Relating protein intake to nutritional status in haemodialysis patients: how to normalize the protein equivalent of total nitrogen appearance (PNA)?

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Abstract

Background. The protein equivalent of total nitrogen appearance (PNA) is assumed to be a reliable estimate of dietary protein intake in haemodialysis patients. Protein requirements are related to body size. In order to standardize PNA to individual differences in body size, PNA is normalized to various terms related to the patient’s body weight. It is not clear which is the most appropriate method to normalize PNA.

Methods. We calculated five commonly used variants of normalized PNA and related them to indices of nutritional status in 57 stable chronic haemodialysis patients, 57 ± 15 (mean ± SD) years of age. PNA, determined by direct dialysate quantification, was normalized to actual post-dialysis dry body weight (DBW), normal body weight (DBWnormal), lean body mass (LBM), normal lean body mass (LBMnormal), and 'normalized' body weight (N). Nutritional status was assessed using an index of nutrition composed of anthropometry derived parameters and plasma albumin concentration.

Results. PNA_{DBW} (0.85 ± 0.14 g/kg/d) tended to be higher than PNA_{DBWnormal} (0.81 ± 0.14 g/kg/d). PNA_{LBM} (1.17 ± 0.19 g/kg/d) did not differ from PNA_{LBMnormal} (1.19 ± 0.21 g/kg/d). PNA_{N} (1.06 ± 0.14 g/kg/d) was significantly higher than PNA_{DBW} and PNA_{DBWnormal}, but lower than PNA_{LBM} and PNA_{LBMnormal}. Actual PNA (61 ± 13 g/d) correlated significantly with DBW (r = 0.52) and LBM (r = 0.63) indicating that large patients eat more protein. Interestingly, actual PNA correlated with plasma albumin (r = 0.33) and with the overall index of nutrition (r = 0.27) as well. PNA_{DBW} correlated negatively with relative DBW (r = −0.32), expressed as a percentage of normal values, indicating that PNA_{DBW} is relatively high in underweight patients. In contrast, PNA_{DBWnormal} correlated positively with all nutritional parameters as well as with the overall index of nutrition (r = 0.33). PNA_{N} and PNA_{LBM} did not correlate with the nutritional status, but PNA_{LBMnormal} correlated positively with relative DBW (r = 0.50) and with overall nutritional status (r = 0.34). PNA_{DBWnormal} and PNA_{LBMnormal} in well-nourished patients showed overlap with the values in patients with evident malnutrition, despite the positive correlation of the normalized PNA values with nutritional status.

Conclusions. Normalizing PNA by DBWnormal and LBMnormal appeared to be the most appropriate method to standardize protein intake in haemodialysis patients. Since actual PNA is the purest estimate of protein intake that correlated with nutritional status, we recommend to evaluate actual PNA as well in studies that relate protein intake to patient outcome.

Key words: dietary protein intake; haemodialysis; nutritional status; protein intake assessment; protein equivalent of total nitrogen appearance; urea kinetic modeling

Introduction

Patients on chronic haemodialysis are at risk of developing malnutrition. Risk factors for malnutrition in these patients include dietary protein and energy intake as well as inflammation [1,2]. Because malnutrition [3,4] and low dietary protein intake [5,6] are associated with an increased morbidity and mortality risk, monitoring of protein intake and nutritional status in haemodialysis patients has become an important issue.

Dietary protein intake can be assessed directly by means of a dietary diary, but this method depends heavily on the prolonged cooperation of the patient and is time consuming [7]. More easily, protein intake can be estimated indirectly from the protein equivalent of total nitrogen appearance (PNA) determined by urea kinetic modelling. PNA is assumed to be a reliable estimate of dietary protein intake, if the patient is in steady state with regard to his protein metabolism.
The nutritional status can be assessed by comparing measurements of nitrogen obtained by anthropometry and biochemical tests to reference values [9].

Since nutritional intake and requirements are related to body size and composition, protein intake is often factored by various terms related to the patients body weight, including dry body weight, normal body weight or lean body mass [8,10]. These normalized protein intake values are used to assess protein intake and to evaluate the relationship between protein intake, nutritional status, and clinical outcome. However, no consensus has been reached about which patient factor is most appropriate for normalizing protein intake in haemodialysis patients. In patients on peritoneal dialysis it has been shown that the relationship between protein intake and nutritional status is greatly influenced by different methods of normalization [11]. The use of various normalization methods may be responsible for the conflicting results found in studies that tried to relate protein intake to nutritional status, morbidity, and mortality in dialysis patients [4–6, 10–16].

