Nutrition in Renal Failure – the Role of Enteral Feeding

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Malnutrition is a common problem in patients with advanced renal failure, regardless of the cause of reduced renal function and the underlying kidney disease. However, from the nutritional point of view the situation differs depending on whether the patient has acute or chronic renal failure, whether treatment is by dialysis or other forms of blood purification, and the type of blood purification method used.

Acute Renal Failure

Acute renal failure is generally secondary to a severe disease episode which causes renal ischemia or generates toxic effects in the renal parenchymal cells or blood vessels. Trauma and shock, sepsis, multiorgan failure, crush syndrome (myoglobin), severe hemolysis (hemoglobin), intoxication with various poisons and drugs, hypersensitivity reactions, and acute glomerular diseases may all cause acute renal failure. Although acute renal failure is in most cases potentially reversible, mortality is high and especially so in patients with trauma, sepsis and multiorgan failure, depending on the underlying disease and its complications. The general principles of treatment are strict monitoring of vital functions, vigorous treatment of disorders observed, and metabolic monitoring and therapy [1]. Patients with severe renal failure need to be treated by some method of blood purification, which should be started early. Standard treatment used to be intermittent hemodialysis until the patient regained life-sustaining renal function. Peritoneal dialysis may also be used as an alternative, especially
in infants and children. In more recent years, continuous hemodialysis (diffusive transport), hemofiltration (convective transport), and hemodiafiltration (a combination of convective and diffusive transport) are techniques that are increasingly being used as alternatives to intermittent treatment, with the major advantage that fluid removal is facilitated by slow continuous ultrafiltration, and parenteral nutrition is facilitated [2].

**Nutritional Requirements in Acute Renal Failure**

Nitrogen requirements in acute renal failure vary with the extent of net protein catabolism, which depends on the severity of trauma, the presence of infection, and other catabolic factors. Recommended intakes in acute renal failure may be based on excess urea nitrogen over nitrogen intake [3]. Recommended nitrogen intake in adult patients is 0.10–0.15 g/kg body weight/day (protein intake 0.6–0.9 g/kg-day) when catabolism is mild, but as high as 0.2–0.3 g/kg-day (protein intake 1.3–1.9 g/kg-day) in severely catabolic patients. Recommended energy intake is between 30 and 40 kcal/kg, depending on the severity of the condition. Infants and children have higher nitrogen and energy requirements. Requirements for vitamins and minerals should be satisfied.

**Route of Administration of Nutrients in Acute Renal Failure**

**Oral Nutrition**

Some patients with acute renal failure, especially after intoxications or allergic episodes, may not be overtly sick, provided that blood purification is adequate. In such patients oral feeding is to be preferred, without any restrictions except for water, sodium, and potassium intake when there is oliguria or anuria.

**Parenteral Nutrition**

Patients with acute renal failure who have multiple trauma, sepsis, or severe intoxication are most commonly admitted to intensive care units and often require artificial respiration. Intravenous nutrition is normally used in these patients and is given through the venous blood line of the extracorporeal system into a central vein [1]. The potential risk of enhancing nitrogen retention and uremic intoxication is offset by efficient extracorporeal blood purification (continuous or daily intermittent), and fluid overload is prevented by ultrafiltration.

**Enteral Nutrition in Acute Renal Failure – Experimental Studies**

There are experimental studies suggesting that enteral nutrition might be beneficial in acute renal failure. Roberts et al. [4] infused peptide-based nutrition or water in rats through a duodenal feeding tube before inducing acute renal failure by intramuscular glycerol. Enteral feeding was associated with lower serum urea and creatinine, better survival, and higher glomerular filtration rate and renal plasma flow than in the water group. Mouser et al. [5] compared enteral and parenteral isocaloric or isonitrogenous nutrition given to rats for 7 days before subtotal nephrectomy and for the following 3 days. On day 11, serum creatinine
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was lower and histological changes in the kidney were less marked in the enteral nutrition group than in the parenteral nutrition group. It is doubtful whether these studies have any clinical relevance, considering that enteral nutrition was started before acute renal failure was induced and that there may be marked species differences.

