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Nutrition in chronic renal failure

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BACKGROUND

Malnutrition in patients with chronic renal failure is very common and is generally of mixed type with low body weight, loss of somatic protein (low muscle mass), low plasma levels of serum albumin and other visceral proteins as well as depletion of energy (adipose tissue) stores. In various studies, signs of malnutrition have been observed in 10-70% of HD patients and patients treated with continuous peritoneal dialysis (CAPD)[1]. Several reports suggest that anthropometric and biochemical signs of malnutrition are risk factors for morbidity and mortality in HD and CAPD patients[2,3].

Malnutrition in patients with renal failure may have many causes, including disturbances in protein and energy metabolism, hormonal disturbances, as well as low food intake, caused by uremic toxicity, superimposed illness and psychosocial problems[4]. Although some of the catabolic effects of chronic uremia may diminish or disappear after start of maintenance dialysis therapy, others may still persist. To these are added the catabolic effects of the dialytic treatment *per se,* which may increase protein requirements above those of non-dialyzed uremic patients and further aggravate malnutrition.

Assessment of malnutrition

History of malnutrition, weight loss and symptoms such as anorexia, nausea and vomiting are signs of impending or established malnutrition. It is useful to evaluate body mass status by calculating body mass index or relative body weight in % of standard body weight for equal sex and height (obtained from standard tables). Anthropometric measurements (skinfold thickness, arm muscle circumference, hand-grip strength) may give additional information about body composition. Subjective global nutritional assessment is a valuable tool for assessment of nutritional status which has been successfully applied in patients with end state renal disease (ESRD)[5,6]. Fluid status has to be taken into account, since CRF patients are frequently fluid overloaded.

Newer and more sophisticated methods are bioelectrical impedance (total body water and fluid spaces), dual emission X-ray absorptiometry (DEXA; skeletal mineral mass and fat mass) whole body nitrogen by neutron activation analysis and nuclear magnetic resonance or computerized tomography (muscle surface area), the latter three methods are mainly research tools. Several plasma protein are considered to be nutritional markers for protein deficiency, e.g. albumin (most common), prealbumin and transferrin. However these proteins are also influenced by several non-nutritional factors[7]. Nutritional intake can be estimated from dietary history and records. Intake of protein can be estimated from urea appearance rate measured directly in 24 urine and peritoneal dialysate[8], or, in hemodialysis (HD) patients, by urea kinetics, based on blood urea determinations[9].

PROTEIN AND ENERGY REQUIREMENTS

In normal adults, the average requirements for protein are about 0.6 g/kg of 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 (daily allowance) to 0.75 g/kg/day[10]. This variability is due to genetic differences, sex, age, physical activity, environment, chemical form of nutrients and effects of other dietary constituents.

Studies in non-dialyzed patients with chronic renal failure indicate that 0.6 g/kg body weight of protein of high quality (a high content of essential amino acids) may sustain nitrogen balance. Diets with lower protein content (about 0.3 g/day) supplemented with essential amino acids or mixtures of essential amino acids and nitrogen-free ketoacid analogues have also been used successfully, especially in situations when dialysis resources are inadequate[11].

The daily requirements of protein in dialysis patients are considerably higher than in normal individuals and non-dialyzed patients with chronic renal failure. On the basis of nitrogen balance studies and epidemiological studies, an intake of 1.2 g protein / kg body weight / day is generally recommended for HD and CAPD patients[1]. Children have generally higher requirements of protein per kg body weight than adult patients[12].

Energy requirements depend on the level of physical activity, an intake of 35 to 40 kcal / kg of body weight/day being recommended for adult individuals not performing heavy physical exercise. There are data showing that during a given physical activity the energy expenditure of HD patients does not differ from that in normal subjects[13]. Nor is there any evidence that the energy requirement in CAPD patients differ from normal. However, there are also conflicting data showing that resting energy expenditure is actually higher in HD patients than in normal controls[14].