Aim of the present study was to evaluate which normalization method is appropriate to assess protein intake in stable chronic haemodialysis patients by relating different normalized PNA variants to commonly used indices of the nutritional status.

**Patients and methods**

**Patients and haemodialysis treatment**

The patients participated in a Dutch multicentre study on haemodialysis adequacy and nutrition (Groningen Utrecht Dialysis and Diet Study (GUDDS)) and were recruited from five dialysis centres in The Netherlands. The patients were asked to participate in the study if they had been treated by haemodialysis three times weekly for at least 3 months, had a residual renal clearance lower than 3 ml/min, and were in a stable clinical condition without hospitalization in the preceding 3 months. Patients with inflammatory diseases, diabetes mellitus, active systemic diseases or known malignancies were excluded. The study was approved by the Medical Ethical Committee of the participating centres and all patients had given informed consent for participation.

Fifty-seven patients (40 males and 17 females), 57±15 years of age, were included in this multicentre study. None of the included patients had overt oedema. Primary causes of their renal disease were: glomerulonephritis \((n=8)\), interstitial nephritis \((n=5)\), cystic kidney diseases \((n=11)\), congenital kidney diseases \((n=3)\), renal vascular diseases \((n=14)\), unknown \((n=10)\) and other \((n=6)\).

The patients were dialysed three times weekly for 3–4.5 h per dialysis session and blood flow was set individually at a constant rate of 200–300 ml/min. The patients were dialysed using a single-pass or dialysate recirculation dialysis machines with bicarbonate-based dialysate at a flow of 500 ml/min and low-flux (ultrafiltration coefficient <10 ml/mmHg h) dialysers with low complement activation. Delivered Kt/V eq was calculated using the equation by Daugirdas [17].

A diet containing 0.9–1.0 g/kg ideal body weight/day of protein was prescribed to the patients. Patients were encouraged not to change their usual dietary protein intake.

**Sampling and laboratory analysis of blood, urine and dialysate**

Blood samples were drawn in heparinized tubes from the fistula immediately before starting the dialysis, at 15 min after termination of the dialysis and before the next dialysis session.

Urine production in 10 of the 57 patients was more than 200 ml per 24 h. These patients collected 24-h urine on the day before the modelled dialysis session. Renal urea and creatinine clearance were calculated from the 24-h urinary output measurements and the time-averaged-concentrations. The residual renal clearance in these 10 patients, defined as the mean of the urea and creatinine clearances, was 1.5±0.8 ml/min.

Dialysate was collected by continuous partial dialysate sampling [18]. For the single pass dialysis machines, total dialysate volume was calculated by multiplying the dialysate flow by duration of the dialysate collection. The dialysate recirculating machines were adapted for dialysate collection as previously described [19]. Total dialysate volume was calculated by multiplying the number of transfers by the transfer volume. The transfer volume was determined before the study and was not changed during the study.

Urea and creatinine concentrations in plasma and urine were determined using routine laboratory methods. Plasma albumin concentration was determined using the cresol-green method. The dialysate urea concentration was determined together with series of standard dialysate samples containing known amounts of urea (3.0–8.0 mmol/l) in fresh dialysate. The measured urea concentration in the patient dialysate samples was corrected for measurement error using the regression equation determined from the urea concentration values in the standard dialysate samples.

**Protein equivalent of total nitrogen appearance measurements**

PNA was determined from the rise in plasma urea concentration during the interdialytic interval and an estimate of the patients urea distribution volume (UDV) during three midweek haemodialysis sessions 4 weeks apart. UDV was calculated from the total urea output in the dialysate corrected for intradialytic urea appearance and ultrafiltration, and the decrease in urea concentration during the modelled dialysis sessions [18]. The averaged value of the three available UDV measurements was used in the PNA equations. PNA \((g/d)\) was calculated from urea nitrogen appearance (UNA) and corrected for unmeasured nitrogen losses (45 mg protein per kg actual body weight per day) [5,8] according to the formulae:

\[
\text{UNA} = C_{\text{d}} \times \left( \frac{U_2 + U_3}{2000} + U_3 \times \frac{W_3 - W_2}{T_{\text{ID}}} + \text{UDV} \times \frac{(U_3 - U_2)}{T_{\text{ID}}} \right)
\]

where \(C_{\text{d}}\) is residual renal clearance (ml/min), \(U\) and \(W\) are the urea concentration (mmol/l) and body weight (kg) after the modelled dialysis \((U_2\) and \(W_2)\) and before the next dialysis \((U_3\) and \(W_3)\), \(T_{\text{ID}}\) is the interdialytic interval (min), and \(\text{UDV}\) is the urea distribution volume (l).

