Influence of different treatments and schedules on the factors conditioning the nutritional status in dialysis patients

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Malnutrition in dialysis patients

Protein–energy malnutrition is present in a large proportion of maintenance dialysis patients [1–4]. In various studies of haemodialysis (HD) patients [5–9], a low percentage ideal body weight or low body mass index was found in 10–30%, a low triceps skinfold thickness in 20–60%, and a low arm muscle circumference in 0–44%. Low serum albumin was observed in 13–70% and low transferrin in 30–60% of HD patients. There is also a high prevalence of protein–energy malnutrition in continuous ambulatory peritoneal dialysis (CAPD) patients, with 18–56% of CAPD patients showing anthropometric and biochemical evidence of malnutrition [10–12]. In a multi-centre study, comparing 609 HD and 138 CAPD patients, Nelson et al. [13] noted no difference in nutritional status between the two groups. However, Cianciaruso et al. found that in patients <65 years of age, malnutrition was more likely to be present in CAPD patients than in HD patients. On the other hand, maintenance HD patients older than 76 years of age were more likely to be malnourished than CAPD patients [14].

It is generally accepted that suboptimal nutritional status is associated with increased morbidity and may impair rehabilitation and the quality of life [3,5,15]. A number of studies have documented the increased mortality and morbidity in dialysis patients suffering from malnutrition [16–18]. Lowrie and Lew [6] reported that there was a strong association between a low serum albumin concentration and mortality in a population of >12,000 HD patients. Similar observations have been made in CAPD patients. The CANUSA study showed that the CAPD technique failure and hospitalization rates were increased with decreased serum albumin concentration [19,20], and, furthermore, the nutritional status was a strong independent predictor of patient survival. Similar results were reported in HD patients [21]. Foley et al. found that hypoalbuminaemia is strongly associated with cardiac diseases both in HD and CAPD patients. The authors suggested that low serum albumin may be a risk factor for developing cardiac diseases in dialysis patients [18].

It is interesting to note that in the end-stage renal disease (ESRD) patient, malnutrition is rarely documented as a cause of death. However, in a multi-centre study, Maiorca et al. found that malnutrition is an important cause of death both in CAPD and HD patients [22]. Furthermore, malnutrition may have contributed to the high death rate, due to infection, and it may have been partly the reason why some of the patients were taken off dialysis or died from unknown causes [22].

Factors conditioning the nutritional status in dialysis patients

Malnutrition in dialysis patients may be a consequence of multiple factors, including disturbances in protein and energy metabolism, hormonal derangements, infections and other superimposed illnesses, and poor food intake because of anorexia, nausea and vomiting, caused by uraemic toxicity [23]. With maintenance dialysis therapy, some of these factors, but far from all, can be partly or fully corrected [1]. In addition, several iatrogenic factors may contribute to poor nutrition. Multiple drug therapy may interfere with appetite, and corticosteroids may enhance net protein catabolism. Frequent blood sampling in uraemic patients contributes to loss of proteins and other vital compounds. On the other hand, metabolic and nutritional problems may be caused by the method of dialysis [2]. Many of these factors act simultaneously in the progression from suboptimal nutrition to apparent malnutrition.

Increased requirements for protein and energy in dialysis patients

In normal adults, the average minimum requirements for protein are ~0.6 g/kg body weight/day which,
after correction for 25% variability to include 97.5% of the population of young adults, raises the safe level of intake to 0.75 g/kg [24]. This suggested intake of protein for normal individuals does not necessarily apply to dialysis patients, who may require higher levels due to concurrent abnormalities. On the basis of clinical results with protein and energy supplements to the diet, it was suggested that 1.2 g of protein, primarily of high biological value, and an energy intake of 35 kcal/kg body weight/day should be prescribed for HD patients [1,25,26]. These suggested levels of dietary protein intake (DPI) are clearly much higher than for the normal population, and there are a number of identified factors that actually increase the requirement for protein intake in dialysis patients.

In CAPD patients, the protein requirements also appear to be increased, compared with normal individuals. The results of nitrogen balance studies, in a group of CAPD patients, using two levels of protein intake, 0.8 and 1.5 g protein/kg body weight/day, suggest that the protein requirements for CAPD patients are considerably greater than those for normal individuals [27]. On the basis of these results, a protein intake of \( \geq 1.2 \) g/kg body weight/day was recommended for patients treated with CAPD to ensure nitrogen equilibrium or a positive nitrogen balance (Table 1).

