K_{dialysis}$ > 1.2), adequate dietary protein intake (estimated by interdialytic protein nitrogen appearance, PNA > 1.1 g/kg body weight/day) and energy prescription (30–35 kcal/kg body weight/day), adequate and stable nutritional status, as indicated by BMI > 20 kg/m² and serum albumin > 3.5 g/dl, during the previous 3 months. We excluded patients with diabetes mellitus, cancer, active cardiovascular disease, advanced liver or gastrointestinal disease, depression, alcoholism and any superimposed acute illness during the previous 3 months. We therefore enrolled 28 patients out of 164 patients in maintenance haemodialysis.

**Treatment modalities**

To reduce the negative effects of both haemodialysis and uraemia on appetite and nutritional status, we dialysed the patients three times weekly with bicarbonate haemodialysis, a prescribed $K_{dialysis}$ > 1.2, low-flux biocompatible membranes not reused, dialysate containing 1.0 g/l of glucose and 39 mmol/l of bicarbonate. The dialytic treatment was delivered in each patient throughout the study with the same artificial system (Integra Hospal, Bologna, Italy; System 1000 Drake-Willok Althin, Roma, Italy), same low-flux membrane (Polysulfone 1.8 m², Fresenius, Palazzo Pignano, Italy; PMMA 2.0 m², Estor, Pero, Italy; Cellulose-Diacetate 2.1 m², Baxter, Milano, Italy), constant blood (300–350 ml/min) and dialysate (500 ml/min) flow rate and dialysis time (225–255 min). The vascular access in all patients was a native artero-venous fistula. During and immediately after each haemodialysis session, we monitored the patients to verify the presence of cramps, vomiting and significant hypotensive episodes, defined as a decline of systolic arterial pressure > 20 mmHg or reaching a value < 100 mmHg.

We maintained the haematocrit at the target value of 33% (range 30–36). To this aim recombinant human erythropoietin was administered in 21 patients (mean dose = 9800 ± 700 IU/week).

We prescribed a diet containing 1.2 g/kg body weight/day of protein, with a large part of high biologic value, and 30–35 kcal/kg body weight/day, and water-soluble B and C vitamins as multivitamin tablets to all patients.

Throughout the study, we monitored monthly dry weight by clinical assessment as well as the main factors predisposing chronic haemodialysis patients to malnutrition, such as the development of active cardiovascular and peripheral vascular disease (defined by clinical symptoms, electrocardiography, echocardiography and echo-Doppler), active gastrointestinal disease and acute infections. The onset of one of these conditions and hospitalization for any cause during the study represented criteria for exclusion.

**Measurements**

During the 1-year period, every 4 months, we studied the patients each day throughout an entire week. In order to check urea kinetic and daily protein intake, we drew blood samples before and at the end of the three dialysis session of the week, and at 24, 48 and 60 h during the long interdialytic period, and at 24 and 44 h during the short interdialytic period. We also obtained additional pre- and post-dialysis blood samples each month, in order to verify the delivered dose of dialysis. We analysed the blood samples drawn before and immediately after the HD session following the long interdialytic period to determine the serum concentration of urea nitrogen (SUN), creatinine (Creat), albumin (ALB), sodium (Na), bicarbonate ($HCO_3$), C-reactive protein (CRP) and $\alpha_2$-macroglobulin, haematocrit (Htc) and white blood cells (WBC). We measured SUN, creatinine, albumin (by BromoCresol Purple, normal range = 3.5–4.8 g/dl), sodium and CRP (normal range = 0–0.5 mg/dl) by an autoanalyzer (Olympus AU 400, Olympus Italia, Segrè-Milano, Italy); bicarbonate by an automatic haemogas-analyser (ABL 625 analyzer, Radiometer, Copenhagen, De Mori, Italy) immediately after blood sampling; $\alpha_2$-macroglobulin by electrophoresis (REP, Helena Lab. S.p.a., Asiago-Milano, Italy); white blood cells and haematocrit by a blood cell counter (Cell-Dyn 3500 R, Abbot Diagnostics, Germany).

At each experimental time, we measured body weight and systemic arterial pressure. The reported values of systolic and diastolic blood pressure were the mean of three consecutive measurements obtained after the patient has been lying in bed for 15 min at 22–24°C.