**Methods of normalization**

Five normalization methods were used to standardize PNA to body size. First, the PNA values were factored by the following equations:

\[
PNA_{\text{ID}} = \frac{C_{\text{d}} \times (U_2 + U_3)/2000 + U_3(T_{\text{ID}})}{W_2 W_3} \\
PNA_{\text{ID}+\text{UNA}} = \frac{C_{\text{d}} \times (U_2 + U_3)/2000 + U_3(T_{\text{ID}})}{W_2 W_3} + \frac{\text{UNA}}{W_2 W_3} \\
PNA_{\text{ID}+\text{ID_1}} = \frac{C_{\text{d}} \times (U_2 + U_3)/2000 + U_3(T_{\text{ID}})}{W_2 W_3} + \frac{\text{UNA}}{W_2 W_3} + \frac{C_{\text{d}} T_{\text{ID}}^{0.5}}{W_2 W_3} \\
PNA_{\text{ID}+\text{ID_2}} = \frac{C_{\text{d}} \times (U_2 + U_3)/2000 + U_3(T_{\text{ID}})}{W_2 W_3} + \frac{\text{UNA}}{W_2 W_3} + \frac{C_{\text{d}} T_{\text{ID}}^{0.5}}{W_2 W_3} + \frac{C_{\text{d}} T_{\text{ID}}^{0.5}}{W_2 W_3} \\
PNA_{\text{ID}+\text{ID_3}} = \frac{C_{\text{d}} \times (U_2 + U_3)/2000 + U_3(T_{\text{ID}})}{W_2 W_3} + \frac{\text{UNA}}{W_2 W_3} + \frac{C_{\text{d}} T_{\text{ID}}^{0.5}}{W_2 W_3} + \frac{C_{\text{d}} T_{\text{ID}}^{0.5}}{W_2 W_3} + \frac{C_{\text{d}} T_{\text{ID}}^{0.5}}{W_2 W_3} \\
\]
patients actual post-dialysis dry body weight (DBW). Secondly, PNA was factored by the patients normal dry body weight (DBW\textsubscript{normal}). Normal dry body weight was defined as the median body weight of normal Americans adjusted for sex, frame size, height and age, described in the National Health and Nutrition Examination Surveys (NHANES) I and II [20]. Thirdly, PNA was factored by lean body mass (LBM). LBM was calculated from the percentage body fat as estimated from skinfold thickness measurements and post-dialysis body weight [21]. Fourthly, PNA was factored by normal lean body mass (LBM\textsubscript{normal}). Normal LBM was calculated from lean body mass and median triceps skinfold thickness of the NHANES reference population [20,21]. Fifthly, PNA was factored by a ‘normalized’ body weight (N). Normalized body weight was calculated from the patient’s UDV by dividing UDV by 0.58 for males and 0.55 for females [8].

### Nutritional status assessment

In all patients the anthropometric measurements were performed after the dialysis session by a single observer (WDK). One male patient refused anthropometry. DBW was determined as a measure of overall nutrition. Skinfold thickness was measured using a Harpenden skinfold caliper (British Indicators Ltd) at four sites. Biceps and triceps skinfold thickness was measured on the opposite arm of the A-V fistula. Subscapular and suprailiac skinfold thickness was measured on both sides and the values were averaged. Skinfolds were measured thrice to the nearest 0.50 mm and the averaged value was recorded. The sum of the four skinfolds thickness measurements were used in the body fat and LBM calculations [21]. Bone-free arm muscle area (AMA) on the opposite arm of the A-V fistula was calculated from the mid-arm circumference and triceps skinfold thickness (TSF) [20]. AMA was determined as a measure of somatic protein supplies. In order to assess the reproducibility of the anthropometric parameters the measurements were performed twice 4 weeks apart. The pre-dialysis plasma albumin concentration was used as a measure of the visceral protein status.

In order to assess the condition of the patient’s nutritional status the absolute values of DBW, TSF, and AMA were expressed as percentages of the NHANES reference values [20]. Relative dry body weight (%DBW = DBW/NDBW x 100%) was calculated as a measure of overall nutritional status. Relative TSF (%TSF) was calculated as a measure of body fat stores. Relative AMA (%AMA) was calculated as a measure of the somatic protein status.