Inappropriately high resting energy expenditure (REE) is another proposed mechanism for the increased requirements for protein and energy in HD patients. Ikizler and Hakim recently have reported that REE is actually higher in HD patients, even on non-dialysis days, compared with age-, sex- and body mass index-matched normal controls [28]. Interestingly, this higher level of REE was increased further during the HD procedure when the nutrient losses and catabolism are at a maximum. This increase in REE during non-dialysis periods and HD comprise an additional increase of 8–16% of REE compared with normal individuals. On the other hand, Monteon et al. [29] measured energy expenditure in normal subjects, non-dialysed uremic patients and maintenance HD patients and found no difference among the three groups with the subjects sitting, exercising or in the post-prandial state. This finding suggests that during a given physical activity the energy expenditure of HD patients does not differ from that in normal subjects. Nor is there any evidence that the energy requirements in CAPD patients differ from normal. In a recent study of REE (measured with indirect calorimetry), 12 CAPD patients did not differ from 11 healthy control subjects [30]. Thus, CAPD patients are recommended a total energy intake (including peritoneal glucose absorption) of at least 35 kcal/kg body weight, similar to recommendations for healthy individuals [10].

### Low nutritional intake and anorexia

Considering all the evidence that requirements for protein and energy are increased in HD and CAPD patients, low protein and energy intakes must be especially harmful in such patients. It may be difficult to fulfil the nutritional requirements since some dialysis patients seem to lose their appetite and reduce their protein and energy intakes spontaneously.

Nutritional surveys indicate that the mean intake of protein in HD patients is \(< 1\) g/kg body weight/day in a large proportion of maintenance HD patients [7,8,17]. Jacob et al. [7] noted in 61 HD patients that 45% had a protein intake \(< 1\) g/kg body weight/day. The energy intake is also low in groups of HD patients, with a mean intake of 26–29 kcal/kg body weight/day [7,31], i.e. much less than the 35 kcal/kg body weight/day generally recommended. This is in keeping with observations that a high proportion of HD patients show signs of energy depletion, and energy deficiency may in fact be more common than protein deficiency among HD patients [32].

A large proportion of CAPD patients also ingest considerably lower amounts of protein than the recommended intake of 1.2 g/kg body weight/day [8,33]. Lysaght et al. [34] observed that the protein intake (protein catabolic rate; PCR) was \(~ 18\%\) lower in CAPD compared with HD patients (0.91 and 1.13 g/kg body weight/day, respectively) and that some CAPD patients had a PCR as low as 0.4–0.5 g/kg body weight/day. Retrospective observations by our group also demonstrate that the protein intake in CAPD patients is generally lower than in HD patients. The energy intake in CAPD patients has been reported to be low in spite of the additional supply of energy as glucose by the peritoneal route [35,36]. There is also a decrease in protein and energy intake with time which is paralleled by a fall in nitrogen balance [37,38]. The reduced nutritional intake with time on CAPD seems to be caused by anorexia, with a reduced nutritional intake as a consequence, probably because CAPD patients become underdialysed as the total solute clearance falls, due to a decrease in residual renal function.

Some factors which may contribute to a low intake of protein and energy are listed in Table 2. Anorexia may be due to unpalatable or inadequate diets, gastrointestinal (in diabetic patients with autonomic neuropathy), medications, psychosocial and socioeconomic factors such as loneliness, depression, ignorance and poverty, especially in elderly patients, and those with alcohol and drug problems. Nausea and vomiting, during and immediately after HD, which frequently

### Table 1. Recommended protein and energy intake

<table>
<thead>
<tr>
<th>Group</th>
<th>Protein intake (g/kg body weight/day)</th>
<th>Energy intake (kcal/kg body weight/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy adults</td>
<td>(\geq 0.75)</td>
<td>(\geq 35)</td>
</tr>
<tr>
<td>CRF patients (non-dialysed)</td>
<td>0.60? (high quality)</td>
<td>(\geq 35)</td>
</tr>
<tr>
<td>HD patients</td>
<td>(\geq 1.2)</td>
<td>(\geq 35)</td>
</tr>
<tr>
<td>CAPD patients</td>
<td>(\geq 1.2)</td>
<td>(\geq 35)</td>
</tr>
</tbody>
</table>
Table 2. Causes of anorexia and low nutritional intakes in maintenance dialysis patients