Enteral Nutrition in Acute Renal Failure Patients

In adult intensive care patients with acute renal failure, enteral nutrition is rarely feasible, as these patients may have problems with gastrointestinal motility, enteral absorption, vomiting, and aspiration. However, in patients who are less severely ill, enteral feeding may be an alternative to parenteral nutrition. Enteral nutrition is more often used in infants and children with acute renal failure, who are as a rule treated with peritoneal dialysis.

Malnutrition in Chronic Renal Failure

Malnutrition in patients with chronic renal failure is very common and is generally of mixed type, with weight loss, loss of somatic protein (low muscle mass), low levels of serum albumin and other visceral proteins, and depletion of energy (adipose tissue) stores. In various studies, signs of malnutrition have been observed in 30–70% of patients treated with intermittent hemodialysis or continuous ambulatory peritoneal dialysis (CAPD) [6]. Several reports show that anthropometric and biochemical signs of malnutrition are risk factors for morbidity and mortality in patients with end-stage renal failure.

Malnutrition in patients with chronic renal failure may have many causes, including disturbances of protein and energy metabolism, hormonal imbalances, and low food intake because of inhibition of appetite by uremic toxins, superimposed illness, and psychosocial problems [7].

Although some of these disturbances may diminish or disappear after the start of maintenance dialysis therapy, others may persist. To these are added adverse effects of the dialysis treatment per se, which may lead to loss of protein and amino acids and enhanced protein catabolism, thereby increasing protein requirements above those of nondialyzed uremic patients [6].

Nutritional Requirements in Chronic Renal Failure

Studies in nondialyzed 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 a lower protein content (about 0.3 g/day), supplemented with essential amino acids or mixtures of essential amino acids and nitrogen-free keto acid analogs, may also be adequate for selected patients with a very low glomerular filtration rate (GFR, <5 ml/min), thus prolonging the period before start of renal replacement therapy [8].
The daily requirements of protein in dialysis patients are considerably higher than in normal individuals and nondialyzed patients with chronic renal failure. A protein intake of 1.2 g/kg body weight/day is generally recommended for hemodialysis and CAPD patients [6]. Energy requirements depend on the level of physical activity, an intake of 35–40 kcal/kg 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 hemodialysis patients does not differ from that in normal subjects [9], and there is no evidence that the energy requirement in CAPD patients differs from normal. However, there are also conflicting data showing that resting energy expenditure is actually higher in hemodialysis patients than in normal controls [10].

Children have generally higher requirements of protein and energy per kilogram of body weight than adult patients [11].

**Nutrition in Chronic Renal Failure**

Traditionally, low protein diets with a high energy content are recommended for nondialyzed chronic renal failure patients. Such regimes are based on observations that a low protein intake results in alleviation or disappearance of uremic symptoms such as nausea and vomiting, concurrently with a reduction in blood urea nitrogen. In patients with near end-stage renal failure (GFR <5–10% of normal), very low protein diets (0.3 g/kg body weight/day), supplemented with essential amino acids or amino acid/keto acid mixtures, may be used as an alternative to starting dialysis treatment in selected patients [8]. However, the feasibility of traditional nutritional regimen based on low protein diets has been questioned in recent years, considering that such regimens are difficult to carry through, require skill and dedication by doctors and dieticians (if available), and are bound to fail if the progression towards end-stage renal failure is too rapid. The risk of malnutrition has to be taken into account, especially if the patients are not appropriately educated and supervised, or are noncompliant. Instead, it is recommended that patients with progressive renal failure start relatively early (healthy start) before they develop malnutrition, as malnutrition at the start of dialysis carries an unfavorable prognosis [12].

As dialysis patients tend to have increased requirements for protein, it is recommended that they receive a high protein diet with an adequate energy supply. However, many of these patients may develop malnutrition because their intakes of protein and energy are far below the recommended requirements. Anorexia may be caused by uremia (underdialysis), in which case appetite may improve when the intensity of dialysis is increased. Various medical complications and psychosocial factors may also contribute to food aversion and inability to ingest food orally [13]. Patients with chronic renal failure may be hypercatabolic for a variety of reasons (acidosis, infection, heart failure, and
other comorbidity). If measures taken to increase the oral intake of nutrients fail, artificial nutrition is indicated. The most common method in hemodialysis patients is intradialytic parenteral nutrition (IDPN), which implies that a mixture of amino acids, glucose, and lipids is infused into the extracorporeal blood line during dialysis (4–5 h) [14]. In CAPD patients there is a continuous uptake of glucose from the dialysis fluid, which adds to the oral energy intake. Protein malnutrition in such patients may be treated or prevented by use of one or two daily exchanges of dialysis fluid containing amino acids, which are absorbed through the peritoneal membrane [15]. Both IDPN and peritoneal nutrition with amino acids may induce nausea and vomiting, which limits the amounts of nutrients that can be given.