**Calculations**

We calculated the delivered dialysis dose measured by the urea kinetic index ($K_{dialysis}$) according to the second-generation equation (where $K$ is the urea clearance, $t$ represents the duration of dialysis treatment and $V$ is the volume of urea distribution) [11]. We estimated the protein intake by measuring the protein nitrogen appearance (PNA), calculated according to the following formula:

$$[6.49 \times \text{UNA} + 0.294 \times V],$$

where UNA, the urea nitrogen appearance, is calculated according to the formula:

$$UNA = [SUN_f – SUN_i] \times V + [(BW_f – BW_i) \times SUN_f],$$

with $f$ and $i$ that are the final and initial values for each period of measurement) and represents the net production of urea nitrogen in the body (g/day), and $V$ is the urea distribution volume and is considered equal to: [dry body weight (dBW) * 0.58] [12]. We normalized PNA to dry body weight.
We calculated both the mean interdiarytic (PNAi) and the daily (PNA) protein nitrogen appearance. As the length of the last day of each interdiarytic period was 20h, we normalized the calculation of UNA for this period of time to 24h. We also expressed interdiarytic body weight gain as mean interdiarytic weight gain (WGi) and daily weight gain (WGd); weight gain is the percentage of weight increase, according to the formula \([\text{WGd} = \text{BW}_{t+1} - \text{BW}_t]/\text{BW}_t * 100\). We calculated the creatinine index (iCreat), corresponding to the creatinine synthesis rate (mg/day), according to the formula: \([i_{\text{Creat}} = (SCrea_{t+1} - SCrea_t) * dBW * 0.58 + (BW_{t+1} - BW_t) * s\text{Creat} + [0.38 * s\text{Creat} * dBW]/3\). We calculated the mean arterial pressure (MAP) as diastolic pressure + (systolic – diastolic pressure)/3.

Assessment of dietary protein and energy intake

To determine dietary protein (DPI) and energy (DEI) intake, patients recorded in dietary diaries the amount of ingested food and the daily number of meals (breakfast, lunch, dinner and snacks), during a whole week, every 4 months throughout the 1-year period. A skilled dietician trained patients how to record the total food intake in the diary by household measures, and also instructed them to take the measures of the utensils before starting food record [14]. After each day, patients checked the diary by a 24-h recall. The same person analysed all food records over the study period, computing DPI, DEI and sodium intake for separate days.

Interventional study

On the basis of the results obtained in the first 12 month period, we performed an additional interventional study in LOW aimed at verifying the cause–effect relationship between reduction of nutrient intake at L3 and alterations of nutritional status. We instructed patients not to miss any meal during the long interdiarytic period while minimizing the assumption of water and sodium. Thus, we studied LOW patients for an additional 6-month period. During this interventional study, we kept patients at the same modalities of treatment of the previous study period and, every 3 months, we submitted them to the same determinations described previously.

Statistics

We reported values as mean ± standard error of the mean (SEM). We tested intergroup comparisons by two-tailed Student’s t-test for unpaired data, and intragroup comparisons by ANOVA for repeated measures and Bonferroni post-hoc test. We used the correlation analysis and Fisher’s test where appropriate and considered statistically significant a two-tailed P-value < 0.05.

Results

Patient’s characteristics

We enrolled into the study, after attainment of informed consent, 28 patients (eight females, 20 males; mean age 57.8 ± 2.8 years). One patient dropped out from the study because of the development of an active gastric peptic ulcer. The causes of renal failure in the 27 patients completing the study were glomerulonephritis \((n = 8)\), tubulo-interstitial nephropathy \((n = 7)\), nephroangiosclerosis \((n = 3)\), hereditary nephropathy \((n = 2)\) and unknown \((n = 7)\). The antihypertensive drugs prescribed were angiotensin-converting enzyme inhibitors \((n = 9)\), calcium blockers \((n = 9)\) and \(\beta\)-blockers \((n = 5)\). Dose and type of antihypertensive drugs did not significantly vary during the entire study period. Patients received calcium carbonate \((n = 17)\) and/or aluminium hydroxide \((n = 9)\) and vitamin D \((n = 13)\).

The incidence of hypertensive episodes during and immediately after all the haemodialysis sessions over the entire study period, was very low \((n = 19 [0.5\% \text{ of haemodialysis}] \text{ in 5 pts})\); the same held true for vomiting \((n = 2 [0.05\% \text{ of haemodialysis}] \text{ in 2 pts})\) and cramps \((n = 24 [0.6\% \text{ of HD}] \text{ in 7 pts})\).