<table>
<thead>
<tr>
<th>Cause</th>
</tr>
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<tbody>
<tr>
<td>General</td>
</tr>
<tr>
<td>Uraemic toxicity (underdialysis)</td>
</tr>
<tr>
<td>Unpalatable or inadequate diets</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
</tr>
<tr>
<td>Inflammation, infection, sepsis</td>
</tr>
<tr>
<td>Medications</td>
</tr>
<tr>
<td>Psychosocial and socioeconomic factors like poverty, loneliness and depression</td>
</tr>
<tr>
<td>Dialysis factors</td>
</tr>
<tr>
<td>Effects of the HD procedure</td>
</tr>
<tr>
<td>Cardiovascular instability</td>
</tr>
<tr>
<td>Nausea, vomiting</td>
</tr>
<tr>
<td>Post-dialysis fatigue</td>
</tr>
<tr>
<td>Effects of the PD procedure</td>
</tr>
<tr>
<td>Abdominal discomfort</td>
</tr>
<tr>
<td>Absorption of glucose and amino acids</td>
</tr>
<tr>
<td>Peritonitis</td>
</tr>
</tbody>
</table>

are associated with cardiovascular instability and post-dialysis fatigue, may lead to a reduction in food intake during the dialysis days. In CAPD patients, abdominal distension may interfere with gastric emptying, and intestinal motility may lead to feelings of fullness and discomfort. It is also possible that peritoneal glucose or amino acid absorption from the dialysis fluid, as well as hyperosmolality and high fill volume, may exert inhibiting effects on food consumption [12,39]. However, Davies et al. recently reported that peritoneal absorption of glucose in CAPD patients does not suppress appetite but provides a useful and significant proportion of the total energy intake that does not cause excessive obesity or have a negative effect on patient survival [40]. A recent study from our group also indicates that the inhibition of appetite caused by peritoneal dialysis solutions containing glucose or amino acid is specific to each nutritional constituent and not simply an effect of hyperosmolality or large filling volume [41].

By far the most important anorectic factor, common to both HD and CAPD patients, is persistent uraemia due to inadequate dialysis. It is quite clear that decreasing clearance of uraemic substances is associated with progressive anorexia at all stages of renal failure. The progression of renal failure was associated with a spontaneous decrease in dietary protein intake [42]. Lindsay and Spanner [43] reported a correlation between the dose of dialysis (Kt/V\textsubscript{urea}) and the PCR which, in metabolically stable patients, reflects the protein intake. They increased the dose of dialysis (Kt/V) in individual patients and observed that the protein intake (PCR) increased spontaneously.

In general, CAPD patients have a lower weekly dialytic clearance of urea than do HD patients. The dietary protein intake has been reported to decrease in patients after switching from HD to CAPD, and to increase in patients after switching from CAPD to HD [1]. This suggests that a less efficient removal of critical uraemic toxins in CAPD may have suppressed appetite. However, in a retrospective analysis of Kt/V and PCR in a group of 115 unselected HD patients and a group of 29 patients on CAPD, we found that the relationship between Kt/V and PCR in the CAPD patients differed from that in the HD patients, most of whom were treated with cellulosic membrane [1,44]. At the same low Kt/V levels, the protein intake (PCR) in the CAPD patients was higher than in the HD patients, and the protein intake increased more for the same increase in Kt/V in the CAPD than in the HD patients. An attractive hypothesis for explaining the different relationships between Kt/V and PCR in CAPD and HD patients might be that the anorectic factor(s) are molecules of larger size than urea, which are dialyzed relatively more efficiently by the peritoneal route than by the cellulosic membranes in the artificial kidney [45]. This hypothesis is supported by the challenging observation by Lindsay and Spanner mentioned earlier [43], indicating that with a permeable membrane (AN 69) protein intake increases proportionally more with the same increase in Kt/V\textsubscript{urea} than with cellulosic membranes. The peak concentration hypothesis, presented by Keshaviah et al., affords an alternative explanation, namely that the periodic pre-dialysis peak concentration of urea and other small uraemic toxins in HD may have a better correlation to clinical outcome than the time-averaged concentration [46]. If this is relevant, the Kt/V\textsubscript{urea} for HD should be higher than for CAPD to match the peak HD concentration to the steady-state CAPD concentration. Furthermore, a positive factor in favour of CAPD as compared with HD is that the residual renal function which may affect the nutritional status (as discussed later) seems to be better preserved in CAPD patients than in HD patients after starting dialysis [47].

