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Protein Intake in Renal and Hepatic Disease

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Abstract: The kidney and the liver play a central role in protein metabolism. Synthesis of albumin and other proteins occurs mainly in the liver, whereas protein breakdown and excretion are handled through an intricate interaction between these two organ systems. Thus, disease states of either the liver and/or the kidney invariably result in clinically relevant disturbances of protein metabolism. Conversely, metabolic processes regulated by these two organs are directly affected by dietary protein intake. Of particular importance in this respect is the maintenance of acid/base homeostasis. Finally, both the amount and composition of ingested proteins have a direct impact on renal function, especially in a state of diseased kidneys. Consequently, dietary protein intake is of paramount importance in patients with chronic nephropathy and renal insufficiency. Limitation of ingested protein, particularly from animal sources, is crucial in order to slow the progression of chronic kidney disease and impaired renal function. In contrast, patients with chronic renal failure undergoing renal replacement therapy by hemodialysis or peritoneal dialysis, have an increased protein demand. The syndrome of "protein-energy malnutrition" is a relevant factor for morbidity and mortality in this population and requires early detection and vigorous treatment. Protein intake in patients with cirrhosis of the liver should not be diminished as has been earlier suggested but rather increased to 1.0–1.2 g/kg body weight/day, in order to prevent protein malnutrition. Moderate restriction depending on protein tolerance (0.5–1.2 g/kg body weight/day), with the possible addition of branched chain amino acids (BCAA), has been recommended only in patients with advanced hepatic encephalopathy. Proteins of plant origin are theoretically superior to animal proteins.

Key words: Kidney, liver, nephropathy, hepatic encephalopathy, metabolic acidosis, renal replacement therapy, protein-energy-malnutrition

1. The role of kidney and liver in protein metabolism in health and disease

Whereas a detailed review of systemic protein metabolism is given in chapter 2, the following synopsis will focus on the hepatorenal interplay in protein synthesis and breakdown.

Albumin and total protein synthesis and deficiency in disease states

Albumin is the most abundant circulating protein, produced only by the liver, in a quantity between 12 and 25 g daily [1]. This may account for up to 50 % of total hepatic protein synthesis under extreme conditions, but less than 10 % of total protein production by the liver in one day under normal conditions. Approximately 6 % of daily nitrogen intake is required for albumin synthesis. Total calorie and protein intake are the main dietary factors regulating albumin production, and have far greater effects on its synthesis

than on that of other proteins. Subnormal serum concentrations of albumin may result from inadequate protein intake, decreased hepatic synthesis, and/or renal loss in patients with certain forms of kidney disease. Relevant structural damage of the liver, such as in cirrhosis, negatively impacts on protein synthesis in general, and on that of albumin in particular. Decreased serum albumin concentrations are also a hallmark of many severe diseases (see also chapter 9).

Albumin regulates fluid distribution through the body by its colloidal properties, being responsible for 75 % of the normal oncotic pressure. Permanently low serum albumin concentrations may result in generalized edema formation due to low oncotic pressure. In addition, albumin plays a key role in substrate binding and transport, thereby having a major impact on the pharmacokinetics of drugs. Thus, the dosage of drugs with a substantial binding to albumin may have to be adjusted in order to ensure their therapeutic efficacy. Apart from albumin, muscle proteins account for approximately one half of the total protein pool in the body. Obviously, a quantitative and/or qualitative deficit of muscle protein may result in relevant changes in muscle mass and function and may have a profound impact on strength, mobility, control of posture, etc.

Nitrogen metabolism

Turnover of both ingested and endogenous proteins involves nitrogen generation and disposal, which are accomplished in a concerted effort by the liver and the kidney.

Amino acids (AA) are the basic elements of all proteins and their common structure is made up by a nitrogen (→ amino, NH_2) and a carboxyl (→ COOH) group. Protein intake from food is the most abundant source of nitrogen entering the body. As nitrogen cannot be stored, and amino acids in excess of the biosynthetic needs of the cells are immediately degraded, the elimination of protein breakdown products is of paramount importance. Nitrogen is primarily metabolized to ammonia (NH_3), which, in small amounts, is excreted in the urine (Figure 1). The major part of ammonia, however, is used in the synthesis of urea and glutamine. While ammonia- and ureagenesis take place in the liver, glutamine and urea are quantitatively excreted with the urine along with other nitrogen metabolites such as glutamate, uric acid, and creatinine. Obviously, the functional capacity and the interaction of these two organ systems are crucial for the maintenance of a balanced turnover and elimination of dietary and endogenous proteins.