Protein and energy intakes

Table 1 depicts the dialytic and nutritional data of the 27 HD patients. The value of standard PNAi was constantly > 1.1 g/kg body weight/day and did not change throughout follow up. In contrast, serum albumin and creatinine slightly but significantly decreased.

When evaluating the daily behaviour of protein-energy intake, a striking daily variability became evident. DPI and DEI progressively decreased during

<table>
<thead>
<tr>
<th>Table 1. Dialytic and nutritional parameters, at baseline and after 12 months in the whole group of haemodialysis patients</th>
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<tr>
<td>Kt/VUREA</td>
</tr>
<tr>
<td>PNAi (g/kg body weight/day)</td>
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<tr>
<td>WGi (% body weight/day)</td>
</tr>
<tr>
<td>Body weight (kg)</td>
</tr>
<tr>
<td>SAlb (g/dl)</td>
</tr>
<tr>
<td>SCreat (mg/dl)</td>
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</table>

<sup>a</sup>P < 0.05 vs basal (Student’s t-test). Kt/VUREA = delivered dialysis dose. Values are reported as mean ± SEM.
each interdialytic period. The DPI obtained in the second day (of both short and long interdialysis intervals), decreased with respect to the value of the first day but remained always above the threshold of 1.1 g/kg body weight/day. In contrast, the DPI of the third day diminished below this level, resulting the lowest value. We obtained this result at each of the four time points (0, 4, 8, 12 months) during the 12-month study period (Figure 1). The assessment of PNA\textsubscript{d} confirmed the pattern of changes in DPI. The daily energy intake similarly changed during the two short (S) and long (L) interdialytic periods. Likewise, WG\textsubscript{d} declined during the interdialytic periods; at L3, WG\textsubscript{d} significantly correlated with both daily protein and energy intakes ($r = 0.603$, $P < 0.001$; $r = 0.642$, $P < 0.001$, respectively). Also, daily sodium intake diminished during the interdialytic periods, with the maximal reduction observed at L3, and directly correlated with both DPI and DEI ($r = 0.662$, $P < 0.001$; $r = 0.596$, $P < 0.001$, respectively) and WG\textsubscript{d} ($r = 0.741$, $P < 0.001$).

At baseline, the two groups did not differ in the main characteristics, with the exception of gender distribution; female gender was in fact prevalent in LOW (Table 2). LOW and CON patients also showed a similar value of PNA\textsubscript{i}, that was $>1.1$ g/kg body weight/day in both groups.

Table 3 depicts the yearly means of the daily values of dietary intake in LOW and CON. As there were no differences between the two short periods, we have represented only one of the two. The values of DPI in the two groups indicated a pattern of changes similar to that of the whole population; protein intake progressively decreased during the long interdialytic interval in both CON and LOW. In LOW, however, the DPI at the third day was almost half of the respective CON value. Assessment of PNA\textsubscript{d} confirmed the behaviour of daily protein intake measured by dietary diaries. In addition, dietary diaries evidenced a significant difference in the number of meals between CON and LOW only in the third inter-haemodialysis day ($2.6 \pm 0.1$ vs $1.3 \pm 0.1$, $P < 0.001$). At variance with the CON group, in fact, all the eight LOW patients affirmed that they habitually missed at least one of the two main meals in the last day of the long interval to limit the inter-haemodialysis weight gain, being particularly afraid of fluid overload. The DEI changed in parallel with the variations of both DPI and PNA\textsubscript{d}. Also, daily sodium intake and WG\textsubscript{d} significantly

![Fig. 1.](https://academic.oup.com/ndt/article-abstract/18/9/1874/1841878)
declined during the interdialytic periods with the maximal reduction observed in LOW at L3 (Table 3). WGD constant resulted at the four controls of the year <1% in LOW and >1% in CON ($P < 0.05$).

Six patients of the CON group had DEI values <25 and >22 kcal/kg body weight/day in the third day; however, at variance with the LOW patients, the protein intake was constantly >0.8 g/kg body weight/day.

Dietary intakes were also evaluated after adjusting protein and energy intakes for ideal and standard body weight. The results did not change, persisting the significant difference among groups and between the third inter-haemodialysis day and the first and the second day in both groups (data not shown). In addition, when analysing the nutrient intake according to gender, a similar pattern of changes of the daily nutrient intakes in males and females became apparent, and no statistically significant inter-gender difference was observed (data not shown).

