Are there two types of malnutrition in chronic renal failure? Evidence for relationships between malnutrition, inflammation and atherosclerosis (MIA syndrome)

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Introduction

It is believed that malnutrition is common in patients with chronic renal failure (CRF). They have reduced body weight, depleted energy (fat tissue) stores, loss of somatic protein (low muscle mass) and low levels of serum albumin, transferrin, pre-albumin and other visceral proteins. Various studies show signs of malnutrition in 23–76% of haemodialysis (HD) and 18–50% of peritoneal dialysis (PD) patients [1–4]. Such variations in the prevalence of malnutrition may be related to factors such as age, case mix, co-morbid conditions and quality of dialysis therapy. The aetiology of malnutrition in CRF is complex and may include many factors, e.g. poor food intake because of anorexia, nausea and vomiting due to uraemic toxicity, hormonal derangements, acidosis and increased resting energy expenditure.

While malnutrition by definition is caused by poor nutritional intake, laboratory or anthropometric measurements are generally used to define it clinically. Other factors can cause the same changes in body and plasma protein composition, especially inflammatory and infectious complications [5,6] and chronic heart failure (CHF). In addition, factors directly associated with the dialytic procedure, such as bio-incompatibility, nutrient losses in the dialysate and, during PD, poor appetite due to abdominal discomfort and uptake of glucose may also contribute to what we define as malnourishment in CRF. These may exert their action either by direct nutrient loss or by triggering the inflammatory response. However, since malnutrition also occurs in pre-dialysis patients [7], it is evident that dialysis-unrelated factors, e.g. infectious and inflammatory complications as well as co-morbidity, may also be important contributors to malnutrition in CRF.

Assessment of malnutrition in CRF

Many methods have been used to assess the presence of malnutrition in patients with CRF. A history of weight loss and symptoms such as anorexia, nausea and vomiting may indicate impending or established malnutrition. Anthropometric measurements, such as mid-arm muscle circumference, skinfold thickness and hand-grip strength may all be useful tools for estimating malnutrition. Hand-grip strength, in particular, has been shown to be an inexpensive, reliable and easily performed parameter of nutrition [4,8] that also predicts mortality in CRF patients (unpublished observation). Creatinine kinetics have also been advocated as a method to assess nutritional status. However, recent evidence suggests that it is unreliable in individual CRF patients [8,9]. More sophisticated methods used to evaluate nutritional status include bio-electrical impedance, dual-emission X-ray absorptiometry (DXA), nuclear magnetic resonance, computerized tomography, total body potassium and total body nitrogen, but mostly as research tools. Finally, several biochemical markers [e.g. serum albumin, pre-albumin, insulin-like growth factor-1 (IGF-1) and transferrin] have been used to evaluate nutritional status. Of these biochemical markers, serum albumin so far has been the most common to assess malnutrition, and hypoalbuminaemia has sometimes, perhaps erroneously (see below), been used to diagnose malnutrition [10].

Protein and energy requirements in chronic renal failure

The protein requirements in maintenance dialysis patients are not well defined. It can be assumed that the variation in protein requirements is much greater among dialysis patients than in healthy subjects, due to additional causes of variation, such as endocrine and biochemical abnormalities, anaemia, drugs, physical inactivity and co-morbidity, e.g. cardiovas-
cicular disease, diabetes and infections. In addition, specific effects of the dialytic process may increase the protein requirements, especially in patients treated with HD. The daily protein intake recommended is \( \sim 0.6 \text{g/kg body weight/day} \) in non-dialysed patients and at least \( 1.2 \text{g/kg body weight/day} \) in dialysis patients [11]. The energy requirements are dependent on the level of physical activity. In healthy subjects, an energy intake of \( 35–40 \text{kcal/kg body weight/day} \) is recommended for those not performing heavy physical exercise. There is no strong evidence that the energy requirements of chronic dialysis patients always differ from those of normal subjects [12,13] although increased energy expenditure has been reported in the former group [14]. A sufficient energy intake is needed to prevent protein from being utilized as an energy source via gluconeogenesis, and variations in energy intake can probably explain, at least partly, the inter-individual variations in nitrogen balance in CRF patients on similar protein intake [15]. However, the inter-patient variation in nitrogen balance with similar protein intake may also be related in part to the presence and degree of inflammation and/or co-morbid conditions. Thus, more studies are needed to evaluate dietary protein intake and energy requirements in clinically stable dialysis patients and in dialysis patients with co-morbid conditions and/or an inflammatory response [11].

