Total body nitrogen predicts long-term mortality in haemodialysis patients—a single-centre experience.

Pradeep Arora¹, Boyd J. G Strauss², Danny Borovnicar², Dan Stroud², Robert C. Atkins¹ and Peter G. Kerr¹

¹Nephrology Unit and ²Body Composition Laboratory, Monash Medical Centre, Clayton, Victoria, Australia

Abstract

Introduction

Chronic dialysis is an established treatment for patients with end-stage renal disease. The number of new dialysis patients is increasing worldwide. However, the life-expectancy of these patients is still lower than that of the general population [1]. Dialysis patients have an age-adjusted death ratio that is estimated to be 4–5 times more than that of the general population. A considerable proportion of this high mortality in these patients can be explained by a high prevalence of non-renal comorbid conditions such as diabetes mellitus and cardiovascular disease [2]. In recent years, there has been a growing realization that malnutrition in dialysis patients may be associated with poor outcome. Most studies agree that the effect of malnutrition on morbidity and mortality in dialysis patients is substantial. However, most of these studies are retrospective and cross-sectional with limited long-term follow up [3,4]. Moreover, traditional methods of nutritional assessment lack reproducibility and are prone to patient and observer error. We have shown previously that anthropometry underestimates body protein stores in haemodialysis patients and in vivo neutron activation analysis (IVNAA) of total body nitrogen (TBN) is more accurate in the estimation of mortality [5]. This study was designed to assess the predictive value of serum albumin, and total body nitrogen by IVNAA on the long-term morbidity and mortality in haemodialysis patients.

Subjects and methods

The study was approved by the Human Ethics Committee of Monash Medical Centre. Ninety-one patients on haemodialysis between 1989 and 1991 under the supervision of Monash Medical Centre consented and were subjects of the study. All patients had been on haemodialysis for more than 1 month and had had no intercurrent illness in the preceding month. The only other selection criteria were the preparedness to consent to the study and the physical ability to attend for the investigations. Patients were dialysed for 4–5 h,

Original Article

Background. It has been estimated that 30–50% of adult haemodialysis patients have moderate to severe malnutrition. We have previously shown that estimation of total body nitrogen, expressed as a nitrogen index (NI) by in vivo neutron activation analysis (IVNAA) is an accurate tool for estimating total body protein in dialysis patients. It is not clear whether the nitrogen index is predictive of mortality and morbidity in dialysis patients.

Methods. We studied the long-term predictive value of nutritional assessment by IVNAA and serum albumin on mortality and morbidity (including infection episodes requiring hospital admission, ischaemic heart disease (IHD), cerebrovascular or peripheral vascular disease (PVD)). Seventy-six chronic haemodialysis patients were initially studied between 1989 and 1991, with a minimum follow-up of 5 years. The mean age of the patients was 48.3 years (range 21–76). Patients were divided into two groups, group I, n=22, had a NI≤0.8 (NI≤0.8 represents protein malnutrition) and group II, n=54, had a NI>0.8.

Results. Fifteen patients in group II died in the follow-up period compared to nine from group I (P<0.05), but NI≤0.8 did not predict vascular or infective morbidity. Serum albumin≤35 g/day predicted over all mortality (P<0.05) as well as infection episodes (P<0.001). When patients above the age of 50 years were analysed, NI did predict mortality (P<0.05) but serum albumin did not, while the age of>50 itself was a strong predictor of mortality (P<0.001).

Conclusion. We conclude that NI≤0.8 is predictive of long-term mortality. This reinforces the view that low body protein stores are predictive of increased mortality in dialysis patients and that the serum albumin is predictive of mortality because of its reflection of protein stores.

Keywords: haemodialysis; mortality; nutrition; total body nitrogen

© 1998 European Renal Association–European Dialysis and Transplant Association
three times a week, using a hollow-fibre dialyser containing either cuprophane or cellulose acetate membranes. Glucose-free acetate or bicarbonate-buffered dialysate was used at the initiation of this study. There was a gradual transition to the exclusive use of bicarbonate-buffered dialysate over the course of the study. Patients routinely used aluminium, magnesium, and calcium-containing phosphate binding agents, and iron supplementation. All patients also received a daily multivitamin supplement and weekly folic acid (5 mg). Erythropoietin was also given whenever considered to be essential, after mid-1990. All patients had been instructed in a diet with a caloric intake aiming to normalize body mass index. This included a dietary protein intake (as recorded by 3-day recall) of 1.0 ± 0.3 g/kg/day and a total caloric intake of 35–50 kcal/kg/day. Prior to the initiation of dialysis, patients had been instructed in a 0.8 g/kg/day protein-restricted diet.