### Clinical and nutritional outcome in LOW and CON groups

During the study, the main dialytic and clinical parameters remained similar in LOW and CON (Table 4). Patients received the same dialysis dose; an inflammatory status was absent in either group since CRP, $\alpha_2$-macroglobulin and white blood cell remained within normal values during the study in all patients; pre-dialysis serum bicarbonate was >20 mEq/l. In contrast, the outcome of the nutritional status differed in the two groups. Body weight and creatinine index declined in LOW, while remained stable in CON (Table 4); also serum albumin and creatinine significantly decreased only in LOW (Figure 2).

In the subgroup of CON with isolated reduced DEI at L3 ($n = 6$), the nutritional status did not vary throughout the study. The initial and final values of body weight ($60.3 \pm 3.4$ vs $59.5 \pm 3.7$ kg, NS), serum creatinine ($10.3 \pm 0.9$ vs $10.2 \pm 0.9$ mg/dl, NS) and serum albumin ($3.98 \pm 0.12$ vs $3.94 \pm 0.08$ g/dl, NS) were not different.
During the interventional study, daily DPI, PNA and DEI significantly increased at L3 (Table 5), while did not change in the first 2 days of the long interval and in the short interdialytic periods as well; indeed, dietary diaries revealed that in the third inter-haemodialysis day, the number of meals significantly increased. In association with the reversal of the abnormal eating behaviour in L3, body weight and serum levels of albumin and creatinine increased during the 6-month period.

**Discussion**

The present study provides first-time evidence on the relationship between variation of daily nutrient intake and impairment of nutritional status in chronic haemodialysis patients with no risk factor of malnutrition. The whole group of patients showed a progressive decline of nutrient intake during the interdialytic intervals, with the maximal reduction reached in the third day of the long interval. Specifically, the dietary protein intake of the second day was lower, as compared with the first day, but still adequate, being always >1.1g/kg body weight/day; on the contrary, the DPI on the third day constantly remained below

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**Table 4. Dialytic and clinical parameters, at baseline and after 12 months, in LOW and CON groups**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>LOW Basal</th>
<th>LOW Month 12</th>
<th>CON Basal</th>
<th>CON Month 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kt/VUREA</td>
<td>1.33±0.09</td>
<td>1.36±0.06</td>
<td>1.39±0.05</td>
<td>1.36±0.03</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>114±6</td>
<td>109±2</td>
<td>111±3</td>
<td>104±3</td>
</tr>
<tr>
<td>Htc (%)</td>
<td>34.6±1.2</td>
<td>35.0±0.9</td>
<td>33.3±0.8</td>
<td>33.3±0.6</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>68.0±5.5</td>
<td>65.8±5.9a</td>
<td>66.9±2.3</td>
<td>66.7±2.5</td>
</tr>
<tr>
<td>SCreat (mg/day)</td>
<td>835±155</td>
<td>723±106b</td>
<td>987±72</td>
<td>963±65</td>
</tr>
<tr>
<td>CRP (mg/dl)</td>
<td>0.32±0.06</td>
<td>0.30±0.05</td>
<td>0.27±0.04</td>
<td>0.30±0.06</td>
</tr>
<tr>
<td>α2 (g/dl)</td>
<td>0.68±0.04</td>
<td>0.65±0.04</td>
<td>0.77±0.02</td>
<td>0.70±0.05</td>
</tr>
<tr>
<td>WBC (n)</td>
<td>5248±388</td>
<td>4980±365</td>
<td>6150±180</td>
<td>6022±208</td>
</tr>
<tr>
<td>sHCO3 (mEq/l)</td>
<td>22.4±0.8</td>
<td>22.0±0.9</td>
<td>23.7±0.5</td>
<td>23.4±0.5</td>
</tr>
</tbody>
</table>