LOW NUTRITIONAL INTAKES AND ANOREXIA IN DIALYSIS PATIENTS

Considering that requirements for protein are increased in dialysis patients and that an adequate energy supply is mandatory for maintaining the energy stores and optimizing the utilization of ingested protein, low protein and energy intakes must be especially harmful in such patients.

Appetite suppression in CRF patients is multifactorial. Some factors that may contribute to a low intake of protein and energy are listed in table I.

Uremic intoxication may lead to anorexia in non-dialyzed patients resulting in spontaneous reduction in protein and energy intake, starting at a GFR of 25-30 ml/min with further reduction along with progression towards end-stage renal failure[15,16]. Uremic appetite suppression is also observed in underdialyzed HD or CAPD patients. There is a decrease of protein and energy intake with time in CAPD patients[17], probably because they become underdialyzed as the total solute clearance falls, due to a decrease in residual renal function. The pathogenesis of uremic anorexia is not well understood, but several putatively anorexogenic factors have been identified in uremic plasma or in the central nervous system (table III).

Low nutritional intakes may also be due to unpalatable or inadequate diets, medications, gastropathy and reduced intestinal motility, e.g., in diabetic patients with autonomic neuropathy. Congestive heart failure and inflammation-infection (sepsis in HD patients and peritonitis in PD patients), and other forms of co-morbidity are also associated with malnutrition, in which scenario proinflammatory cytokines appear to play a major role *(vide infra).*

Psychosocial and socioeconomic factors, such as loneliness, depression, ignorance and poverty, especially in elderly patients and those with alcohol and drug problems may also be causes of low nutritional intakes.

Nausea and vomiting during and immediately after HD, which are frequently associated with cardiovascular instability and post-dialysis fatigue, may lead to a reduction in food intake during the days on dialysis. In CAPD, the presence of dialysate in the peritoneal cavity may interfere with gastric emptying and intestinal motility and cause discomfort or pain, as may the peritoneal catheter. It is also possible that glucose or amino acids absorbed from the dialysis fluid may exert an inhibiting effect on food consumption as has been shown in experimental studies in rats.

Tabla I. Causes of low nutritional intake in chronic renal failure

Uremic toxicity (underdialysis)
Unpalatable or inadequate diets
Complicating illness
Gastrointestinal illness
Cardiovascular disease
Inflammation, infection, sepsis
Medications
Psychosocial and socioeconomic factors
Loneliness
Depression
Ignorance
Poverty
Poor dental status
Alcohol and drug abuse
Effects of hemodialysis
Cardiovascular instability
Nausea, vomiting
Postdialysis fatigue
Effects of peritoneal dialysis
Abdominal distension and pain
Dialytic uptake of glucose or amino acids

PROTEIN CATABOLIC FACTORS IN CHRONIC RENAL FAILURE

Several factors in ESRD patients tend to decrease protein synthesis and/or increase protein breakdown,

Tabla II. Putative appetite-suppressing compounds in uremia

Leptin
Insulin
Cholecystokinin
Glucagon
Serotonin
Catecholamines
Amino acid imbalances
NO-synthase inhibitors
Pro inflammatory cytokines (TNF, IL-1, IL-6)
Middle molecules (plasma fraction with mol.weight 1 - 5 kd)

resulting in muscle wasting (loss of somatic protein) and low plasma levels of albumin and other plasma proteins (visceral protein loss). However, hypoalbuminemia may have many causes, not directly related to malnutrition, such as inflammation-infection (albumin is a «negative» acute phase protein), dilution (fluid overload), increased capillary leakage, urinary and peritoneal albumin losses. Some of the most important factors leading to net protein catabolism in CRF are listed in table II.

PHYSICAL INACTIVITY

Many patients on renal replacement therapy are physically inactive for various reasons, such as fatigue, anemia, cardiac disease, skeletal-muscular disease, and psychological factors. Physical inactivity may result in muscle wasting and a negative nitrogen balance. The sedentary life-style may also contribute to resistance to insulin action. The insulin sensitivity may in fact be improved by exercise training.

