Relationship between nitrogen balance, protein, and energy intake in haemodialysis patients

A. Alvestrand and A. Gutierrez
Department of Clinical Sciences, Karolinska Institute, Stockholm, Sweden

Introduction
Wasting and other signs of protein-energy malnutrition are present in a large proportion of patients with chronic renal failure [1]. Although the nutritional status may improve in some patients after haemodialysis treatment is started, it deteriorates in others during long-term treatment. Indeed, energy malnutrition, manifest as reduced subcutaneous fat stores (low triceps skinfold thickness), has been found in 20–60% of haemodialysis patients and signs of protein malnutrition, such as low serum albumin and low serum transferrin, have been reported in 15–70% of patients. A large number of studies have documented muscle-wasting and reduced muscle mass, as assessed by anthropometric measurements and total body nitrogen determinations as well as by the observation of low alkali-soluble protein in muscle in relation to DNA content (an index of muscle cell size) [1].

Impaired nutritional status, generally considered to be associated with increased morbidity and mortality, may hinder rehabilitation and impair the quality of life. Acchiardo et al. [2] reported that a protein intake <0.65 g/kg BW/day (estimated from urea appearance rate) was associated with a high mortality rate (14%) and a high rate of hospitalization (2.8 days/patient/year), as compared to no mortality and hospitalization rate of 1.9 days/patient/year in a patient with a protein intake of 1.2 g/kg BW/day. Similarly the National Cooperative Dialysis Study, using urea kinetic modelling to assess the protein catabolic rate (PCR), concluded that a protein intake of <0.8 g/kg BW/day, as measured by PCR, was associated with high rates of morbidity and mortality [3]. Using different protein-energy malnutrition scores, Bilbrey and Cohen [4] and Markmann [5] observed increased mortality rates in clearly malnourished patients than in patients without or with less severe signs of malnutrition. The central role played by malnutrition as a risk factor in haemodialysis patients was further confirmed by Lowrie and Lew [6] who, in a survey of 12000 haemodialysis patients, found that low predialysis serum creatinine concentrations (a marker of scanty muscle mass) and low predialysis urea (indicating a deficient protein intake) were associated with a high risk of death. In addition, the annual risk of death was greater in patients with serum albumin less than 30 g/liter than in those with a normal concentration. In haemodialysis patients, defects in cell-mediated immunity and impaired delayed cutaneous hypersensitivity have been shown to be a reversible manifestation of protein-energy malnutrition, suggesting that human malnutrition may entail the risk of infection and sepsis [7].

Protein and energy requirements in maintenance haemodialysis

Protein requirements
In healthy subjects the daily protein requirement is ~0.6 g/kg BW. However, there is a considerable inter-individual variability due to such factors as age, genetic differences, physical activity, and nutrient sources. To correct for this variability the safe intake should be estimated at 0.75 g/kg BW [8]. The protein requirements in non-dialyzed uraemic patients is generally estimated to be similar to that in healthy subjects, or less if the diet is supplemented with essential amino acids or their keto acids [9]. However, signs of malnutrition have been observed in well-rehabilitated dialysis patients with a daily intake of approximately 1 g protein/kg BW/day, implying that protein requirements are substantially increased in this category of patients. Available nitrogen balance data indicate that the dietary protein should be prescribed at >1.2 g per kg BW/day to provide a safe intake for patients treated by maintenance HD [10]. Although some patients may require less protein to maintain nitrogen equilibrium, it is difficult or impossible to identify those patients with lower requirements.

Energy requirements
There is no evidence that the energy requirements of haemodialysis patients differ from those of normal...
Nitrogen balance, protein, and energy intake in haemodialysis patients

subjects. Nevertheless, a high energy intake is essential for the utilization of protein, as demonstrated by a study of Slomowitz et al. [11] performed in haemodialysis patients who were prescribed diets with varying energy content but a constant protein content (1.1–1.2 g protein/kg BW/day). Diets providing an energy intake of <35 kcal/kg BW/day resulted in negative nitrogen balance, whereas diets providing 35 and 45 kcal/kg BW/day, respectively, resulted in neutral and slightly positive nitrogen balances. On the basis of these data, an energy intake of ~35–40 kcal/kg BW/day have been recommended to patients on chronic haemodialysis. The results of several studies in haemodialysis patients indicate that protein and energy intakes less than the recommended requirements may be an important contributory cause of wasting. A study by Jacob et al. [12] showed that 55% of haemodialysis patients had an energy intake <30 kcal/kg BW/day, whereas 45% of the patients had a protein intake <1 g/kg BW/day.

Catabolic factors in haemodialysis patients

The observation that haemodialysis patients require more protein than normal subjects, suggests that metabolic factors, which are not fully corrected by haemodialysis treatment, enhance protein catabolism or impair protein synthesis. In addition, there is evidence that the dialytic procedure per se induces net protein catabolism. The catabolic effect of uraemia and haemodialysis has been the subject of recent reviews [1]. The following is a brief discussion on the major factors contributing to enhanced catabolism in haemodialysis patients.