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**Table 5. Nutrient intake at the third interdialytic day and nutritional parameters in LOW patients, at baseline and after 12 months and during the nutritional intervention at the 15th and 18th month**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Basal</th>
<th>Month 12</th>
<th>Month 15</th>
<th>Month 18</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPI (g/kg body weight/day)</td>
<td>0.67±0.06</td>
<td>0.67±0.7</td>
<td>0.92±0.07b</td>
<td>0.98±0.05a,b</td>
</tr>
<tr>
<td>PNA (g/kg body weight/day)</td>
<td>0.69±0.04</td>
<td>0.68±0.03</td>
<td>0.96±0.09b</td>
<td>1.01±0.08a,b</td>
</tr>
<tr>
<td>DEI (kcal/kg body weight/day)</td>
<td>19±1</td>
<td>18±1</td>
<td>25±1a,b</td>
<td>26±1a,b</td>
</tr>
<tr>
<td>WGd (% body weight)</td>
<td>0.78±0.06</td>
<td>0.77±0.05</td>
<td>1.25±0.15a,b</td>
<td>1.30±0.09a,b</td>
</tr>
<tr>
<td>Meals (n/day)</td>
<td>1.3±0.1</td>
<td>1.2±0.1</td>
<td>2.3±0.1a,b</td>
<td>2.4±0.1b</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>68.0±5.5</td>
<td>65.8±5.9a</td>
<td>66.0±5.6a</td>
<td>67.4±4.9b,c</td>
</tr>
<tr>
<td>sAlb (g/dl)</td>
<td>3.96±0.07</td>
<td>3.66±0.06a</td>
<td>3.74±0.07a</td>
<td>3.88±0.09b,c</td>
</tr>
<tr>
<td>sCreat (mg/dl)</td>
<td>9.2±1.1</td>
<td>8.1±0.7a</td>
<td>9.0±0.8b</td>
<td>9.2±0.9b</td>
</tr>
</tbody>
</table>

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Fig. 2. Changes of serum albumin and creatinine in low protein-energy intake (LOW, filled circle) and control (CON, open circle) groups during the 12-month study period. Values are reported as mean±SEM; *P<0.05 vs 0 (basal); **P<0.05 vs CON.

Interventional study in LOW group

During the interventional study, dialysis dose and other dialytic parameters did not change with respect to the previous 1-year study period. Daily DPI, PNA and DEI significantly increased at L3 (Table 5), while did not change in the first 2 days of the long interval and in the short interdialytic periods as well; indeed, dietary diaries revealed that in the third inter-haemodialysis day, the number of meals significantly increased. In association with the reversal of the abnormal eating behaviour in L3, body weight and serum levels of albumin and creatinine increased during the 6-month period.

*P<0.05 vs basal.

aP<0.05 vs month 12.

bP<0.05 vs month 15 (ANOVA for repeated measures and Bonferroni post-hoc test).

Values are reported as mean±SEM.
this value throughout the 12 months. A similar pattern of changes was observed in the daily energy intake. Therefore, the entire nutrient intake was altered. Other authors have reported a significant reduction of nutrient intake in the day of haemodialysis session, likely attributable to dialysis malaise that can develop during and immediately after haemodialysis sessions [8]. In the present study, the ingestion of adequate amount of food in the day of treatment was reasonably due to the absence of dialysis stress; the patients, in fact, were exempt from this complication that is generally induced by poor haemodynamic stability and dialysis fatigue. The reduction of daily nutrient intake was associated with mild but significant impairment of serum albumin and creatinine.

The alteration of protein intake was undetectable by means of interdialytic PNAi, that is routinely used in clinical practice as index of protein intake; PNAi, in fact, resulted always > 1.1 g/kg body weight/day because the marked reduction of protein intake in L3 was counterbalanced by the higher intake of protein, and energy as well, in the first days. Therefore, the present study demonstrates for the first time that the standard measurement of PNAi does not consistently allow to diagnosing even marked alterations of daily protein intake, and highlights the importance of dietician survey to identify an abnormal food intake behaviour in haemodialysis patients.

The data also indicate that the evaluation of daily changes of weight gain may represent an alternative tool to properly monitoring daily nutrient intake. Previous cross-sectional studies have shown a direct correlation between WGi and PNAi, suggesting WGi as an index of food intake; the explanation becomes readily apparent when considering the substantial amount of energy contained in solid food, and often in beverages as well [6,7]. The current study adds novel information on this issue; we demonstrate that the daily variation of protein-energy intake correlates with the concomitant changes in daily weight gain, whereas the interdialytic value of WGi, similarly to PNA, does not reveal even relevant changes of the daily nutrient intake.