Despite the above-mentioned positive factors in favour of CAPD, CAPD patients were found to intake less protein and energy as compared with HD patients [12]. Part of the reason may be the low Kt/V\textsubscript{urea} during standard CAPD treatment, especially after residual renal function becomes negligible. Failure to compensate for loss of residual renal function has been shown to lead to malnutrition in CAPD patients, whereas increasing the dialysis dose as renal function decreases can help to maintain good nutritional status [48].

Recently, the CANUSA study showed that low Kt/V\textsubscript{urea} in CAPD was associated with low protein intake [20] and high mortality rate [19]. An increase in dialysis dose has been suggested to increase uraemic toxin clearance in CAPD patients [49,50].

**Increased protein catabolism**

The observation that HD and CAPD patients seem to have a diminished utilization of ingested protein and increased protein requirements compared with normal individuals indicates that metabolic factors, not fully corrected for by dialysis treatment, as well as the treatment per se may enhance net protein catabolism and impair the utilization of dietary protein. Furthermore, many patients on renal replacement therapy are physically inactive for various reasons,
such as fatigue, anaemia, skeletal-muscular disease and psychological factors. Physical inactivity may result in muscle wasting and a negative nitrogen balance [51]. Other catabolic factors are listed in Table 3.

### Low energy intake

Metabolic studies indicate that the utilization of protein is greatly dependent on the energy intake, so that a low energy intake reduces utilization, whereas a high energy intake has a protein-saving effect [52]. This protein-saving effect of energy intake was underlined by our study [53] showing a strong correlation between energy intake and nitrogen balance. Considering that many patients on maintenance dialysis ingest <35 kcal/kg body weight/day as mentioned before, energy deficiency may be an important factor contributing to poor utilization of dietary protein [7,31,32,35,36].

### Metabolic acidosis

Metabolic acidosis seems to promote increased protein breakdown in animals with chronic renal failure [54,55], and the correction of metabolic acidosis in patients with chronic renal failure is associated with reduced protein breakdown [54]. A study of leucine kinetics in normal subjects during acute acidosis and alkalosis showed that total body protein breakdown was as apparent as leucine oxidation increase more during acidosis than during alkalosis [56]. In rats with chronic renal failure, acidosis, rather than uraemia per se, appears to enhance protein catabolism [57]. This effect seems to be mediated by the stimulation of skeletal muscle branched-chain keto acid decarboxylation, which increases the catabolism of the branched-chain amino acids (valine, leucine and isoleucine), which are metabolized mainly in muscle tissue [58]. Our group has reported that the intracellular valine concentration in the muscle of patients treated with maintenance HD is low [1]. The concentration showed a correlation with the pre-dialysis blood standard bicarbonate which varied between 18 and 24 mmol/l, suggesting that even slight and intermittent acidosis may have stimulated the catabolism of valine in muscle, resulting in a valine depletion that may be a limiting factor for protein synthesis. We also found that correction of acidosis by increasing the bicarbonate concentration in the dialysis fluid increased valine, leucine and isoleucine to the same level as in controls [59].

In our experience, acidosis is common in HD patients, despite the use of bicarbonate as the buffer in the dialysis fluid. In a group of 129 HD patients, we observed that 41% of them had pre-dialysis plasma bicarbonate concentrations <21 mmol/l and 17% ≤19 mmol/l. In contrast, in 44 CAPD patients, most of whom were not taking oral sodium bicarbonate, the steady-state plasma bicarbonate concentration was in general less abnormal than in the HD patients pre-dialysis [1,54]. Similar results have been found in other studies [60]. However, the presently most commonly applied lactate concentration of 35 mmol/l may not always be enough to provide full correction of acidosis. A recent detailed study of acid–base balance in 19 stable CAPD patients using a solution with a lactate concentration of 40 mmol/l showed that all of these patients had a normal or high serum bicarbonate concentration without oral bicarbonate supplementation [12].