Ninety-one patients (56 male, 35 female) were enrolled in the study with a mean age of 49 years (range 24–76 years). Of the 91 patients, 76 who had had a minimum follow-up of at least 5 years were the subjects of the study and the rest were excluded (the remaining 15 had either a shorter follow-up period or were lost to follow-up). The primary cause of chronic renal failure was glomerulonephritis in 37, diabetes mellitus 8, reflux nephropathy 8, analgesic nephropathy 3, hypertension and vascular disease 5, polycystic kidney disease 9, and others 6.

Twenty-seven of these 76 patients had had a previous failed kidney transplant. During their transplanted time they had received prednisolone at a daily dose of 20–30 mg. Nine patients had been clinically nephrotic prior to commencing dialysis.

**Anthropometry—Height, weight, BMI**

Skin-fold thickness was measured using a Harpenden calliper at the biceps, triceps, subcapular, and supra iliac regions and percentage body fat was calculated according to the formulae of Durnin and Womersley [5].

Blood was taken immediately prior to dialysis for measurement of serum albumin (bromocresol purple), urea, and creatinine after the longest interdialytic period. In short, after neutron activation, prompt nitrogen and hydrogen gamma emissions were counted and hydrogen used as an internal standard. Body nitrogen content was then calculated as previously described [5]. Total body nitrogen is then reported as a nitrogen index (NI), normalized to the general population. The body protein content is calculated as 6.25 × body nitrogen content.

All these patients were followed up 1–3 monthly. The following parameters were noted: death, episodes of infection requiring admission, anginal episodes, myocardial infarction, clinically evident peripheral vascular disease and cerebrovascular disease.

**Statistical analysis**

Statistical analysis was performed using the Prism graphics and statistics package (Graph Pad Software—Prism version 2.0, San Diego, USA) on an IBM-compatible personal computer. Comparisons between two study populations were made by the use of the Fisher exact test. Observed survival was computed by the Kaplan–Meier method of survival curve comparison.

Nitrogen index ≤ 0.8 was considered to be a marker of malnutrition as previously described [5] and based on the fact that this is 2 SD below the norm for the non-dialysis/non-renal failure population. Thus patients with NI > 0.8 were compared with NI ≤ 0.8 for different morbidity and mortality. Similarly, morbidity and mortality was compared with patients having serum albumin ≤ 35 g/l vs > 35 g/l and serum albumin ≤ 40 g/l vs > 40 g/l at the time of the initial study.

**Results**

Ninety-one patients (56 male, 35 female) were enrolled in the study. Of the 91 patients, 76 who had had a minimum follow-up of at least 5 years were the subjects of the study and the rest were excluded (the remaining 15 having either a shorter follow-up period or were lost to follow-up). The mean pre-dialysis urea was 30.0 ± 8.0 mmol/l and the mean serum albumin was 42.0 ± 4.7 g/l. The mean haemoglobin level at the time of study was 9.3 ± 2.8 g/dl, this being prior to the introduction of erythropoietin.

After a mean follow up of 76 months (range 60–95 months) 24 patients had died, 15 had been transplanted, and five patients had started peritoneal dialysis. Causes of death in the 24 patients were infection (5), myocardial infarction or other direct cardiac causes (7), cerebrovascular disease (1), cessation of dialysis (6), malignancy (2), and various others (3).

On follow up of the non-fatal morbid events, 44 patients had infection episodes requiring admission, with 17 patients having more than one admission. Twelve patients had myocardial infarctions, six had cerebrovascular accidents and 16 had peripheral vascular disease.

The mortality and number of morbid events were compared between patients who had a NI ≤ 0.8 (n = 22) to those who had a NI of > 0.8 (n = 54). As is shown in Table 1, there was no significant difference in episodes of morbidity between the two groups. By the Kaplan–Meier method, NI ≤ 0.8 predicted mortality at 6 years, P < 0.05, hazard ratio 2.62, 95% CI 1.21–7.95 (Figure 1). The prognosis of dialysis patients is different from patients after kidney transplantation. Fifteen of 76 patients were subsequently transplanted. We analysed data on survival after excluding these 15 patients. Patients with a NI ≤ 0.8 still had significantly higher mortality as compared to those with a NI of ≥ 0.8.