**Enteral Nutrition in Chronic Renal Failure**

Nutrition by nasogastric tube, gastrostomy tube, or gastrostomy button are obvious alternatives to intravenous or intraperitoneal nutrition in patients with chronic renal failure, who, for a variety of reasons, do not have an adequate oral nutrient supply. Enteral nutrition has potential advantages over intravenous nutrition as it can be given more slowly (than IDPN), enables the patient to be ambulatory, may provide more balanced nutrition (for example, intravenous solutions contain too little tyrosine, which is an indispensable amino acid in uremia), and is considerably less expensive.

**Enteral Nutrition in Children**

Enteral nutrition has been extensively used as the treatment of choice in infants and children, both nondialyzed and dialyzed (most commonly by peritoneal dialysis), as a supplement to low oral intakes, or in infants as the sole nutrient supply [16]. It is generally possible to reach recommended intake levels for age using enteral nutrition [17, 18]. Some studies also report maintenance of or increase in growth rate [19–22]. Beneficial effects of enteral nutrition have been reported in infants and small children, but no studies are available to evaluate their success in older children and adolescents.

Vomiting is the most common side effect in pediatric patients receiving enteral nutrition. Several other side effects have also been reported, such as aspiration, leak of peritoneal dialysis fluid, exit site and gastric tube infection, peritonitis, tube migration with intestinal obstruction, gastrocutaneous fistula, perforation of the stomach, and parent anxiety [17, 23–27]. Wood et al. [26] reported that patients receiving nasogastric tube feeding had a complication rate of one episode per 6.4 patient months and that the complication rate in patients receiving gastrostomy tube feeding was very similar (one episode per 7.1 patient months). Long-term nasogastric feeding in infants may also result in impaired oral-motor development with persistent difficulties in chewing and swallowing, food refusal, and 'panic attacks' [23, 24].
Enteral Nutrition in Adult Patients with Chronic Renal Failure

Abras and Walser [28] studied four non-dialyzed patients with chronic renal failure, who were continuously fed a mixture of oligosaccharides, amino acids, and nitrogen-free ketoanalogs through a nasogastric tube during repeated periods of 3–10 weeks. They also ingested three small meals daily. The total nitrogen intake was as low as 3.3 g/day, but the nitrogen balance was nevertheless positive (average + 2.2 g/day), thus showing that this extreme regimen could support their nutritional needs and suggesting that continuous enteral nutrition might be advantageous for the utilization of dietary nitrogen.

Parenteral or enteral hyperalimentation has been used as a therapeutic adjunct in patients with end-stage renal failure undergoing elective or nonelective surgery [29]. Among patients with septic complications, the mortality in the nutritional support group was lower than in those not receiving hyperalimentation, regardless of the method of administration.

Long-term enteral nutrition is obviously an alternative to intravenous or intraperitoneal nutrition in adult patients with chronic renal failure in whom oral intake is too low to fulfill their requirements. Anecdotal evidence suggests that enteral nutrition is used in several renal units for selected adult patients with chronic renal failure. However, there are practically no data available demonstrating the feasibility of long-term enteral nutrition or the clinical outcome in this group of patients.

Enteral Nutrition in Renal Failure: Conclusions

Although several studies suggest that aggressive nutritional support may be of benefit in patients with renal failure, there is a lack of data derived from prospective, well-controlled clinical trials that prove the clinical value of such treatments. This is particularly the case with respect to enteral nutrition, where virtually no such data are available in patients with acute renal failure or in adult patients with chronic renal failure. In infants and small children with chronic renal failure, prospective studies suggest that enteral nutrition by nasogastric tube, gastrostomy tube, or gastrostomy button improves nutritional status and supports growth. Hence enteral nutrition appears to be the treatment of choice when artificial nutritional support is needed in nondialyzed as well as in dialyzed infants with chronic renal failure.