Inadequate energy and protein intake

Anorexia is a prominent symptom in advanced renal failure and may be due to the prescription of unpalatable or inadequate diets, altered taste, heavy medication, anaemia, post-dialysis fatigue, depression, and other psychosocial or socioeconomic factors. Many patients, it seems, lose their appetite and reduce their protein and energy intakes spontaneously. Patients participating in the MDRD study in US showed a tendency to reducing their protein intake even when GFR was 25 ml/min or greater, i.e. prior to the appearance of overt uraemic symptoms, and they reduced their intake further as renal insufficiency advanced towards end-stage renal failure. A parallel decrease in energy intake was observed in association with a deterioration of various nutritional parameters, such as body weight, fat mass, serum albumin, and transferrin [13]. The initiation of dialysis treatment generally leads to improved appetite in uraemic patients, implying that some substance(s) that are removed by dialysis may contribute to anorexia. On the other hand, however, factors related to the dialysis procedure may have an anorectic effect. Nausea and vomiting during and immediately after haemodialysis, which are frequently associated with cardiovascular instability, and post-dialysis fatigue may reduce the food intake on the days when dialysis is performed. In the National Cooperative Dialysis Study it was found that haemodialysis patients with a shorter dialysis-time and higher BUN had a low urea appearance rate, reflecting a low protein intake [3]. This suggests that the adequacy of dialysis therapy may directly influence nutrient intake; indeed, appetite and nutritional status may be major indexes of the adequacy of dialysis. An insufficient dose of dialysis can lead to an adaptive decrease in food intake. In keeping with this, the increase in the dose of dialysis (Kt/V) has been reflected in a spontaneous increase in protein intake (PCR) of individual patients [14].

Little is known of what uraemic toxins may cause anorexia. However, Bergström et al. have recently reported results suggesting that toxic middle molecule fractions that are normally excreted in the urine and accumulate in uraemia may suppress appetite in an animal model [15].

Metabolic acidosis

Acidosis has recently been identified as an important catabolic factor in renal failure [16]. Although the acidosis may be corrected in haemodialysis patients by oral and dialytic supplements of bicarbonate the prevalence of moderate acidosis tends to be high in haemodialysis patients and acid-base balance should be kept under strict observation. Nitrogen balance studies in non-dialysis uraemic patients have shown that correction of the acidosis leads to significant decrease in the blood urea nitrogen and in improvement in the nitrogen balance [17]. In normal human subjects, studies using 13C-leucine infusion have demonstrated that induction of metabolic acidosis leads to increased rates of protein degradation and accelerated amino acid oxidation [18]. In nondialyzed uraemic patients the correction of metabolic acidosis resulted in decreases in protein degradation and leucine oxidation. However, in a study on haemodialysis patients the net catabolic effect of acidosis was shown to impair protein synthesis rather than increase protein breakdown [19].

In rat studies, May et al. [20] found that the induction of metabolic acidosis in normal rats results in increased urinary nitrogen excretion and enhanced protein breakdown in isolated skeletal muscle. Similarly, in rats with CRF, metabolic acidosis causes excess muscle protein breakdown, which can be inhibited by the correction of acidosis with the administration of bicarbonate. In acidic haemodialysis patients (serum-bicarbonate <18 mol/l), leucine kinetic studies performed showed a decreased protein synthesis rate and a marked increase in the leucine oxidation rate in dialysis patients, as compared to normal subjects [18]. The results of recent studies on isolated skeletal muscle extracts suggest that acidosis induces catabolism of the branched-chain amino acids (isoleucine, leucine and valine) through both activation and increased availabil-
concentration of serine and low concentrations of several non-essential amino acids but low abnormalities of amino acid metabolism. Typical findings in the plasma aminogram includes high concentrations of several non-essential amino acids but low concentration of serine and low concentrations of essential amino acids, including the branched-chain amino acids. The plasma concentration of tyrosine is low. In muscle, which contains the largest pool of free amino acids in the body, the concentrations of valine, tyrosine and serine are typically found to be low. Some of these abnormalities may depend on suboptimal nutrition, whereas others are caused by loss of metabolizing renal tissue or uraemic toxicity [9]. As discussed above acidosis may have a negative effect on branched-chain amino acid metabolism [21,23]. It is reasonable to believe that some of these amino acid abnormalities may lead to suboptimal nitrogen utilization, although at present the mechanisms are not well understood.

Conclusions

There is a high prevalence of malnutrition in haemodialysis patients. Important contributory factors are anorexia, acidosis and other factors caused by or related to the uraemic syndrome as well as factors associated with the dialysis treatment in itself (Table 1). The clinical challenge is to correct potentially catabolic factors, carefully supervise the patients’ nutritional status and to encourage patients to eat enough protein and calories to compensate for unavoidable dialysis-induced nutrient losses.

<table>
<thead>
<tr>
<th>Table 1. Factors contributing to energy–protein malnutrition in haemodialysis patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inadequate energy and protein intake</td>
</tr>
<tr>
<td>Ureaemic toxicity</td>
</tr>
<tr>
<td>Metabolic acidosis</td>
</tr>
<tr>
<td>Amino acid abnormalities</td>
</tr>
<tr>
<td>Intercurrent illness (infection, sepsis)</td>
</tr>
<tr>
<td>Physical inactivity</td>
</tr>
<tr>
<td>Catabolic effects of haemodialysis</td>
</tr>
<tr>
<td>Loss of amino acids and glucose to the dialysate</td>
</tr>
<tr>
<td>Interaction between blood and dialysis membranes</td>
</tr>
<tr>
<td>Endotoxins</td>
</tr>
</tbody>
</table>

References

Nitrogen balance, protein, and energy intake in haemodialysis patients