Effects of protein disposal on systemic acid/base homeostasis

Ammonia (NH_3) resulting from hepatic protein degradation is the precursor of urea, the major nitrogen-containing compound in urine, and of urinary ammonium (NH_4), which is produced by excess acid following animal protein ingestion. Thus, it is obvious that nitrogen and acid excretion may interfere with each other by competing for ammonia (Figure 1). Basically, high protein turnover may result in metabolic acidosis, as it diverts ammonia from the kidney to the liver for ureagenesis. This effect could even be accentuated, as urea production consumes substantial amounts of bicarbonate, which is the major extracellular buffer

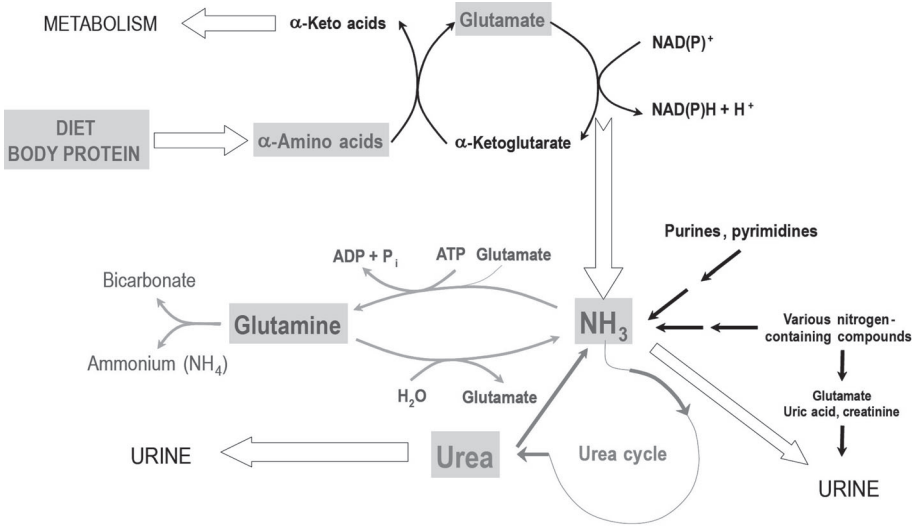

Figure 1: Nitrogen generation and disposal from dietary protein metabolism by the liver (ureagenesis) and the kidney (ammoniagenesis).

for excess acid. Vice versa, metabolic acidosis might impair nitrogen disposal by using ammonia for renal acid excretion. It has only been shown recently that metabolic acidosis in humans leads to stimulated rates of ureagenesis [2]. Thus, the rate of urea production is not directed towards maintenance of acid/base homeostasis but rather driven by the need to remove or retain nitrogen, depending on net protein balance, resulting from protein catabolism or anabolism, respectively. As a consequence, high protein intake may contribute to the development of metabolic acidosis, in addition to the net acid load of an average Western diet rich in animal protein.

2. Effects of protein intake on kidney function

Glomerular filtration is the renal process responsible for the removal of fluid and solutes, including metabolic end products, from the circulation and their disposal into urine. The quantitative measure of this process is termed glomerular filtration rate (GFR), expressed as the volume of fluid filtered through the renal glomerular capillaries into urine per unit time (mL/minute).

In healthy individuals, many factors influence GFR, such as age, gender, body size, and pregnancy. In addition, acute protein loads and changes in habitual protein intake of specific amino acids significantly alter GFR through indirect effects on the hormonal milieu as well as direct effects on renal processes [3].

The quantitative effect of variable amounts of protein in the diet on GFR can be substantial, especially when maintained over prolonged periods of time. Increasing protein intake from low (0.1–0.4 g/kg body weight/day), to medium (1.0–1.4 g/kg body weight/day), to high (2.6 g/kg body weight/day) for 2 weeks is associated with increases in GFR by 9 and 22 %, respectively [4]. In studies of subjects in whom the dietary pattern was maintained for months to years the differences in GFR are more pronounced. In vegetarians, GFR was 40 % lower than in omnivores. Similarly, in patients with chronic malnutrition, GFR was 27 to 64 % lower than after repletion of nutritional status.