### Loss of metabolizing renal tissue

The normal kidneys actively take part in the metabolism of amino acids where, among other processes, phenylalanine hydroxylation to tyrosine [61,62] and glycine conversion to serine take place [63]. Low plasma and intracellular concentration of tyrosine and a reduced ratio of tyrosine to phenylalanine persist in dialysis patients, and serine depletion appears to become more severe than in non-dialysed patients, since not only the plasma concentration but also the muscle concentration of serine is low [1]. One possible explanation for these findings is that the dialysis patients have less metabolizing renal tissue left compared with non-dialysed uraemic patients. This may partly explain why loss of the residual renal function was the factor that was most closely connected to severe malnutrition in a large cross-sectional study of nutritional status in CAPD patients [11]. We observed that HD patients exhibit a more severe serine depletion with significantly reduced intracellular concentrations in muscle than do controls, non-dialysed chronic uraemic patients and CAPD patients [64], which may be, at least partially, explained by better preserved residual renal function in CAPD patients than in HD patients [47].

### Infections

Uremia leads to disturbances in the immune response, with cutaneous anergy and impaired granulocyte function, thus increasing susceptibility to infections. A severe infection is an important stimulus for protein catabolism. HD patients are especially at risk of developing sepsis from infections in arterio-venous fistulae, grafts and in-dwelling venous catheters [65]. On the
other hand, in CAPD patients, peritonitis not only stimulates protein catabolism but also increases the protein and nutrient loss by dialysis [66–68].

Dialysis procedures

In addition to losses of nutrients into dialysate, the HD procedure itself appears to be catabolic. Borah and colleagues [69] demonstrated that nitrogen balance was negative on days patients received treatment as compared with non-treatment days, despite a protein intake of 1.0 g/kg body weight/day. Farrell, Ward and co-workers reported that the urea appearance rate is 30% higher during the HD procedure than in the interdialysis period [70,71]. Therefore, the dialysis procedure itself may exacerbate malnutrition. In patients with poor protein intake, this may become a significant factor in the development of malnutrition.

It is now well established that the type of dialysis membrane used affects the protein metabolism in HD patients. In studies by Gutierrez et al. and Ikizler and Hakim, bioincompatible membranes which vigorously activate the complement system also induce net protein catabolism as compared with dialysis membranes which do not activate this inflammatory response [72–75]. Although both membranes induce net protein catabolism, due to amino acid losses observed during HD, this catabolism is more intense with bioincompatible membranes [75] and can be observed even at 6 h after initiation of dialysis in normal subjects [73].

In a series of experiments with sham-HD in normal individuals, our group found that blood membrane contact within a dialyser with a Cuprophane membrane elicited an enhanced release of amino acids from the leg tissue (mainly skeletal muscle), corresponding to an enhanced protein breakdown of 15–20 g [73,74]. By giving indomethacin before and during the procedure, this catabolic response was abolished, a finding which suggests that the catabolic effect is mediated by prostaglandins. With a more biocompatible membrane, there was no increase in amino acid release [73,74]. These studies demonstrate that in vivo blood-membrane interaction in a dialyser without a dialysate stimulates net protein catabolism, especially when the membrane has a low biocompatibility [72].

The effect of HD membranes on nutritional aspects of HD patients was supported further clinically in studies by Lindsay et al. [43]. These investigators established a link between PCR, a putative marker of DPI in stable HD patients, and the modality and dose of dialysis. They further suggested that at a given dialysis dose, patients dialysed with a biocompatible dialysis membrane had a higher PCR compared with patients dialysed with a bioincompatible membrane. Parker et al. also reported that HD patients dialysed long-term with a biocompatible membrane had higher serum albumin and insulin-like growth factor 1 (IGF-1), and significantly increased body weight as compared with patients dialysed with a bioincompatible membrane [76]. However, in a recent multi-centre study, patients dialysed with low-flux and high-flux polysulfone membrane did not show better nutritional status assessed anthropometrically and biochemically compared with patients dialysed with Cuprophan membrane during 2 years follow-up [77].