Hypoalbuminaemia as a marker of malnutrition and mortality

It is well established that a low serum albumin level is a strong independent predictor of total and cardiovascular mortality in HD [16] and PD [17,18] patients. On the other hand, in non-renal patients, no association was found between serum albumin and cardiovascular disease [19], suggesting that a low serum albumin level per se does not necessarily contribute to cardiovascular mortality. Moreover, Koch et al. [20] have reported that the nutritional status alone does not predict overall or cardiovascular mortality, and Struijk et al. [21] have shown that serum albumin merely reflects the presence of systemic disease in dialysis patients. It has been proposed that the primary cause of hypoalbuminaemia in CRF is malnutrition [22]. However, poor food intake does not often result in hypoalbuminaemia if CRF is not present [23] and, although the food intake is markedly lower in patients with anorexia nervosa, serum albumin levels and the catabolic rate of albumin have been shown to be similar to those of control subjects [24]. Furthermore, in a prospective 24 week study in which healthy volunteers were subjected to semi-starvation (1500 kcal/24 h), serum albumin decreased only moderately (from 42.8 to 38.6 g/l) despite a 23% reduction in body weight (from 69.3 to 53.6 kg) and muscle mass [25]. Serum albumin levels may be low even in apparently well nourished HD patients, and they decrease in relation to the degree of malnutrition [4]. Although they differ markedly in patients with or without inflammation, they do not differ significantly between well-nourished and malnourished pre-dialysis patients [8], suggesting that serum albumin is a poor nutritional marker also in dialysis patients [26,27]. Despite these findings and the fact that today several alternative methods are available for assessing nutritional status, serum albumin still seems to be, by far, the most commonly used nutritional marker in CRF patients.

Serum albumin concentration is best seen as being regulated by several factors, especially protein malnutrition, inflammation and external losses. The latter is important in PD, where transperitoneal losses may be as great as \( 20 \text{g/24 h} \) [28], and in HD, especially following re-use with bleach [29], although other processes may also increase dialysate permeability to albumin. While dietary protein insufficiency may also cause a modest reduction in serum albumin concentration, inflammation by itself can lead to a very marked reduction [30]. Inflammation can cause hypoalbuminaemia by suppressing albumin synthesis [30] and by causing transfer of albumin from the vascular to the extravascular space. The combination of inflammation and reduced protein intake will lead to a significant reduction in serum albumin concentration [31], as shown in Figure 1.

Pro-inflammatory cytokines cause malnutrition and cardiovascular disease

In recent years, several reports have suggested that inflammation, alone or in combination with a low protein intake, plays a significant role in causing hypoalbuminaemia in CRF patients [31–34] (Figure 1). This is not unexpected since both serum albumin and C-reactive protein (CRP) participate reciprocally in the same acute-phase process. It has been established recently that moderately elevated plasma concentrations of CRP are associated with an increased risk of cardiovascular disease in otherwise healthy subjects. In non-renal patient populations, elevated levels of CRP are associated with cardiovascular morbidity [35], ischaemic stroke [36] and mortality in the elderly [37]. Likewise, several groups recently have reported that an increased CRP is also a strong risk factor for death [33,38,39], cardiovascular mortality [38] and hospitalization [40] in dialysis patients. Furthermore, recently we have found a strong relationship between malnutrition, elevated CRP levels and atherosclerosis in pre-dialysis patients [7].