Similarly, episodes of morbidity and mortality were compared between patients who had serum albumin ≤ 35 g/dl vs those with > 35 g/dl (Table 2). Serum albumin ≤ 35 g/dl was associated with higher hospital admissions due to infections. Serum albumin ≤ 35 g/dl also predicted mortality on long-term follow-up (P < 0.05, as assessed by Kaplan–Meier survival curves (Figure 2a)). In contrast, serum albumin < 40 g/dl was not predictive of morbidity or mortality (Table 3, Figure 2b).

Age may also be a factor determining prognosis and mortality. There was no correlation between age and nitrogen index (Pearson’s r = 0.112, P = 0.34). Thirty-
Table 1. Nitrogen index and morbidity. Absolute number of patients with morbid events during the period stratified according to nitrogen index (NI) above or below 0.8

<table>
<thead>
<tr>
<th>Event</th>
<th>NI &gt; 0.8 (n=54)</th>
<th>NI &lt; 0.8 (n=22)</th>
<th>P value</th>
<th>Relative risk</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Infection</td>
<td>33</td>
<td>13</td>
<td>1.0</td>
<td>1.03</td>
<td>0.69–1.56</td>
</tr>
<tr>
<td>2. Angina</td>
<td>15</td>
<td>6</td>
<td>1.0</td>
<td>1.09</td>
<td>0.45–2.28</td>
</tr>
<tr>
<td>3. Myocardial infarction</td>
<td>9</td>
<td>3</td>
<td>1.0</td>
<td>1.2</td>
<td>0.36–4.10</td>
</tr>
<tr>
<td>4. Cerebrovascular accident</td>
<td>5</td>
<td>3</td>
<td>0.46</td>
<td>2.0</td>
<td>0.26–16.41</td>
</tr>
<tr>
<td>5. Peripheral vascular disease</td>
<td>13</td>
<td>3</td>
<td>0.37</td>
<td>1.7</td>
<td>0.55–5.5</td>
</tr>
</tbody>
</table>

Table 2. Serum albumin and morbidity. Absolute number of patients with morbid events during the study period stratified according to serum albumin (S. Alb) above or below 35 g/l

<table>
<thead>
<tr>
<th>Event</th>
<th>S. Alb &gt; 35 g/l (n=61)</th>
<th>S. Alb &lt; 35 g/l (n=15)</th>
<th>P value</th>
<th>Relative risk</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Infection</td>
<td>32</td>
<td>12</td>
<td>0.03</td>
<td>1.65</td>
<td>0.46–1.93</td>
</tr>
<tr>
<td>2. Angina</td>
<td>19</td>
<td>2</td>
<td>0.21</td>
<td>2.3</td>
<td>0.61–10.95</td>
</tr>
<tr>
<td>3. Myocardial infarction</td>
<td>11</td>
<td>1</td>
<td>0.67</td>
<td>2.3</td>
<td>0.33–16.6</td>
</tr>
<tr>
<td>4. Cerebrovascular accident</td>
<td>5</td>
<td>1</td>
<td>1.00</td>
<td>1.5</td>
<td>0.20–12.16</td>
</tr>
<tr>
<td>5. Peripheral vascular disease</td>
<td>12</td>
<td>4</td>
<td>0.72</td>
<td>0.73</td>
<td>0.28–1.90</td>
</tr>
</tbody>
</table>

Table 3. Serum albumin and morbidity. Absolute number of patients with morbid events during the study period stratified according to serum albumin (S. Alb) above or below 40 g/l

<table>
<thead>
<tr>
<th>Event</th>
<th>S.Alb &gt; 40g/l (n=44)</th>
<th>S.Alb &lt; 40g/l (n=32)</th>
<th>P value</th>
<th>Relative risk</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Infection</td>
<td>24</td>
<td>20</td>
<td>0.63</td>
<td>0.87</td>
<td>0.60–1.28</td>
</tr>
<tr>
<td>2. Angina</td>
<td>11</td>
<td>10</td>
<td>0.68</td>
<td>0.80</td>
<td>0.39–1.65</td>
</tr>
<tr>
<td>3. Myocardial infarction</td>
<td>6</td>
<td>6</td>
<td>0.75</td>
<td>0.72</td>
<td>0.26–2.05</td>
</tr>
<tr>
<td>4. Cerebrovascular accident</td>
<td>4</td>
<td>2</td>
<td>1.0</td>
<td>1.4</td>
<td>0.28–7.4</td>
</tr>
<tr>
<td>5. Peripheral vascular disease</td>
<td>8</td>
<td>8</td>
<td>0.57</td>
<td>0.7273</td>
<td>0.31–1.73</td>
</tr>
</tbody>
</table>

Fig. 1. Kaplan–Meier plot of patient survival according to nitrogen index. All patients were followed for a minimum of 60 months (range 60–95 months).