It is conceivable but not proven that enteral nutrition is also of clinical value as a simpler and less expensive alternative to enteral nutrition in adult patients with chronic renal failure and signs of malnutrition. Prospective clinical trials investigating the effect of enteral nutritional support on survival, hospital admission rate, functional status, and quality of life are now urgently needed.
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Discussion

Dr. Larsson: You were discussing different requirements for these patients regarding nitrogen, energy, and so on. What do we know about the utilization of nitrogen, for example in acute renal failure? Can they use 0.25 g nitrogen/kg day, or don’t we know that?

Dr. Bergström: There is no strong evidence on this; my figures were based on clinical observations. But I could turn the question around and ask whether intensive care patients who have no acute renal failure can utilize this amount of nitrogen, because I don’t think there’s very much difference in the requirements as long as the patients are adequately treated with dialysis or other forms of blood purification.

Dr. Larsson: There’s been some debate regarding critically ill patients.

Dr. Bergström: Yes, but I don’t think that we should view the renal failure as a factor which means that patients should be treated in a different way nutritionally. What you have to do is to dialyze the patients so that their renal failure has no clinical impact. I would say that in any intensive care situation, it’s never the renal failure that kills the patient because you can treat it very effectively. So the prognosis depends on other factors.

Dr. Young: Would you care to comment on the role of keto acids as a component of the amino acid protein and peptide support of patients with chronic renal failure?

Dr. Bergström: This stems from the observations that for some of the essential amino acids it is not the whole amino acid that is essential but the carbon skeleton. A keto acid, for instance α-ketovaleric acid which is the keto acid of valine, can take up an amino group from glutamate and form the complete amino acid. If you are in a situation where you want to spare nitrogen as much as possible, you could substitute some of the branched chain amino acids with their keto analogs, methionine with the hydroxy analog, and phenylalanine with the keto analog, and hope that they will transaminate. These patients certainly have an excess of nitrogen in the body, but unfortunately most of it is in urea, which is fairly inert except that it can be transformed into ammonia in the gut, but that’s a limited mechanism. The interest in using keto acids stems from the early 1970s when we didn’t have good resources for hemodialysis. Thus we tried to prolong the period before the patient needed dialysis, and one way of doing that is to give very low protein diets, as uremic toxic symptoms are associated with a high intake, or high metabolism, of protein. So by giving a low protein diet we could reduce these symptoms. If we add essential amino acids or keto acids and a high intake of energy, patients, even with a GFR of 5 ml/min, may be brought into positive nitrogen balance. This has gone out of fashion now because the tendency is to start dialysis relatively early.

Dr. Wernerman: Could you comment on acidosis in relation to nutrition. I’m referring in particular to chronic renal failure patients who have an acidosis that may be more or less corrected. From animal experiments there seems to be a upregulation of protein degradation in acidosis. However, in humans, at least in skeletal muscle, it seems that acidosis has more of an effect on synthesis?

Dr. Bergström: It’s evident that in experimental animals acidosis has two detrimental effects on protein metabolism. It increases the transcription of catabolic enzymes which
results in increased muscle protein catabolism, and it induces branched chain keto acid hydrogenase, which results in increased oxidation of the branched chain amino acids. We’ve shown in muscle biopsies that acidotic uremic patients have low intracellular concentrations of valine, leucine, and isoleucine [1]. This can be corrected by giving bicarbonate. In any case I would say that acidosis is not a big clinical problem because it is so easy to treat.

**Dr. Grimble:** I was very interested in your comment on intraperitoneal feeding and I wondered if you’d considered the possibility of using small peptides instead of amino acids for intraperitoneal feeding, for the good reason that their pKa is normally about one unit higher, and you get around the problems of peritoneal irritation that occur with amino acids?

**Dr. Bergström:** You are right, that is worth considering, especially in relation to the problem with tyrosine. We have animal studies going on now with peptides.

**Dr. Grimble:** I had something in mind that was a bit more radical, to use formulations that were entirely di- and tripeptides, not just to meet the requirements of selected amino acids.

**Dr. Bergström:** We have very recently obtained preliminary data on such a study in the rat. I can’t tell you much about the results yet, except say that they are very fascinating!

**Dr. Déchelotte:** Our colleagues in the nephrology unit are increasingly convinced that malnutrition carries a poor prognosis, but we are not yet able to say when we should be doing something active in these patients, such as providing them with a gastrostomy or a button. Clearly our clinical results are not yet convincing enough for our nephrology colleagues. How should a clinical trial be planned to answer this question?