The delayed response of GFR to changes in habitual protein intake raises the possibility of structural as well as hemodynamic alterations. Indeed, renal enlargement and hyperfiltration have been noted in patients receiving total parenteral nutrition. Conversely, the kidneys of Jamaican children who died with malnutrition were smaller than those of age-matched children who died of other causes. In addition, kidney sizes of well-nourished Jamaican children were smaller than those of their age-matched American counterparts, perhaps reflecting the higher protein content of the American diet.

The effects of dietary protein intake and glomerular filtration rate are of particular interest with regard to the preservation of renal function in diseased kidneys, and will be discussed extensively in section 6.

3. Protein intake as a modifier of kidney disease progression

Kidney disease is associated with variable degrees of renal tissue damage, which may subside spontaneously or be controlled by medical treatment. A substantial proportion of patients, however, will experience a continued disease process resulting in progression of organ damage. This course is termed "chronic kidney disease" (CKD) and is invariably accompanied by the development of renal insufficiency. The latter describes impairment in renal function, defined mainly as a decrease in glomerular filtration rate (GFR) and, thus, in the excretory capacity of the kidney. This process is usually continuous in nature with a linear and progressive decline in GFR over months to years. Once residual renal function reaches approximately 10 percent of its normal capacity, the implementation of renal replacement therapy by dialysis or kidney transplantation becomes inevitable to prevent substantial medical complications or death. As the kidney also fulfills multiple metabolic and endocrine functions, chronic renal insufficiency impacts on systemic regulation beyond the excretion of excess fluid and waste products. In particular, impaired kidney function is associated with arterial hypertension, anemia, disorders of mineral and bone metabolism, and metabolic acidosis, among others. Medical therapy is directed towards slowing the progression of CKD, in order to delay dialysis therapy or transplantation.

A much-debated modifier of progressive renal disease is dietary protein intake. As elaborated in the previous chapter, specific amino acids do have a modulatory effect on glomerular filtration rate (GFR). Sustained glomerular hyperfiltration from various causes, including high protein intake, has been postulated to be a promoting factor for accelerated loss of renal function [5]. Moreover, structural damage of renal tissue results in urinary protein loss (or "proteinuria") and has been invariably associated with progression of kidney disease [6]. A causal relation-

ship exists between protein nutrition and proteinuria independent of the hemodynamic effects of proteins mentioned earlier. Therefore, modification of diet with regard to protein intake in patients with chronic kidney disease (CKD) has been considered for many decades to be a major measure to slow progression of renal insufficiency.

The original rationale for the restriction of protein in chronic uremia (clinical term for "renal insufficiency") was to lower blood urea concentration, thereby limiting the symptoms associated with this condition, such as nausea and vomiting. Beyond lowering production of nitrogenous compounds, decreased nutritional protein content could limit sodium and phosphate intake and optimize serum levels of bicarbonate and potassium. Moreover, it may prevent the development of severe secondary hyperparathyroidism, and reduce proteinuria. Whereas symptom reduction actually may be achieved with this strategy, concerns were raised that reducing protein intake below 0.8 g/kg body weight/day might confer an increased risk of malnutrition. Thus, common recommendations did not limit nutritional protein content. In patients with signs of malnutrition and difficulties in increasing protein intake, dialysis was advocated based on the notion that it improves dietary intake and nutritional status.

It was not until the early 1990s that a large prospective, controlled randomized trial was conducted to examine these opposite concepts and the effect of modified protein intake in non-diabetic patients with chronic kidney disease [7]. In the MDRD (Modification of Diet in Renal Disease) study by Klahr *et al.*, 585 patients with glomerular filtration rates of 25 to 55 mL/minute (moderate to mild renal insufficiency) were randomly assigned to a usual-protein diet or a low-protein diet (1.3 or 0.58 g of protein/kg body weight/day). An additional 255 patients with GFR of 13 to 24 mL/minute (severe to moderate renal insufficiency) were randomly assigned to the low-protein diet (0.58 g per kilogram per day) or a very-low-protein diet (0.28 g per kilogram per day) with a keto acid-amino acid supplement. The mean follow-up was 2.2 years.