LOW ENERGY INTAKE AND PROTEIN CATABOLISM

Metabolic studies in healthy individuals, non-dialyzed CRF patients, HD patients and CAPD patients indicate that the nitrogen balance is highly dependent on the energy intake, so that a low energy intake results in negative nitrogen balance, whereas a high energy intake has a protein-saving effect[1]. Accordingly, a low energy intake, which is common in non-dialyzed and dialyzed patients with chronic renal failure, may impair the utilization of dietary protein, thus enhancing net catabolism of protein.

Tabla III. Protein catabolic factors in chronic renal failure

Physical inactivity
Low energy intake
Metabolic acidosis
Amino acid abnormalities
Endocrine abnormalities
Glucose intolerance and insulin resistance, Hyperglucagonemia
Growth hormone and IGF-1 resistance
Hyperparathyroidism
Renal anemia
Corticosteroid therapy
Co-morbidity
Cardiac disease
Inflammation, infection, sepsis
Other
Dialysis associated catabolism
Amino acid losses (HD; PD)
Protein losses (PD)
Low-grade inflammation (HD, PD?)

METABOLIC ACIDOSIS

It has become increasingly evident that metabolic acidosis is an important stimulus for protein breakdown in muscle[18]. Acidosis elicits its catabolic effects in muscle by stimulating the ubiquitin-proteasome proteolytic pathway and enhancing branched-chain amino acid catabolism by increasing the expression of branched-chain ketoacid dehydrogenase. Moreover, acidosis attenuates the generation of serum albumin by the liver[19]. In non-dialyzed chronic uremic patients, the correction of metabolic acidosis improves the nitrogen balance[20] and reduces urea appearance and muscle proteolysis[21]. There are also some studies suggesting that correction of acidosis may correct amino acid abnormalities[22] and improve nutritional status in dialysis patients[23].

Considering that metabolic acidosis is the only «uremic toxin» known to enhance protein catabolism and that acidosis may also have other harmful effects, full correction should obviously be a goal of treatment.

AMINO ACID ABNORMALITIES

Patients with chronic renal failure exhibit several abnormalities in amino acid metabolism due to nutritional inadequacy, endocrine disturbances, toxic influences on amino acid metabolism, loss of metabolizing renal tissue, and reduced renal excretion. The plasma aminogram is abnormal, with low concentrations of most essential amino acids and high concentrations of some non-essential amino acids, and is in many respects similar to that observed in individuals suffering from protein malnutrition.

Typical intracellular free amino acid abnormalities in skeletal muscle and erythrocytes are also observed in CRF patients.

ENDOCRINE ABNORMALITIES

Glucose intolerance, hyperinsulinemia, hyperglucagonemia, hyperparathyroidism and calcitriol deficiency are typically present in renal failure patients and have been suggested to enhance protein catabolism, although their roles in this respect are not well defined. In some cases with severe hyperparathyroidism the nutritional status may improve markedly after parathyroidectomy.

Growth hormone and insulin-like growth factor-1 (IGF-1) resistance: Alterations in the growth hormone/IGF-1 axis have been described in renal failure, possibly as a consequence of uremia and associated malnutrition. The basal serum levels of growth hormone are elevated while there is an acquired resistance to growth hormone. Serum IGF-1 levels are normal or increased but its bioactivity seems to be impaired. Growth failure in children with chronic renal failure is multifactorial, but may to a large part be attributed to growth hormone/IGF-1 resistance, which may be overcome by treatment with pharmacological doses of human recombinant growth hormone.

Anemia and erythropoietin: Renal anemia is usually present in most HD patients and may be severe, especially in anephric patients and in patients who are inadequately dialyzed. Anemia leads to fatigue, diminishing exercise capacity, and physical inactivity, which may contribute to muscle wasting and malnutrition. Correction of anemia with recombinant human erythropoietin (rHu-EPO) is reported to improve nutritional status to a moderate degree in groups of HD patients [24], which is presumably a secondary effect of anemia correction on general well-being, appetite and physical work capacity rather than a specific effect of rHu-EPO. Improvement of amino acid status has been observed in HD patients after correction of anemia with rH-EPO.

Corticosteroids: CRF patients may require corticosteroid therapy for their primary disease or other diseases. They increase appetite but stimulate net protein catabolism, which may result in protein malnutrition.