In addition, the degree of nutrition was determined by a modified version of the nutritional index described by Harty et al. [11]. The index was derived from four subscores based on the values of DBW, TSF, AMA and the albumin concentration. A value of 3, 2, 1 or 0 was obtained for each anthropometric parameter (>15th, 10th–15th, 5th–10th or <5th percentile of the reference population, respectively) and for the albumin concentration (>40 g/l, 35–40 g/l, 30–35 g/l or <30 g/l, respectively). Summation of the four subscores defined an index of nutrition ranging from a maximum of 12 to a minimum of 0. Evident malnutrition was defined as a score ≤1 in at least two of the four subscores or a score ≤2 in at least three of the subscores.

### Statistical analysis

The mean of the three PNA measurements available for each patient were used in the statistical analyses. Results are presented as mean ± SD. Differences in PNA or nutritional status variables within patients were tested using paired Student’s t-tests and between patient groups using unpaired Student’s t-tests. Correlation was tested with Spearman’s correlation analysis. Reproducibility of the anthropometric parameters was evaluated by calculating the repeatability coefficient (RC) and the variation coefficient (VC) as recommended by Bland and Altman [22]. RC was defined as twice the SD of the differences between paired measurements, and VC as the SD of the differences divided by their average expressed as a percentage. A two-sided P-value of <0.05 was considered statistically significant.

### Results

In the total group mean actual PNA was 61 ± 13 g/d. Mean PNA in males (65 ± 13 g/d) was higher than in females (52 ± 6 g/d). Delivered Kt/V\textsubscript{eq} was 1.02 ± 0.15. The UDV in the total study group was 33.0 ± 6.0 l. UDV expressed as a percentage of DBW was 46 ± 6% and was higher in males (48 ± 5%) than in females (42 ± 6%) (P < 0.001).

The values of the various measures of body mass that were used to normalize PNA are shown in Figure 1A. In the total group, actual DBW (72 ± 11 kg) tended to be lower than normal DBW, derived from the NHANES reference population (75 ± 8 kg) (P = 0.05). Actual LBM (52 ± 8 kg) did not differ from normal LBM (52 ± 8 kg). As expected, mean values of actual DBW, LBM and N in males (75 ± 10 kg, 57 ± 5 kg and 61 ± 9 kg, respectively) were higher than that in females (66 ± 9 kg, 43 ± 5 kg and 50 ± 8 kg, respectively) (P < 0.001).

Actual PNA correlated with LBM (r = 0.63, P < 0.001), DBW (r = 0.52, P < 0.001) and AMA (r = 0.46, P < 0.001). The strongest correlation was observed between PNA and N (r = 0.77, P < 0.001).

Values of the normalized PNA variables are shown in Figure 1B, which not surprisingly is more or less the mirror image of Figure 1A. In the total group, actual DBW (0.85 ± 0.14 g/kg/d) tended to be higher than that PNA\textsubscript{DBWnormal} (0.81 ± 0.14 g/kg/d) (P = 0.05). PNA\textsubscript{LBM} (1.17 ± 0.19 g/kg/d) did not differ significantly from PNA\textsubscript{LBMnormal} (1.19 ± 0.21 g/kg/d). PNA\textsubscript{AMA} (1.06 ± 0.14 g/kg/d) was higher than PNA\textsubscript{DBW} and lower than PNA\textsubscript{LBMnormal}. Interestingly, PNA\textsubscript{AMA} in males (1.14 ± 0.22 g/kg/d) was significantly lower than in females (1.30 ± 0.15 g/kg/d) (P < 0.01). PNA\textsubscript{DBW}, PNA\textsubscript{DBWnormal}, PNA\textsubscript{LBM}, and PNA\textsubscript{AMA} did not differ between male and female patients.

Reproducibility of the anthropometric parameters was satisfactory (Table 1). No significant differences were observed for any anthropometric measurements performed 4 weeks apart. Measurement of LBM using anthropometry was very reproducible (VC, 1.4%).

The parameters of nutrition of the patients are shown in Table 2. DBW was below the 15th percentile of the reference population in 11 (19%) patients. TSF was below the 15th percentile of the reference population in 12 (21%) patients. For AMA this was the case in 15 (27%) patients. In the total patient group mean
SSSF (mm) 14.5 ± 0
NHANES reference values. Mean TSF, however, was different from DBW (%DBW: 95 ± 12%) and AMA (%AMA: 89 ± 22%) were below normal values (P < 0.05). In the
female patients AMA (%AMA: 114 ± 17%) was above normal, whereas TSF (%TSF: 79 ± 27%) was below normal (P < 0.01). The albumin concentration was < 40 g/l in 14 (25%) patients. Twenty-four (43%) patients had the maximum nutritional index score of 12. Seven (12%) patients had evident malnutrition. In these patients the index of nutrition (6.4 ± 1.3) ranged from 8 to 4.