In those patients with only moderate to mild renal insufficiency (GFR 25–55 mL/minute) the projected mean decline in the glomerular filtration rate at three years did not differ significantly between the diet groups. In patients with more severe renal insufficiency at baseline (GFR 13–24 mL/minute), the very-low-protein group had a marginally slower decline in glomerular filtration rate than did the low-protein group. The difference, however, did not reach statistical significance, even when longer follow-ups of up to 6 years were evaluated later on. Also, there was no delay in the time to the occurrence of end-stage renal disease or death.

In one of several post-hoc analyses to this study, the effects on nutritional status among the different dietary regimens as *per protocol* (considering only patients adhering to the prescribed diet) were analyzed. Various indices of nutritional status remained within normal range during follow-up in each diet group. However, in the low-protein and very-low-protein diet groups, serum albumin rose, while serum transferrin, body weight, percent body fat, and arm muscle area declined. It was cautioned that these declines are of concern because of the adverse effect of protein-calorie malnutrition in patients with end-stage renal disease. Physicians who prescribe low-protein diets were advised to carefully monitor patients' protein and energy intake and nutritional status. Of note, analysis of the subgroups of patients achieving prescribed protein intakes revealed a more rapid drop in GFR of borderline statistical significance in the group who averaged 0.69 g protein/kg body weight/day than in the 0.46 g/kg body weight/day plus keto acid group.

The only other prospective controlled and randomized trial published since 1994 examining the effect of dietary protein modification in 423 patients with CKD was performed in Italy from 1999 to 2003 with a mean follow-up of 48 months [8]. Unlike the MDRD trial the study compared protein diets with 0.8 and 0.55 g/kg body weight/day. Again, the differences with regard to decline in renal function and time to dialysis or death were not significant between groups. However, progression of kidney disease, incidence of renal failure, and mortality were all rather low in this cohort and, thus, the study may have been underpowered to detect an effect. Another difficulty with this study was the achieved protein intakes, which were 0.73 and 0.90 g/kg body weight/day in the respective groups (instead of 0.55 and 0.8 g/kg body weight/day). The fact that less than one third of the patients strictly adhered to the low-protein diet indicates the problems of compliance with such regimens. Of note, only 3 patients developed relevant signs of protein-calorie malnutrition.

Positive results from restricted protein intake were found in several other studies. However, most studies examining the effects of low protein intake in patients with chronic renal insufficiency were clearly limited by rather low numbers of participants. Nevertheless, based on secondary analyses of the MDRD trial results along with several meta-analyses supporting the role of supervised low-protein diets (ranging from 0.6–0.75 g/kg body weight/day), the National Kidney Foundation in its Clinical Practice Guidelines for Nutrition in Chronic Renal Failure recommended in

the year 2000 consideration of a planned low-protein diet in non-dialyzed patients with chronic kidney failure [9]. In addition to retarding kidney disease progression, they argued, this strategy would potentially ameliorate metabolic complications and preserve nutritional status.

In a meta-analysis, data from 1494 patients were analyzed. A 39 % reduction in renal death was observed ($p < 0.001$) in patients on a low-protein diet [10]. When examining the effect of low protein intake on the GFR of more than 1900 patients, Kasiske *et al.* detected a protective effect in those with the lowest protein intakes; GFR was "spared" significantly by 0.53 mL/minute/year [11].

Additional support for lowering protein intake in CKD came from large population-based epidemiological studies. In a prospective cohort of 1624 women enrolled in the Nurse's Health Study, Knight *et al.* found that the relationship between the quantities of protein ingested and change in estimated GFR varied with baseline renal function [12]. Whereas no association between protein consumption and GFR change in women with normal function at enrollment (defined as a GFR of at least 80 mL/minute) was found, each 10 g/day increase in protein consumption was linked with an adjusted decrease in GFR of 1.69 mL/minute in the subset of 489 women with mild renal insufficiency (GFR 56–80 mL/minute). The effect was even more pronounced when assessing those women with renal insufficiency in the highest quintile of protein intake, which experienced an average adjusted decline in GFR that was 4.77 mL/minute greater than those in the lowest quintile. Further analyses of the findings by Knight *et al.* revealed that the effect was restricted to non-dairy animal protein, but was not found for dairy and vegetable protein. Animal protein appears to have the most pronounced effect on renal hemodynamics, followed by dairy protein and, finally, plant protein. Thus, reducing the proportion of animal protein may be a suitable therapeutic strategy when total protein restriction is not feasible.