Apparently the peritoneal dialysis procedure is not such a strong catabolic stimulus as HD, provided that the patient is free from peritonitis. In CAPD patients, the catabolic effect of dialysis is mainly because of the losses of nutrients into the dialysate. However, there is a possibility that in CAPD the dialysis procedure per se elicits a low-grade inflammatory response, induced by substances other than live bacteria, thereby stimulating protein catabolism. These substances could be microbial products (endotoxins), acetate, plastics, silicon, glucose or other products from the system which elute into the peritoneal cavity [2].

Despite the catabolic effect of the dialysis procedure, several studies have shown that dialysis may have an anabolic effect [78,79]. Kinetic leucine studies in CAPD patients by Goodship et al. showed that the protein turnover and the rate of protein oxidation were lower than in controls and that the balance between synthesis and breakdown was higher after 3 months on CAPD, suggesting protein anabolism [78]. Furthermore, Flanagan et al. reported that initiation of dialysis treatment led to protein anabolism characterized by a rise in whole body protein turnover, an increase in protein synthesis and an improved net leucine balance [79].

Nutrients losses in dialysis

Loss of amino acids

During HD, the average loss of free amino acids in the dialysis fluid has been reported to be 5–8 g/dialysis, of which about one-third are essential amino acids [80,81]. Moreover, 4–5 g of peptide-bound amino acids are lost per dialysis [80]; thus, the total losses of amino acids are ~10–13 g/dialysis. Ikizler et al. examined amino acid losses in patients undergoing HD with three different types of dialyser membranes [75]. Patients undergoing HD with high-flux polysulfone (HF-PS) membranes lost 8.0±2.8 S D g of amino acid per dialysis session as compared with patients dialysed with low-flux polymethylmethacrylate membranes, who lost 6.1±1.5 S g of amino acids (P<0.05), and those dialysed with cellulose acetate membranes, who lost 7.1±2.6 S g. These small differences in amino acid losses may be due to variations in the dialyser surface area and blood flow rates, and are probably biologically insignificant.

The losses of free amino acids into the dialysate during CAPD are of the same magnitude (per week) or smaller than with HD. The reported average dialysate losses of free amino acids during CAPD vary between 1.2 and 3.4 g/24 h in different studies [10]. About 30% of the amino acids lost into the dialysate are essential amino acids. Obviously, the losses of amino acids per se by dialysis are too small to account
fully for the increased protein requirements in maintenance dialysis patients.

**Protein losses**

Protein losses during HD are typically very small. However, with high-flux (e.g., polysulphone) dialysers, losses might be expected to be greater. Moreover, reuse of these HF-PS dialysers after reprocessing with bleach and formaldehyde resulted in a rather marked increase in protein losses due to increased permeability of these membranes [82]. Ikizler et al. [75] found that albumin losses became apparent after the sixth reuse of the HF-PS membrane. These losses increased significantly, from 1.5 ± 1.3 g per dialysis session by the fifteenth reuse to 9.3 ± 5.5 g at the twentieth. Kaplan et al. observed similar results [17]. The amino acid losses increased by 50% after the sixth reuse in the HF-PS membranes. Blood sequestered in the haemodia- lysate, clotted or leaking dialysers, oozing of blood from the needle punctures of the vascular access site, and blood sampling for laboratory testing may contribute to protein losses. Approximately 5–10 ml of blood may be trapped in the dialyser at the end of each dialysis. This could account for another 0.6–1.4 g of protein lost per dialysis session [9].

In contrast, substantial loss of protein into the dialysate is a major drawback of peritoneal dialysis. In CAPD, the reported average loss of protein into the dialysate varies between 5 and 15 g in different studies, with large interindividual differences [10,38]. Thus, dialysate protein loss may vary between 20 and 140 g/week in different patients. In CAPD patients with mild peritonitis, the dialysate protein losses increased by 50–100% to an average of 15.1 ± 3.6 g/day [66], and remain elevated for several weeks. Also, dialysate losses of protein increase with increased peritoneal permeability such as in high peritoneal transport rate patients [83]. The substantial loss of protein may contribute indirectly to various nutritional and metabolic disturbances in patients on CAPD, e.g. hypercholesterolaemia, altered amino acid metabolism and metabolic bone disease due to losses of vitamin D-binding protein.