**Dr. Bergström:** Attempts have been made to assess intradialysis parenteral nutrition but none of these studies has been convincing, except in infants. In a situation where you need hard endpoints like morbidity and mortality, you will need very large numbers of patients and the study will end up prohibitively expensive. My personal view on malnutrition and renal failure is that if you look at mortality in these patients you will see that they very rarely die from malnutrition or from causes directly related to malnutrition. They die from cardiovascular disease. We have recently published data showing that patients with cardiovascular disease on hemodialysis are much more malnourished than patients with no cardiovascular disease [2]. They are also older. An interesting finding is that they have evidence of inflammation, which is related to C-reactive protein. The strongest predictor of mortality up to now has been serum albumin, which has generally been taken as a nutritional marker. Serum albumin is indeed to some extent as a nutritional marker, and patients who are malnourished generally have low values. But there are many patients without obvious signs of malnutrition who have a low serum albumin, which may be related to cytokines and the acute phase reaction. There are several different reasons why these patients have raised proinflammatory cytokines. We should learn from the cardiologists: they are increasingly viewing atherosclerosis as an infectious or an inflammatory disease because of its association with C-reactive protein, chlamydia antibodies, and cytokines. What is valid for the general population with regard to inflammation, heart disease and malnutrition should also be valid for patients with renal failure.

**Dr. Larsson:** It could be a good thing to combine albumin measurements with C-reactive protein measurements.

**Dr. Bergström:** C-reactive protein is the easiest and most sensitive inflammatory marker, though the response is a little too rapid if you want to see what happens over a long period of time.

**Dr. Fürst:** I think that dipeptides could be used in dialysis for nutritional purposes, because they should be immediately cleaved. By using specific peptides you could provide
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a uremic patient with tyrosine, cysteine, or whatever. This would also help maintain the osmotic pressure during dialysis: thus the combined use of nutritional dipeptides with a short half-life together with ones that are released slowly would help maintain the osmotic pressure over a prolonged period while simultaneously providing the organs with the nutrients they need. It would, however, be expensive to synthesize these peptides and tailor them for specific purposes, and it may not be practicable for economic reasons.

Dr. Bergström: But if something is badly needed, the price will go down.

Dr. Fürst: I hope so.

Dr. Bergström: But there is another option. This is to use partly degraded starch, the so-called polyglucose, which is already used in commercial solutions for peritoneal dialysis, especially for the overnight period when patients take up so much glucose that the osmotic effect is lost. The hypothetical problem has been that the end product becomes maltose which accumulates, but if you only use polyglucose for one exchange a day you will dialyze away the maltose and no one has ever reported any untoward effects. A combination of peptides and polyglucose would probably be ideal, because some of the polyglucose is taken up and utilized. But we are talking about solutions which may perhaps be on the market 5 years from now.

Dr. Millward: I wanted to ask you about appetite in these patients. I remember reading that leptin levels are raised in renal patients, and I believe raised leptin is also part of the inflammatory response. Does this contribute to the poor appetite in renal patients?

Dr. Bergström: Leptin is induced by proinflammatory cytokines. It’s raised in patients with renal failure and very much so in relation to fat mass. There is discussion about whether it is inappropriately elevated in relation to fat mass. It is also dependent on insulin which is raised in patients with renal failure because of insulin resistance. The situation is thus very complicated. There is only indirect evidence of an effect on appetite. There are at least 20 different factors that could influence appetite in renal failure!

Dr. Young: You mentioned cardiovascular disease complications in chronic renal failure and that reminded me that the kidney is an important site for the metabolism of homocysteine. What is known about homocysteine levels in these patients? Might they be a contributing factor to the cardiovascular pathology?

Dr. Bergström: They are increased about threefold in chronic renal failure patients and some, probably mutants, may have a very high levels. This is a very confused subject, because homocysteine is also related to nutrition. We have published a study in Kidney International [3] showing that malnourished hemodialysis patients have lower homocysteine levels than patients with normal nutritional status and that those with lower homocysteine levels have the highest mortality. I believe this is because they were malnourished with low serum albumin. Most people measure total homocysteine and homocysteine is 75% bound to serum albumin. It’s a unique binding because it’s the only albumin binding that is higher in uremia than in normal subjects.

References