4. Recommendations on protein intake in chronic kidney disease

Available data suggest a beneficial effect of limiting dietary protein intake in patients with chronic kidney disease. In general, the benefit seems to be inversely related to renal function, being increasingly greater in patients with more advanced renal insufficiency (GFR < 50 mL/minute). Moreover, protein restriction may (indirectly) improve metabolic control of patients with CKD, such as serum phosphorus levels, parathyroid function, metabolic acidosis, insulin resistance, and arterial hypertension. However, as proof of this concept from prospective controlled randomized trials is still lacking so far, there are several caveats that have to be raised before recommending protein restriction to every patient with CKD:

If dietary protein intake is limited, it has to be ensured that energy intake meets the recommended levels (i. e. 35 kcal/kg body weight/day for patients aged less than 65 years and 30–35 kcal/kg body weight/day for those aged 65 years or over)

Protein composition in restricted diets has to be of high biological value.

In general, protein intake less than 0.75 g/kg body weight/day should be recommended with caution and only if signs of protein-energy malnutrition (PEM) are absent. If lower levels of protein intake are to be prescribed, supplements of essential amino acids or keto acids should be considered so as to prevent essential amino acid deficiency.

Of note, nutritional requirements of children with CKD are not covered by this review and need to be considered separately and with special emphasis on growth requirements.

Finally, any dietary interventions depend on the compliance of the patient and require continuous counseling and close surveillance, especially with regard to signs of malnutrition.

5. Protein malnutrition in patients with end-stage renal disease (ESRD)

Whereas current evidence suggests that limiting protein intake is beneficial in patients with chronic kidney disease not undergoing dialysis, the situation is different altogether in the setting of renal replacement therapy. Surveys using classic measures of nutritional status indicate that approximately 18–75 % of patients with CKD undergoing maintenance dialysis therapy show evidence of wasting. Malnutrition in uremic patients is characterized by insidious loss of somatic protein stores and visceral protein concentrations. Most importantly, multiple prospective and retrospective studies have demonstrated that the presence of malnutrition in chronic dialysis patients sharply increases mortality and morbidity in this population. An important aspect of the pathogenesis in this regard

is the chronic inflammatory process that is highly associated with CKD. The combination of malnutrition, protein-energy wasting, and inflammation in the context of renal failure has also been coined "Malnutrition Inflammation Complex Syndrome" (MICS) [13]. It accounts for many derangements and pathologic conditions typically inherent to patients on chronic renal replacement therapy, such as loss of body weight, reduced body-mass index (BMI), atherosclerotic cardiovascular disease, and vascular calcification. Thus, MICS is viewed as a major cause of increased morbidity and mortality in chronic renal failure [14]. The present review will focus on the aspects of protein malnutrition contributing to this syndrome.

Causes of impaired nutritional status in patients with ESRD

The pathogenesis and causes of impaired nutritional status in patients on renal replacement therapy are complex and multifactorial. *First*, dialysis treatment by itself is accompanied with substantial losses of nutrients into the dialysate. During hemodialysis, amino acid losses average about 6 to 12 g per treatment. With peritoneal dialysis, protein losses range from about 8 to 12 g/day and amino acid losses are about 3 g/day. Assuming maximal losses in a 70 kg patient, the calculated additional protein needs for hemodialysis patients would be about 0.06 g/kg body weight/day (9 g of amino acids per session, 27 g/week, or 3.8 g/day) and about 0.2 g/kg body weight/day for peritoneal dialysis patients (15 g of protein and amino acids per day) [15].

Second, protein and energy intake in chronic dialysis patients is clearly inadequate. Typically, patients undergoing maintenance dialysis therapy have reduced intake of both protein and energy. In our own analysis of a Swiss hemodialysis (HD) cohort population, we found the average energy intake to be only 81 % of daily allowance [16]. Accordingly, carbohydrate intake and nutritional protein content met only 69 and 84 %, respectively, of calculated daily requirements. Typically, estimated protein intake from calculated normalized protein catabolic rate (nPCR) is less than 1.0 g/kg body weight/day, namely 0.83 ± 0.19 g/kg body weight/day in our analysis of 60 Swiss HD patients. The causes of impaired protein-energy intake in patients with end-stage renal disease are multifactorial. One major reason is anorexia, presumably from induction and accumulation of cytokines. An additional factor is age, which is known to be associated with both lesser appetite and reduced protein-energy intake. This is of relevance, as dialysis patients represent an older population with a median age of 71 years in Switzerland.