Actual and normalized PNA values were related to the nutritional status of the patients (Table 3 and Figure 2). Actual PNA correlated positively with %TSF (r = 0.32), plasma albumin (r = 0.33) and the overall index of nutrition (r = 0.27) (Figure 2). PNA normalized to actual DBW correlated negatively with %DBW (r = -0.32) and tended to correlate negatively with the index of nutrition as well (r = -0.22, P = 0.10). Thus, PNA_{DBW} is relatively high in underweight and malnourished patients. PNA normalized to DBW_{normal} correlated positively with all nutritional parameters and with the index of nutrition as well (Figure 2). PNA_{LBM} correlated only with %AMA. However, PNA normalized to LBM_{normal} correlated positively with %DBW, %AMA and the index of nutrition (Figure 2). PNA_N did not correlate with any nutritional parameters or with the index of nutrition. PNA_{DBWnormal} and PNA_{LBMnormal} varied significantly in patients without any signs of malnutrition. In these patients there was no correlation between normalized PNA and Kt/V_{eq}, age or gender. Despite the significant positive correlation between PNA_{DBWnormal} and PNA_{LBMnormal} and the index of nutrition, the normalized PNA values in well-nourished patients showed overlap with the values in patients with evident malnutrition.

**Discussion**

The PNA has proved to be a useful estimate of dietary protein intake in dialysis patients. Since protein requirements are related to body size and body size varies considerably among haemodialysis patients due to differences in sex, height and age, PNA is normalized by various measures of body mass. Normalized PNA can only be considered a relevant and useful marker of protein intake in haemodialysis patients, if the normalized PNA values are positively related to nutritional status. 

In our study the nutritional status of the haemodialysis patients was assessed using anthropometry and comparing the anthropometric measures to the NHANES reference values. As anthropometric measurements are prone to large interobserver variation, anthropometry was performed by a single observer in all patients [9]. Reproducibility of these anthropometric measurements was satisfactory. Using the sum of all four skinfold measurements in the LBM calculation resulted in very reproducible LBM values. Comparing different measures of nutrition to normal reference values is an accepted method to assess the nutritional status in haemodialysis patients [8,9]. We are aware that the NHANES data set comprises American refer-

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**Table 1. Reproducibility of anthropometric measurements (M1 and M2) in 56 stable haemodialysis patients**

<table>
<thead>
<tr>
<th></th>
<th>Average of M1 and M2</th>
<th>Difference (M2 - M1)</th>
<th>RC</th>
<th>VC (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DBW (kg)</td>
<td>71.3 ± 10.4</td>
<td>0.93 ± 0.85</td>
<td>1.7</td>
<td>1.2</td>
</tr>
<tr>
<td>BSF (mm)</td>
<td>6.2 ± 3.1</td>
<td>0.14 ± 0.92</td>
<td>1.9</td>
<td>14.8</td>
</tr>
<tr>
<td>TSF (mm)</td>
<td>12.6 ± 5.4</td>
<td>0.16 ± 0.94</td>
<td>1.9</td>
<td>7.5</td>
</tr>
<tr>
<td>SSSF (mm)</td>
<td>14.5 ± 5.9</td>
<td>0.14 ± 0.97</td>
<td>1.9</td>
<td>6.7</td>
</tr>
<tr>
<td>SISF (mm)</td>
<td>17.5 ± 7.9</td>
<td>-0.47 ± 1.70</td>
<td>3.4</td>
<td>9.7</td>
</tr>
<tr>
<td>Sum SF (mm)</td>
<td>50.8 ± 18.0</td>
<td>-0.02 ± 2.50</td>
<td>5.0</td>
<td>4.9</td>
</tr>
<tr>
<td>MAC (cm)</td>
<td>29.5 ± 2.7</td>
<td>-0.04 ± 0.81</td>
<td>1.6</td>
<td>2.7</td>
</tr>
<tr>
<td>AMA (cm²)</td>
<td>43.7 ± 9.8</td>
<td>-0.50 ± 3.94</td>
<td>7.9</td>
<td>9.0</td>
</tr>
<tr>
<td>LBM (kg)</td>
<td>52.2 ± 8.2</td>
<td>-0.01 ± 0.71</td>
<td>1.4</td>
<td>1.4</td>
</tr>
</tbody>
</table>