Discussion

Several different factors may influence mortality in dialysis patients. Of the different parameters studied in this paper, serum albumin ≤35 g/dl, NI ≤0.8, and age > 50 years were predictive of long-term mortality when all patients included. When patients over 50 years of age were studied separately, NI ≤0.8 was predictive of mortality while serum albumin was not.

while 13 of 22 patients with a serum albumin of >35g/dl died (P=0.64, relative risk 0.75, 95% CI 0.3349–1.689).

The effect of age alone on long-term survival, irrespective of serum albumin and NI, was studied. Seventeen of 31 patients over the age of 50 years died compared to 7/45 with ages <50 years, P<0.01, relative risk 3.525, 95% CI (1.68–7.479). (Figure 4).

The patients with pre-existing nephrotic syndrome did not fare any differently from the group as a whole.

The nitrogen index results for this group ranged from 0.45 to 1.26, with five having values below 0.8; survival was also similar.

one patients were over 50 years of age. Eleven of these 31 patients had a NI of ≤0.8 while 20 had a NI > 0.8. Nine of the 11 patients with a NI ≤0.8 died in the 6-year follow-up period while 8/20 with a NI >0.8 died (Figure 3) P≤0.05, with relative risk 2.84 95% CI 1.21–3.745). The influence of serum albumin in patients over 50 years was also studied: 9/31 patients had a serum albumin of ≤35, of whom four died,
However, serum albumin $\leq 35$ g/dl was associated with increased hospital admissions due to infection episodes. Approximately 1/3 of the haemodialysis patients died over 5 years, leading to an annual mortality of 6.5%, which is lower than the average mortality rate in Australia, at 11% p.a. [6]. The reasons for the good survival in this group of patients may relate to better dialysis, a low number of diabetic patients and probably low age at onset of dialysis; particularly as age was also predictive of death. It should be noted that the patients were not selected for the trial with any bias beyond their ability to attend for the nutritional assessments. It has been reported that 5 years survival is 15% lower in patients aged $>65$ years compared to younger age groups [2]. The mean age of our patients was 49 years. Diabetics also have poorer survival than non-diabetics; our group had low numbers of diabetics compared to the often quoted North American studies [1,3,4].

Malnutrition is present in 13–70% of haemodialysis patients, depending upon the nutritional parameters studied [7–11]. Judged by NI $\leq 0.8$ and serum albumin $\leq 35$ g/dl as markers of poor nutritional state, malnutrition may be present in 29 and 20% of the patients in this study respectively. As previously reported, this suggests that NI is a more sensitive indicator of malnutrition [5]. Several predictors of survival on renal replacement therapy have been described in short-term and cross-sectional studies. These include demographic characteristics such as age, gender and diabetic status, nutritional status as assessed by albumin, prealbumin, creatinine, cholesterol, IGF1, and dialytic factors such as dose of dialysis [12,13].

Serum albumin has been extensively utilized as a nutritional index in many published reports, primarily due to its easy availability [14–19]. Several studies in haemodialysis patients have indicated that a low albumin concentration is associated with poor prognosis. In a large retrospective study by Lowrie and Lew [3], who analysed laboratory data from more than 12,000 haemodialysis patients treated at National Medical Care Inc. centres in the United States, low serum albumin was the marker most highly associated with a high probability of death with a graded risk for values lower than 40 g/l. (The odds ratio for death was 1.48 for a serum albumin concentration of 3.5–3.9 g/dl and 3.13 for a concentration of 3.0–3.4 g/dl [3].) Similar results were shown by Iseki et al. in Japanese patients [14]. Although the nutritional state is an important regulator of albumin synthesis, it may be affected by factors other than nutrition. Conditions that promote an acute-phase response such as infection or trauma can induce a
prompt and significant decrease in the serum albumin concentration. In this context a decrease in serum albumin concentration often reflects the degree of illness and inflammation rather than the overall nutritional status [20]. The utilization of serum albumin as a nutritional index is further complicated when one considers that serum albumin has a half-life of 20 days and its serum concentration is adjusted by intravascular and extravascular shifts as well as compensatory changes in synthesis and catabolism; its response as a visceral protein to insidious malnutrition is rather late in the course of the disease and to a variable extent [21–24].