Third, the uremic milieu in patients with chronic renal failure is considered a potentially maladaptive state for balanced protein turnover [17]. It has been argued extensively whether uremia is a net protein catabolic state in and of itself. However, more recent data convincingly demonstrate that renal insufficiency does not induce net protein breakdown as shown by nitrogen balance studies, as well as whole-body amino acid turnover kinetic studies. In fact, there is a concomitant decrease in both protein synthesis and degradation in patients with advanced uremia due to low protein turnover rate. Consequently, net nitrogen balance is not different from matched healthy controls. Thus, patients with severely impaired renal function seem to be able to compensate for reduced protein intake and synthesis by a slowdown of protein breakdown. However, this balance is fragile and limited to clinically stable patients. At times of accelerated protein degradation due to increased metabolic needs, such as acute illnesses or stress conditions, it is likely that the appropriate compensatory mechanisms, such as increased protein synthesis, fail.

Finally, the hemodialysis procedure has been shown to be a protein catabolic or, rather, anti-anabolic state with an imbalance between protein breakdown and synthesis, the net result being a substantial loss in both whole-body and muscle protein during hemodialysis.

An additional factor contributing to negative protein balance in renal failure is metabolic acidosis, a consequence of impaired renal function being highly prevalent in dialysis patients. In experimental animal studies, chronic metabolic acidosis causes increased nitrogen excretion despite the same dietary protein intake as control animals [18], and, in humans, profound acidemia causes cachexia. Accordingly, correction of acidosis decreases proteolysis and amino acid oxidation in chronic renal failure patients, and results in normalization of muscular essential amino acid content.

6. Nutritional requirements and prevention of protein malnutrition in hemodialysis patients

The findings from many studies that maintenance hemodialysis patients have a high incidence of protein-energy malnutrition (PEM) underscore the im-

portance of maintaining an adequate nutrient intake. Few studies have directly assessed the dietary protein requirements for HD patients. No randomized long-term clinical trials have been conducted to assess different dietary protein levels with regard to morbidity, mortality, or quality of life. Thus, recommendations for dietary protein intake in HD patients are somewhat circumstantial. However, from the facts mentioned before, and the available literature on outcomes in patients on renal replacement therapy, it can be concluded that protein-energy intake in maintenance hemodialysis patients clearly needs to be higher compared to those with pre-dialysis chronic kidney disease.

7. Nutritional recommendations for patients on hemodialysis (based on reference [9])

- Protein intakes of less than 0.75 g/kg body weight/day are inadequate for most maintenance HD patients. Ingestion of 1.1 g of protein/kg body weight/day may maintain good protein nutrition in some hemodialysis patients but is not sufficient to maintain good nutrition in the great majority of clinically stable patients ingesting 25 or 35 kcal/kg body weight/day. It is therefore recommended that a safe dietary protein intake that will maintain protein balance in almost all clinically stable maintenance hemodialysis (MHD) patients is 1.2 g protein/kg body weight/day.
- At least 50 % of the protein ingested should be of high biological value. Protein of high biological value has an amino acid composition that is similar to human protein, is likely to be an animal protein, and tends to be utilized more efficiently by humans to conserve body proteins. The increased efficiency of utilization of high biological value protein is particularly likely to be observed in individuals with low protein intakes.
- From experience it is difficult for most HD patients to maintain this level of daily protein intake. Techniques must be developed to ensure this level of intake for all patients. Education and dietary counseling should be the first steps in attempting to maintain adequate protein intake. If this approach is unsuccessful, nutritional support, such as that outlined in the section below should be considered.