DBW, dry body weight; BSF, biceps skinfold; TSF, triceps skinfold; SSSF, subscapular skinfold; SISF, supra iliac skinfold; MAC, mid arm circumference; AMA, upper arm muscle area; LBM, lean body mass; RC, reproducibility coefficient; VC, variation coefficient.
Table 2. Actual and relative parameters of nutrition and the distribution of haemodialysis patients over the nutritional index subscores

<table>
<thead>
<tr>
<th>Actual values</th>
<th>Relative values (%)</th>
<th>Distribution of subscores (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD (range)</td>
<td>Mean ± SD (range)</td>
</tr>
<tr>
<td>DBW (kg)</td>
<td>72 ± 11 (50–105)</td>
<td>97 ± 14 (69 ± 161)</td>
</tr>
<tr>
<td>TSF (mm)</td>
<td>13 ± 6 (4–30)</td>
<td>88 ± 31 (39 ± 168)</td>
</tr>
<tr>
<td>AMA (cm²)</td>
<td>44 ± 11 (27–86)</td>
<td>96 ± 24 (50 ± 156)</td>
</tr>
<tr>
<td>Albumin (g/l)</td>
<td>41 ± 3 (34–46)</td>
<td>—</td>
</tr>
</tbody>
</table>

DBW, dry body weight; TSF, triceps skinfold; AMA, upper arm muscle area. Relative values are expressed as percentage of the median value of the NHANES I/II reference population. N, number of patients in each category of nutritional index subscore.

Table 3. Correlation between parameters of nutritional status and PNA variables in 56 stable haemodialysis patients

<table>
<thead>
<tr>
<th></th>
<th>PNA</th>
<th>PNA_{DBW}</th>
<th>PNA_{DBW,normal}</th>
<th>PNA_{LBM}</th>
<th>PNA_{LBM,normal}</th>
<th>PNA_{N}</th>
</tr>
</thead>
<tbody>
<tr>
<td>%DBW</td>
<td>0.22</td>
<td>−0.32³</td>
<td>0.47³</td>
<td>0.05</td>
<td>0.50³</td>
<td>−0.09</td>
</tr>
<tr>
<td>%TSF</td>
<td>0.32³</td>
<td>−0.17</td>
<td>0.33³</td>
<td>0.02</td>
<td>0.22</td>
<td>−0.06</td>
</tr>
<tr>
<td>%AMA</td>
<td>−0.004</td>
<td>−0.13</td>
<td>0.34³</td>
<td>0.29³</td>
<td>0.55³</td>
<td>0.08</td>
</tr>
<tr>
<td>Albumin</td>
<td>0.33³</td>
<td>0.30³</td>
<td>0.26³</td>
<td>0.24</td>
<td>0.12</td>
<td>0.10</td>
</tr>
<tr>
<td>Index of Nutrition</td>
<td>0.27³</td>
<td>−0.22</td>
<td>0.33³</td>
<td>0.09</td>
<td>0.34³</td>
<td>0.02</td>
</tr>
</tbody>
</table>

%DBW, relative dry body weight; %TSF, relative triceps skinfold thickness; %AMA, relative arm muscle area. Relative values are expressed as percentage of the median values of the NHANES I/II reference population. r, Spearman’s correlation coefficient. *P < 0.05.

Fig. 2. Actual and normalized PNA values in relation to the index of nutrition. Shown is the regression line with 95% confidence limits. r, Spearman’s correlation coefficient.
ence values and that these values may not necessarily compare to normal values in Dutch patients. However, there is no data available about normal anthropometrical values in The Netherlands or Europe. We also used the plasma albumin concentration in the assessment of the nutritional status. Besides a marker of visceral protein nutrition, plasma albumin also is a negative acute-phase protein. Thus, both protein malnutrition and inflammation can reduce synthesis and hence plasma concentration [2]. By studying only stable haemodialysis patients without inflammatory diseases we tried to reduce the influence of an acute-phase response as much as possible. To divide the patients into groups with different degrees of nutrition, we used a modified version of the nutritional index, described by Harty et al. [11]. To prevent bias of one of the nutritional indices, we used measurements of overall body mass, body fat, somatic protein and visceral stores only once in our index of nutrition. We realize that dividing patients into different degrees of nutrition according to the nutritional index is arbitrary. Despite the shortcomings of the applied index of nutrition we think that it is a valid method to assess nutrition, since it represents measurements of overall body mass, body fat and somatic as well as visceral protein stores.