In this study, serum albumin \( \leq 40 \text{ g/dl} \) was not associated with an increased risk of death on long-term follow-up, while serum albumin \( \leq 35 \text{ g/dl} \) was associated with an increased risk of death when studied in all patients, but not when analysed in patients with age \( > 50 \) years. Low serum albumin did not predict mortality, though age \( > 50 \) years in this study was associated with a very high risk of mortality. Although a recent study has suggested that enrolment serum albumin is a useful predictor of long-term survival in haemodialysis and peritoneal dialysis patients [25], our data suggests that serum albumin may not be a good predictor of mortality in the long term (compared to the shorter follow-up of Lowrie and Lew [3]). Further, whilst albumin has been demonstrated to be a strong predictor of mortality, this does not necessarily mean it reflects the nutritional status of the patient.

The established gold standard for the measurement of body protein is the direct measurement of protein stores by prompt \textit{in vivo} neutron activation analysis [26,27]. The technique was initially introduced in 1973 [28] and has been shown to correlate directly with muscle mass [26,27]. It exposes patients to a biological and vascular morbidity.

Because nitrogen has a direct relationship with protein (6.25 g of protein/g nitrogen), the measurement of nitrogen accurately reflects body protein mass. Unlike the serum albumin, NI is not subject to day-to-day variation and reflects long-term nutritional changes. Pollock et al. [29,30] studied the influence of TBN by IVNAA in dialysis patients, and found that patients having a TBN < 0.8 had a 48% probability of death within 12 months. Further they also found that patients who remained alive had a significantly higher NI compared with those who died. In this study we took only those haemodialysis patients who had completed more than 5 years of follow-up since the initial TBN assessment and found that at a mean follow up of 76 months, NI \( \leq 0.8 \) was predictive of mortality. When we analysed those patients over 50 years of age (\( n = 31 \)), NI \( \leq 0.8 \) was again predictive of mortality (\( P < 0.001 \)). Thus, unlike the serum albumin, the nitrogen index is a strong predictor of mortality regardless of the age of the patient.

It is generally accepted that a suboptimal nutritional status is associated with increased morbidity and may impair rehabilitation and quality of life. Although there are few studies on the influence of serum albumin on morbidity [15,31] there is very little information on the value of the NI in predicting morbid events. We studied the influence of both in this paper. Serum albumin was associated with a higher rate of infection requiring hospital admission, but it did not predict vascular morbidity. Nitrogen index \( \leq 0.8 \), indicating malnutrition, was not predictive of any of the morbidity events studied. This could be explained by the fact that serum albumin could have been a marker of a concurrent medical illness rather than being predictive of infection. Similarly, Spiegel et al. [15] found that serum albumin was an indicator of increased hospitalization in PD patients but when they compared serum albumin in patients who had infectious episodes vs those who did not, they found no significant difference in the serum albumin level.

Foley et al. [31] studied the relationship of hypoalbuminaemia and cardiac morbidity in patients on haemodialysis and peritoneal dialysis. They found hypoalbuminaemia was independently associated with echocardiographic abnormalities, \textit{de novo} ischaemic heart disease, and recurrent ischaemic heart disease, and moreover their analysis suggests that low serum albumin preceded these cardiac events and not \textit{vice versa} (but in peritoneal dialysis patients, low serum albumin levels were not associated with ischaemic heart disease). We studied the incidence of angina, myocardial infarction, cerebrovascular, and peripheral vascular disease in patients with serum albumin \( > 35 \text{ vs } < 35 \), serum albumin \( > 40 \text{ vs } < 40 \), and NI \( > 0.8 \text{ vs } < 0.8 \) and did not find any of these parameters predicted these vascular events. This difference in results could be either due to a lower number of patients, lower number of vascular morbidity events, or it may be possible that there may not be any cause-and-effect relationship between malnutrition and vascular morbidity.

The nutritional status of patients entering a dialysis programme may be influenced by the underlying cause of renal failure, particularly if nephrosis is evident. In this group of patients nephrosis did result in five of nine patients having nitrogen index values below 0.8; those who did not, they found no significant difference in serum albumin, NI is not subject to day-to-day variation and reflects long-term nutritional changes.

The nitrogen index is not a widely available technique and as such will remain a research tool. However, the results in this study reinforce the view that (low) body protein stores are predictive of mortality in dialysis patients. The serum albumin has been widely popularized as being predictive of mortality in dialysis patients but it is not an accurate indicator of nutrition, being subject to many other influences. The nitrogen index results presented here add credence to the view that albumin predicts mortality via protein stores.

References