8. Nutritional requirements in chronic peritoneal dialysis patients

Whereas hemodialysis provides disposal of metabolic end products over an artificial filter (hemodialyzer), peritoneal dialysis (PD) is performed via the natural surface of the peritoneal membrane (i.e. the membrane confining the intestinal organs within the abdominal cavity) against a glucose-containing solution (dialysate). Due to these differences, loss of endogenous protein is more pronounced in PD patients compared to those undergoing HD treatment. Moreover, anorexia due to glucose absorption from dialysate may also contribute to reduced dietary intake and malnutrition. As a consequence, the nutritional recommendations for PD patients with regard to protein intake differ from those for hemodialysis patients.

9. Nutritional recommendations for patients on peritoneal dialysis

- Dietary protein intake in clinically stable PD patients should be at least 1.2 g protein/kg body weight/day, as it is almost always associated with neutral or positive nitrogen balance. A dietary protein intake of 1.3 g/kg body weight/day probably increases the likelihood that adequate protein nutrition will be maintained in almost all clinically stable individuals. At least 50 % of the protein should be of high biological value.
- Patients who do not have an adequate dietary protein intake should first receive dietary counseling and education. If dietary protein intake remains inadequate, oral supplements should be prescribed.
- If the oral supplements are not tolerated or effective and protein malnutrition is present, consideration should be given to use tube feedings to increase protein intake.
- Amino acids may be added to dialysis solutions to increase amino acid intake and to replace amino acid losses in dialysate.

10. Nutritional supplements in patients on chronic renal replacement therapy

The high prevalence of uremic malnutrition in ESRD patients indicates that the attempts to increase dietary protein intake by dietary counseling alone is not always successful to maintain neutral nitrogen balance in this patient population. In subjects with obvious signs of uremic malnutrition, other forms of nutritional intervention have also been proposed, such as oral, tube-fed, and parenteral nutritional supplementation.

Oral nutritional supplements

Only a limited number of (controlled) studies are available on the effects of added protein intake from nutritional supplements given by the oral route. Nevertheless, dietary prescriptions given during hemodialysis sessions in the form of a combination of yogurt, cream, and protein-enriched milk powder, or oral amino acid supplements, improve measures of nutritional status as well as muscle strength and mental health [19–21]. Although preliminary, with findings that warrant larger, randomized clinical trials, oral nutritional supplementation as a practical measure should be attempted in malnourished dialysis patients if the problems that could be responsible for reducing nutrition intake cannot be resolved. However, oral nutritional supplements are not considered as "medication" and therefore are not covered by the basic health insurance ("Grundversicherung") in Switzerland. A reassessment of the reimbursement practice should be strongly considered by the responsible health authorities (i.e. the BAG).

Intradialytic parenteral nutrition (IDPN)

Nutritional supplementation by IDPN capitalizes on the availability of a permanent vascular access in hemodialysis patients. Thus, substantial amounts of protein and energy can be administered during each HD session without the need of an additional central venous catheter and additional treatment time. Also, unlike oral supplements, IDPN is reimbursed by health insurance despite its considerably higher costs. IDPN has been shown to promote a 96 % increase in whole-body protein synthesis and a 50 % decrease in whole-body proteolysis during a HD session compared to no treatment. In addition, it provides a change from negative (muscle loss) to positive (muscle accretion) balance in forearm protein synthesis. Unfortunately, treatment costs are high and long-term studies with relevant clinical endpoints are scarce. Indeed, the largest prospective controlled trial conducted so far with a total of 186 malnourished hemodialysis patients, comparing oral nutritional supplements with or without one year of IDPN, was negative without improvement in two-year mortality, hospitalization rate, Karnofsky score, body mass index, or laboratory markers of nutritional status in patients supplemented with IDPN [22].

In fact, both groups demonstrated improvements in body mass index and in the nutritional parameters serum albumin and prealbumin, which were associated with a substantial decrease in two-year mortality, as well as reduced hospitalizations and improved general well being.

In conclusion, there are no data to show that aggressive enteral nutritional supplementation is inferior to parenteral supplementation in dialysis patients. Until controlled studies comparing various forms of nutritional supplementation in similar patient groups are completed, one should be cautious in choosing very costly nutritional interventions.

11. Protein intake in chronic liver disease

Obviously, performing its role as the central machinery of protein synthesis, the liver very much depends on the availability of the necessary precursors to perform this task. However, unlike for the kidney, the literature is scarce with regard to the specific effects of dietary protein intake on hepatic growth and function. A major role in this respect is attributable to growth hormone (GH), which stimulates production of insulin-like growth factor 1 (IGF-1) in the liver, which is a major target organ of GH itself. GH secretion can be stimulated by either a protein meal or infusion of arginine. From these observations it can be inferred that proteins are not only synthesized predominantly in the liver, but are also a major determinant of liver growth and function.