Not surprisingly, actual PNA correlated with the various measures of body mass, indicating that large patients eat more protein. PNA correlated strongly with LBM and AMA. As LBM and AMA reflect the somatic protein pool, the strong correlation of PNA with LBM and AMA probably emphasizes the mutual relationship between these protein parameters. This observation confirms the correlation between total urea nitrogen appearance and mid-arm muscle circumference in haemodialysis patients participating in the NCDS study [12]. In CAPD patients, actual PNA correlated with LBM \( (r = 0.53) \) and AMA \( (r = 0.51) \) as well [11]. A new finding for haemodialysis patients was the positive correlation between actual PNA and plasma albumin \( (r = 0.33) \), suggesting that actual protein intake is also associated with visceral protein stores. Our study confirms the correlation between actual PNA and plasma albumin \( (r = 0.29) \) in CAPD patients [11]. The strong correlation between PNA and N is probably mainly due to the fact that PNA and N are not independent variables, as both are calculated from UDV.

Normalized PNA can only be considered a relevant measure of protein intake, if the normalized PNA values are positively related to markers of nutritional status. The negative correlation between PNA\(_{\text{DBW}}\) and %DBW and the index of nutrition, indicate that PNA\(_{\text{DBW}}\) is relatively high in underweight and malnourished patients and relatively low in patients with a normal nutritional status. Thus, actual dry body weight is not an appropriate measure of body mass for normalizing protein intake. Interestingly, PNA\(_{\text{DBW}}\) did significantly correlate with albumin confirming the results obtained by Kayser et al. [2]. Positive correlations were observed between PNA\(_{\text{DBWnormal}}\) and all of the parameters of nutrition. These results are consistent with the observations made by Harty et al. [11] in CAPD patients. PNA\(_{\text{DBW}}\) was significantly higher in malnourished than in well-nourished CAPD patients. In addition, actual PNA and PNA\(_{\text{DBWnormal}}\) correlated positively with albumin and these were highest in well-nourished CAPD patients. Thus, DBW\(_{\text{normal}}\) is a more appropriate measure of body mass to normalize PNA than actual DBW. PNA\(_{\text{LBM}}\) correlated with none of the nutritional parameters, as was the case in CAPD patients [11]. In the calculations of normalized body weight (N) it is assumed that UDV is a fixed percentage of post-dialysis body weight that amounts to 58% in males and 55% in females. In our patients these fixed percentages overestimated UDV calculated from urea output in dialysate. UDV determined by urea kinetics was about 48% of post-dialysis body weight in males and 42% in females and ranged from 32% to 60%. These UDV values correspond to values observed in other studies [18,23,24]. Therefore, a normalized body weight calculated from fixed percentages derived from healthy subjects should not be used to normalize PNA, because of the invalidity of this body mass measure due to inter-individual variation and systematic overestimation. Using LBM\(_{\text{normal}}\) to normalize PNA appeared to be more appropriate than using actual LBM. PNA\(_{\text{LBMnormal}}\) showed the strongest correlation with %DBW, %AMA and the index of nutrition, whereas PNA\(_{\text{LBM}}\) did not correlate with most of the nutritional parameters.

The use of PNA\(_{\text{DBW}}\) or PNA\(_{\text{LBM}}\) in previous studies could be responsible for the fact that in these studies no association was observed between protein intake and nutritional status or mortality in dialysis patients. In the NCDS study no association between PNA\(_{\text{DBW}}\) and the nutritional status or patient outcome was found [13]. In contrast actual urea nitrogen appearance not standardized to body weight was positively associated with the nutritional status and patient outcome. Enia et al. [14] studying a group of patients treated by haemodialysis or CAPD for at least 4 months found no difference in PNA\(_{\text{DBW}}\) between well-nourished and malnourished patients classified using subjective global assessment. Morgenstern et al. [15] did not find any correlation between PNA\(_{\text{DBW}}\) and anthropometric parameters in 23 stable non-diabetic haemodialysis patients. In addition, PNA\(_{\text{DBW}}\) had no predictive value in two longitudinal studies on morbidity and mortality in haemodialysis patients [4,16]. Hospitalization or survival differed in dialysis patients with a low or a high PNA\(_{\text{DBW}}\) and PNA\(_{\text{DBW}}\) was not an independent factor affecting mortality [4]. In a group with elderly haemodialysis patients PNA\(_{\text{LBM}}\) did not predict mortality over 3 years follow-up [15]. We agree with the conclusion of Harty et al. [11] that normalizing PNA may flaw the nutritional value of PNA, particularly when actual or ‘normalized’ body weight is used.