A more in-depth analysis of both pathogenesis and effects of this abnormal daily eating behaviour was obtained by grouping the patients; we compared with controls at adequate nutrient intake (CON) the group of patients (LOW) that, throughout the study, had in the third inter-haemodialysis day (L3) protein and energy intake below the minimal threshold required to maintain a neutral nitrogen balance in haemodialysis [2,15]. In haemodialysis patients, several factors lead to anorexia [4,5,8]; nonetheless, the careful study design allowed us to eliminate inadequate dialysis, acidosis, anaemia and intercurrent illnesses as the cause of poor dietary protein intake. In LOW, the anorectic effect of accumulating uraemic toxins during the interdialysis interval may have contributed to the observed decrease of protein-energy intake [16]; however, as both the dose and the modalities of dialysis or the pre-dialysis blood urea nitrogen were similar in the two groups, such an effect can be excluded. Alternatively, dietary diaries evidenced that the patients of LOW group spontaneously diminished the nutrient intake; they, in fact, habitually missed one meal in L3 in order to prevent excessive interdialytic weight gain, being particularly afraid of fluid overload. Groups were similar in terms of demographic and clinical features, with the exception of a greater prevalence of female gender in the LOW group. On this regard, it has been reported that females seem to be more prone than males to the spontaneous reduction of nutrient intake in the pre-dialytic stages of chronic renal failure [17]; however, in the present study, no statistical difference became apparent after grouping patients according to gender.

In the LOW group, the very low amount of food at L3 was associated with a significant progressive impairment of the nutritional indexes of recognized prognostic value in dialysis, such as serum albumin, creatinine and body weight. Hypoalbuminaemia is not necessarily synonymous of under-nutrition as it can be secondary to extracellular volume expansion or inflammatory processes [18]. However, the unvaried blood pressure and the constancy of the Htc and WGi during the study reasonably excluded a ‘dilution’ effect. Furthermore, an acute phase reaction was absent, as demonstrated by the normal values of PRP, α2-macroglobulin and blood white cells count. Therefore, the moderate decrease of plasma albumin in these patients indicated a mild impairment of nutrition. We observed a decrement in the plasma creatinine that, reflecting the creatinine production in anuric patients, estimates the lean body mass independently from the hydration state [19]. Also, the creatinine index diminished in LOW, suggesting a decline of muscle mass [20]. The significant reduction of body weight by 3.2% within 1 year, confirmed the decline of lean body mass indicated by the changes of creatinine. Overall, the data suggest the impairment of both visceral and somatic proteins, that is, the onset of a nutritional status deficiency.

We verified the hypothesized relationship between daily eating behaviour and nutritional status by means of the interventional study that started after instructing LOW patients not to miss any meal in the long inter-haemodialysis period. In the subsequent 6-month period we observed the increase of the number of meals and a concurrent enhancement of protein-energy intake in the third day of the long inter-HD period. The correction of abnormal eating behaviour led to a progressive improvement of body weight and nutritional indices. Although body weight, creatinine and albumine increased significantly during the interventional status, the highest values were still the basal values. The protocol does not allow us to clarify why the nutritional indices did not further improve; it is possible in these patients takes longer time to overcome the basal conditions. Nevertheless, this prospective, self-controlled, 6-month interventional study further sup-
ports the hypothesis that in stable haemodialysis patients without risk factors for malnutrition a poor daily food intake, even if limited to a single day of the week, induces a reversible impairment of nutritional stores.

It is puzzling how patients assuming adequate nutrient intake during 6 days of the week can develop impaired nutrition. Protein turnover is a dynamic and rapid process, with the nitrogen balance becoming negative during fasting and positive after meal. Haemodialysis patients, in fact, even though capable to adapt to a low protein intake by decreasing amino acid oxidation and protein degradation, are unable to achieve a daily neutral nitrogen balance if the protein-energy intake in the course of the entire day is very low [20]. In our patients, the higher nutrient intake at the beginning of the long interdialytic period was still insufficient to counterbalance the very low intake of the third day in terms of weekly nitrogen balance, with the consequent long-term development of mild impairment of nutritional status.

The study, being aimed at evaluating the independent effect of daily food intake, was performed in well-nourished patients with no recognized risk factor for malnutrition, that is, in a population of ‘relatively healthy’ patients. Because of the careful selection and the consequent low number of patients studied, the data, although extremely suggestive, cannot be considered conclusive with respect to the general population. It is reasonable to hypothesize, however, that such abnormal eating behaviour may play a role even more critical in dialysis patients affected by major risk factors.

In conclusion, stable well-nourished haemodialysis patients can develop a moderate impairment of nutritional status secondary to abnormalities of daily eating behaviour. In our patients, a persistent and marked spontaneous decline of protein-energy intake in the third day of the long interdialytic interval, related to the fear of fluid overload, induced a reversible alteration of nutritional stores. The present study therefore highlights the importance of a balanced nutrient intake during the interdialytic period and that a careful dietician survey, rather than the standard measurement of interdialytic protein nitrogen appearance, is the tool adequate to discovering the abnormalities of daily nutrient intake.

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