Protein malnutrition and restriction in patients with chronic hepatopathy

Moderate to severe malnutrition has been found to be prevalent in more than 50 % of patients with liver cirrhosis from different etiologies [23]. Thus, mal-

nutrition is a common complication, particularly in advanced stages of liver disease, and progressively increases with the severity of liver failure (as classified by the Child-Pugh score). Different patterns of malnutrition were found with muscle-mass depletion being more prevalent in males and fat depletion in females [24]. Whereas the pattern of malnutrition in female patients is similar to that observed in other chronic diseases or starvation, the pattern in male patients with cirrhosis resembles that of critical illnesses. The reduction of muscle mass in malnourished male cirrhotic patients is attributable in part to hormonal alterations. Moreover, protein-energy malnutrition (PEM) is a common finding in cirrhotic patients, which also may contribute to muscle wasting [23]. Multiple factors have been considered in the etiology of PEM in chronic liver disease, with a particular emphasis on metabolic alterations induced by impaired liver function. Specifically, insulin resistance and impaired glucose utilization, which have been documented in patients with liver cirrhosis, are of particular pathogenetic relevance and may be instrumental in skeletal muscle and adipose tissue catabolism.

Several studies have shown malnutrition to be related with poorer survival in patients with (alcoholic) hepatitis and liver cirrhosis. Although the presence of nutritional alterations should not be considered as a consequence of chronic liver disease only, it nevertheless seems to accelerate the natural history of the disease and adversely affect the patients' outcome.

With regard to dietary measures, oral re-feeding has been proven to retain nitrogen at rates increased above normal in malnourished cirrhotic patients, similarly to that of underweight individuals without organ diseases, and to induce a significant increase in protein synthesis. At any rate, in these patients, a regimen of chronic protein restriction, by favoring progressive protein depletion, may be harmful. In addition, a protein-adequate diet is suggested because muscle tissue may substitute for the failing liver in ammonia detoxification, which is impaired in patients with cirrhosis due to the inability of hepatic urea synthesis.

Apart from liver cirrhosis, hepatic encephalopathy (HE) as a potential complication of liver failure, merits special consideration. It has been estimated that at least 25 % of patients with liver cirrhosis will experience HE during the natural history of the disease [25]. Although pathogenetically complex, accumulation of ammonia is considered a major contributor to the condition, which presents with neurological symptoms ranging from subclinical cognitive dysfunction to overt changes in the behavior and the state of consciousness that may reach a state of deep coma. HE is more frequent in patients with more severe liver insufficiency and in those with spontaneous or artificially created porto-systemic shunts. The treatment of HE was traditionally based on the correction of the precipitating factor, and the administration of non-absorbable disaccharides or non-absorbable antibiotics to decrease intestinal generation or ammonia absorption through the intestinal tract. Moreover, the restriction of protein intake has long been considered a mainstay for the treatment of HE. Convincing evidence from more recent studies, however, clearly suggests maintaining protein intake in patients with hepatic encephalopathy. Several authors have shown that protein restriction rather worsens the clinical condition of HE, whereas higher protein intake was associated with improvements in mental status. Proteins of vegetable origin have some theoretical benefits over animal proteins in the dietary regimen of patients with HE; their clinical usefulness, however, is controversial. Branched-chain amino acids, finally, are associated with better recovery from HE, although no advantage could be proven in patient survival.

12. Recommendations on energy and protein supply in chronic liver disease

Table I: Below are described the recommendations of the 1997 ESPEN consensus group [26]

Clinical condition	Non-protein energy kcal./kg/day	Protein or amino acids g/kg/day
Compensated cirrhosis	25–35	1.0–1.2
Complications, inadequate intake, malnutrition	35–40	1.5
Low-grade encephalopathy	25–35	Transient 1.0–1.5 if protein intolerance: vegetable protein or BCAA supplement
High-grade encephalopathy	25–35	0.5–1.2 BCAA enriched amino-acid solution

Oral and enteral routes are preferred and parenteral nutrition is used only when enteral feeding is not possible or impracticable

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