DIALYSIS PROCEDURES AS STIMULI OF NET PROTEIN CATABOLISM

The fact that maintenance dialysis patients appear to have much higher requirement for protein than healthy individuals and non-dialyzed patients with chronic renal failure indicates that there are elements in the dialytic procedures which induce net protein catabolism. There is evidence that this is due to both reduced protein synthesis and incerased protein breakdown.

Loss of amino acids and protein: 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. Moreover, 4-5 g of peptide-bound amino acids are lost per dialysis. Thus, the total losses of amino acids are about 10-13 g/dialysis[1]. Protein losses are insignificant except after several reuses of dialyzers with high-flux polysulfone membranes, using bleach as disinfectant. The losses of free amino acids into the dialysate during CAPD are of the same magnitude (per week) or smaller than with HD. However, substantial loss of protein into the dialysate (20-100 g/weak) is a major drawback in peritoneal dialysis[1]. Protein loss increases during and after peritonitis. Also, loss of protein is higher in high peritoneal transport rate patients.

Biocompatibility: Blood-membrane contact elicits an inflammatory response, the intensity of which depends on the membrane material used, and which is more marked with cellulosic than with synthetic membranes. Inflammation induced by blood-membrane interaction may lead to muscle proteolysis[25], presumably mediated by monocyte activation with release of proinflammatory cytokines.

CO-MORBIDITY AND MALNUTRITION

Infection and inflammation

Uremia leads to disturbances in the immune response, with cutaneous anergy and impaired granulocyte function, thus increasing the susceptibility to infection[26]. A severe infection is an important stimulus for protein catabolism. HD patients are especially at risk for developing sepsis from infections in arteriovenous fistulas, grafts and in-dwelling venous catheters. In CAPD patients, peritonitis not only stimulates protein catabolism but also increases the loss of protein and other nutrients by dialysis. Chronic inflammation as in SLE, rheumatoid arthritis and other systemic diseases, also increases protein catabolism. In patients with renal transplant failure chronic inflammation and treatment with corticosteroids may act in concert to stimulate protein catabolism.

Elevated plasma concentrations and increased generation by peripheral blood monocytic cells of proinflammatory cytokines (IL-1, IL-6, TNF-α) are reported in non-dialyzed CRF patients and also in HD and CAPD patients without other signs of inflammation or infection[27,28]. High circulating IL-6 levels are associated with loss of body weight and reduced arm-muscle circumference[29] and TNF-levels are more elevated in anorectic peritoneal dialysis patients than in patients without anorexia[30].

CARDIAC DISEASE AND MALNUTRITION

Several studies demonstrate that patients with chronic cardiac failure without renal disease may de-

velop weight loss, hypoalbuminemia and other signs of malnutrition, in its most advanced form (loss of < 10% of lean body mass) called cardiac cachexia[31]. Inactivity, sympathetic overactivity and malabsorption are present in cardiac failure patients, and there is evidence that TNF-α and other proinflammatory cytokines are major pathogenic factors in the development of malnutrition by enhancing protein catabolism and suppressing appetite. Infection and inflammation are also implicated as pathogenetic factors in atherosclerosis[32], conceivably mediated by proinflammatory cytokines. Cardiovascular disease and cardiac failure are frequently present in CRF patients and are the most common causes of death. Malnutrition, cardiac disease and inflammation (elevated C-reactive protein) are associated in CRF patients, and all three are strong predictors of mortality.

INTERVENTIONS TO INCREASE FOOD INTAKE AND STIMULATE APPETITE

Since uremia *per se* may cause anorexia, nausea and vomiting, a prerequisite for successful intervention is that uremic intoxication is alleviated or eliminated. In non-dialyzed patients this may be achieved by ordering a low protein diet. Such a diet should have a high energy content and may need to be supplemented with essential amino acids or their ketoanalogues to prevent protein malnutrition, and the nutritional status has to be monitored regularly to detect signs of malnutrition. Low protein diets are not recommended for patients with advanced renal failure without back up by dedicated dieticians and doctors; instead, early start of dialysis is then recommended[33].