Canaud et al. [10] made a plea for normalizing PNA by LBM that mainly consists of muscle mass. In our study, however, PNA\(_{\text{LBM}}\) did not correlate with most of the nutritional parameters. The authors suggested
that the LBM to DBW ratio can be used as an index of nutritional status of haemodialysis patients [10]. They argued that a ratio equal or above 0.70 indicates preserved nutritional status, while a ratio below 0.70 is indicative for wasting. We do not agree with them. The $LBM_{\text{normal}}$ to $DBW_{\text{normal}}$ ratio in our patient group, ranged from 0.58 to 0.83 with a mean of 0.69. In addition, the nutritional index was higher in patients with a $LBM/DBW$ ratio $<0.7$ ($11.2 \pm 1.0$) than in patients with a ratio $\geq 0.7$ ($9.8 \pm 2.2$) ($P < 0.05$). These results indicate that the $LBM/DBW$ ratio does not give any information about the nutritional status of individual patients, but only gives information about the relative amount of fat free mass. We therefore think that a simple classification using the $LBM/DBW$ ratio violates the true complexity of the nutritional status.

According to the nutritional index, the nutritional status was normal in 43% of the patients, whereas there was evident malnutrition in 12%. In male patients particularly muscle mass was reduced, reflected by the reduced AMA values. In female patients particularly fat mass was below normal, reflected by the low TSF values. The discrepancy in reductions of muscle mass and fat mass according to sex has been observed in other studies as well [12]. LBM mainly consists of muscle mass that corresponds to the major somatic protein status and endogenous nitrogen store. Interestingly, PNA normalized by $LBM_{\text{normal}}$ was significantly lower in males than in females. This low protein intake and consequently low nitrogen intake in males relatively to their $LBM_{\text{normal}}$ may be responsible for the susceptibility of male haemodialysis patients for developing muscle mass depletion.

It should be emphasized that in our patient group the relationship between the nutritional status and PNA is not very strong and normalized PNA values varied considerably in patients without malnutrition. Besides, normalized PNA values in well-nourished patients showed overlap with the values in malnourished patients. Consequently, normalized PNA was a poor indicator of nutrition. This might partly be due to the relatively small number of patients with evident malnutrition. Day-to-day variation in protein intake was probably not an important factor, since we determined PNA thrice over an 8 weeks period and used only averaged PNA values in the analyses. Differences in dialysis dose, age or gender were not responsible for the variation in PNA values. Possibly, variation in energy intake may partly explain the variation in PNA values in the well-nourished patients, as nitrogen balance is greatly dependent on energy intake [1]. Finally, it cannot be excluded that the nutritional status of well-nourished patients with a PNA in the lower range will deteriorate on the long-term.

Based on the results of our study, we feel that normalizing PNA by the normal value of the patient’s DBW or LBM is the most appropriate normalization method. Probably the $LBM_{\text{normal}}$ is preferable above $DBW_{\text{normal}}$ in view of the mutual relationship between protein intake and somatic protein stores. We agree with Harty et al. [11] that the positive association between $PNA_{DBW_{\text{normal}}}$ or $PNA_{LBM_{\text{normal}}}$ and the nutritional indices observed in our study may reflect the change in the denominator and not the PNA in itself. We therefore think that both normalized PNA values and actual PNA should be considered in studies on the relationship between protein intake and nutritional status. At present no studies are available that analyse the relationship between PNA normalized by $DBW_{\text{normal}}$ or $LBM_{\text{normal}}$ and patient outcome. Future studies are needed to reveal the relevance of normalizing PNA by $DBW_{\text{normal}}$ or $LBM_{\text{normal}}$ for predicting changes in nutritional status, morbidity and mortality. Some optimism regarding to the expected results appears to be justified in view of the data presented in our study.

In conclusion, normalization of PNA using normal values of dry body weight or lean body mass is the most appropriate method to adjust protein intake to body size in haemodialysis patients. In addition, we strongly recommend to evaluate actual PNA as well in studies that relate protein intake to patient outcome, because actual PNA is the purest estimate of protein intake in haemodialysis patients that is positively related to nutritional status.

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