**Loss of glucose**

When a glucose-free dialysis fluid is used for HD, ~28 g of glucose is removed during 4 h of HD (area 1 m²), whereas the addition of glucose (11 mmol/l) to the dialysis fluid results in a gain of ~23 g of glucose by the patient [84,85]. To avoid symptomatic hypoglycaemia, glucose removed from the extracellular fluid by dialysis must be replaced by ingested carbohydrate, by breakdown of liver glycogen or by gluconeogenesis from amino acids; the latter should result in an enhanced protein breakdown and urea synthesis. Observations by Wathen et al. [84] showing that pyruvate decreased during glucose-free dialysis, but was unchanged during glucose dialysis, indicate that gluconeogenesis may be stimulated by glucose-free dialysis. However, Ward et al. [71], Gutierrez et al. [85] and Farrell and Hone [70] have reported that the urea appearance rate is stimulated to a similar extent by dialysis, whether glucose is present in the dialysis fluid or not.

CAPD patients are provided with glucose continuously by the peritoneal route, which potentially is beneficial by providing an additional energy supply [40]. However, glucose uptake may also have negative metabolic effects, such as hyperglycaemia, hyperinsulinaemia, hyperlipidaemia and obesity [10].

**Other catabolic factors**

In addition to the above-mentioned factors, hormonal and metabolic disturbances observed during the predialysis stage may persist or even worsen during the renal replacement stage of ESRD, irrespective of the modality of dialysis (Table 3). Hormonal disturbances include insulin resistance, increased glucagon concentration, secondary hyperparathyroidism and abnormalities in growth hormone and the IGF-1 axis [3]. Furthermore, placement of permanent or temporary vascular accesses in HD patients and use of the peritoneal cavity in peritoneal dialysis patients induce additional medical problems and hospitalizations due to infections and/or access revisions. Increased frequency of hospitalizations may adversely affect the nutritional status of dialysis patients. Indeed,

**Table 4. Catabolic effect of dialysis procedure**

<table>
<thead>
<tr>
<th></th>
<th>Haemodialysis</th>
<th>CAPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss of amino acids and peptides</td>
<td>9–13 g/dialysis (27–39 g/week)</td>
<td>2–4 g/day (14–28 g/week)</td>
</tr>
<tr>
<td>Loss of glucose</td>
<td>25 g/dialysis (glucose-free dialysate)</td>
<td>(uptake)</td>
</tr>
<tr>
<td>Loss of protein</td>
<td>Minor (5–15 g/dialysis after reuse of high-flux membrane)</td>
<td>5–15 g/day (higher with peritonitis)</td>
</tr>
<tr>
<td></td>
<td>0.5–1.5 g/session due to blood loss</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Blood-membrane contact (with incompatible membranes; protein breakdown corresponding to 15–20 g protein/session)</td>
<td>Low-grade inflammation? (particles, chemicals)</td>
</tr>
<tr>
<td></td>
<td>Complement activation</td>
<td>Peritonitis</td>
</tr>
<tr>
<td></td>
<td>Endotoxin</td>
<td>Cytokine release</td>
</tr>
<tr>
<td></td>
<td>Acetate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cytokine release</td>
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</table>
Ikizler et al. reported that the actual daily protein intake of HD patients admitted to a regular ward is at perilously low levels (0.55 ± 0.33 g/kg/day) and that simultaneous calculations of PCR by urea kinetics revealed a negative estimated nitrogen balance in 80% of these hospitalized patients [86]. Serum albumin concentrations showed a significant decrease with hospitalizations in these patients.

General conclusions

Malnutrition is common in maintenance dialysis patients, irrespective of whether they are treated with HD or CAPD, and it is strongly associated with increased morbidity and mortality. Contributing factors are increased protein requirements and low supply of energy and protein in relation to need. Anorexia with low protein and energy intake results from a variety of factors, of which underdialysis with insufficient control of uremic toxicity seems to be a major factor. CAPD patients have, on average, a lower protein intake than HD patients. The dialysis procedure per se seems to be a strong, intermittent catabolic stimulus in HD patients, whereas in CAPD patients the continuous protein loss in the dialysate, which is greatly enhanced during episodes of peritonitis, is a recognized risk factor for protein malnutrition.

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