Correction of underdialysis: In maintenance dialysis patients who are underdialyzed, the dose of dialysis should be increased so that it becomes adequate, since this may restore appetite and improve general well-being. If this is ignored, all other measures aimed at improving appetite may be futile.

Co-morbidity factors, such as infection, cardiac failure and gastrointestinal dysfunction need to be identified and if possible remedied in order to ensure an adequate nutritional intake. Correction of anemia by treatment with recombinant human erythropoietin is also reported to improve appetite in dialysis patients[24].

Dietary advice with the aim of increasing the quantity, quality and palatability of the food consumed may be helpful. Attention should be paid not only to the protein intake but also to the energy intake, which needs to be adequate for the optimal utilization of protein. Psychosocial and economical support should be provided whenever needed.

ENTERAL AND PARENTERAL NUTRITION

If severe malnutrition develops despite adequate dialysis and measures to eliminate various anorectic and catabolic factors, enteral or parenteral nutritional supplementation may be necessary to ensure an adequate supply of nutrients. Feeding by a nasogastric tube, a percutaneous gastric catheter or a gastrostomy button is preferable, whenever possible, to parenteral feeding through an indwelling venous catheter, which is more expensive and carries the risk of catheter-related sepsis. The impact of such therapies on morbidity and mortality has not been assessed in adult patients. However, it has been applied successfully in infants and small children with CRF, in whom growth and weight gain has been reported[34].

Intradialytic parenteral nutrition (IDPN) - i.e., the intravenous supply of a mixture of amino acids, glucose and lipids during the HD session - has become increasingly popular in recent years, since it can be given via the dialysis blood line while the patient is treated in the dialysis unit[35]. Favorable effects on nutritional status, including anthropometric parameters and serum proteins, have been reported.in some studies, and also on morbidity and mortality in two not well controlled studies[36] Hence, the issue whether or not IDPN is of proven benefit is still controversial. Nevertheless, it is reasonable to try this form of therapy in severely malnourished HD patients when all other measures fail, and especially during episodes of concurrent illness, with deterioration of nutritional status.

INTRAPERITONEAL AMINO ACIDS

Since protein malnutrition is frequently present in CAPD patients, several investigators have examined the nutritional benefit of substituting amino acids for glucose as osmotic agent in peritoneal dialysis solutions, thereby increasing the net intake of protein precursors[37]. In most of these studies such treatment was associated with improvement of nutritional indicators, including serum proteins, amino acid profiles, nitrogen balance and weight gain. Nutrineal® is a PD solution containing free amino acid in proportions adapted to the requirements of uremic patients, which is commercially available in several countries, has been shown to improve nitrogen balance in malnourished CAPD patients[38]. Long term treatement with Nutrineal® has beneficial effects on nutritional status[39,40].

GROWTH FACTORS

Recombinant human growth hormone (rHGH) is now available for the treatment of growth retarda-

tion and malnutrition; its anabolic effects are mainly mediated through the induction of IGF-1. There is evidence that uremic patients are partly resistant to the metabolic effects of rhIGF[41].

Treatment with rHGH is now an established therapy in growth-retarded uremic and transplanted children[12]. Short-term studies in adult HD patients with malnutrition have demonstrated that the administration of rHGH in combination with parenteral nutrition results in reduced urea appearance, sustained nitrogen retention, and improvement of nutritional status[42]. These results suggest that rHGH potentiates the anabolic effects of IDPN. The short term effects of rHGH has also been evaluated in a group of CAPD patients, in whom blood urea, urea appearance, serum potassium and serum phosphorus, decreased, suggesting protein anabolism[43].

Recombinant human IGF-1 (rhIGF-1) has also been proposed as a nutritional support in malnourished dialysis patients and has been reported to cause anabolism in a small group of CAPD patients[41].

Although data reported suggest that treatment with recombinant growth factors might be beneficial in adult malnourished patients with renal failure, it should be emphasized, that their long-term influence on mortality, morbidity and quality of life adult dialysis patients has not been established.

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