The prevalence of an increased CRP (\( >8–10 \text{mg/l} \)) has been reported to be high in dialysis [4,38,41] and pre-dialysis [7] patients. Serum levels of CRP appear to reflect generation of pro-inflammatory cytokines [interleukin-1 (IL-1), IL-6 and tumour necrosis factor-\( \alpha \) (TNF-\( \alpha \))] which have also been reported to be increased in CRF patients [42,43]. It is well documented that high levels of pro-inflammatory cytokines may cause muscle wasting by stimulating protein cata-
Malnutrition in chronic renal failure

Inflammation is often said to be a major cause of weight loss and wasting. Although REE may be increased in patients with CHF [47], cancer [48,49], rheumatoid arthritis [50] and AIDS [51], either normal [12,13,52] or increased [14] REE have been observed in CRF patients. These discrepant REE findings in dialysis patients are not understood. However, inflammation repeatedly has been shown to be associated with increased REE in other patients with wasting disorders [48–50,53]. On the basis of these observations, some of the reported variations in REE in dialysis patients may reflect differences in the prevalence of inflammation. Thus, the presence of the acute-phase response permits identification of hypermetabolic patients [48]. Indeed, Schneeweiss et al. [13] have reported increased REE in dialysis patients with infections. Therefore, since inflammation increases REE, we suggest that this may be a factor contributing to protein calorie malnutrition in CRF patients.

Increased oxidative stress in malnourished and inflamed patients

Oxidative stress, which occurs in the presence of excessive free-radical production or low anti-oxidant levels, is an important co-factor for development of endothelial dysfunction and atherogenesis. Recent data indicate that increased oxidative stress occurs in dialysis patients [54]. Malnourished pre-dialysis patients have biochemical evidence of more oxidative stress than well-nourished ones [55]. Moreover, malnourished pre-dialysis patients have lower plasma levels of vitamin E [7], suggesting a low intake of anti-oxidants when nutritional intake is low. In addition, recent data show that inflammation is associated with an increase in oxidative stress [56] and that advanced oxidation protein products are associated with monocyte activation [44] by reducing albumin synthesis and by inhibiting appetite [45]. It has also been observed that IL-1, TNF-α and endotoxins may induce net catabolism of muscle protein by stimulating branched-chain ketoacid dehydrogenase, which leads to greater oxidation of branched-chain amino acids [46]. In consequence, increased plasma levels of pro-inflammatory cytokines predict hypoalbuminaemia [34] and mortality [34,43] in dialysis patients. Furthermore, whereas serum albumin and CRP predict mortality in univariate analysis, only CRP is a significant predictor in multivariate analysis [33,38]. Taken together, available evidence suggests that the increased mortality rate observed in CRF may be associated with an acute-phase response rather than low serum albumin levels caused by other mechanisms.

Inflammation increases resting energy expenditure

Energy deficiency due to low energy intake and increased resting energy expenditure (REE) may be another important cause of wasting in dialysis patients. In general, failure to down-regulate REE as an adaptation to anorexia is often said to be a major cause of weight loss and wasting. Although REE may be increased in patients with CHF [47], cancer [48,49], rheumatoid arthritis [50] and AIDS [51], either normal [12,13,52] or increased [14] REE have been observed in CRF patients. These discrepant REE findings in dialysis patients are not understood. However, inflammation repeatedly has been shown to be associated with increased REE in other patients with wasting disorders [48–50,53]. On the basis of these observations, some of the reported variations in REE in dialysis patients may reflect differences in the prevalence of inflammation. Thus, the presence of the acute-phase response permits identification of hypermetabolic patients [48]. Indeed, Schneeweiss et al. [13] have reported increased REE in dialysis patients with infections. Therefore, since inflammation increases REE, we suggest that this may be a factor contributing to protein calorie malnutrition in CRF patients.

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not yet known whether CRF patients have reduced or increased NO production because, although whole-body NO production is reduced [61], excretion of NO is increased in exhaled air of patients with CRF [62]. However, both PD [63] and HD [64] patients have impaired endothelium-dependent vasodilation. It should be noted that NO forms an adduct with serum albumin that has endothelium-derived relaxing properties [65]. Thus, low albumin levels could be associated with impaired endothelial-dependent vasodilation.

Although Kim et al. [66] showed correlations between serum albumin, CRP and serum markers of endothelial function, an infusion of albumin did not normalize endothelial function. Consequently, their findings strongly suggest that the relationship between low serum albumin levels and endothelial dysfunction may be secondary to other factors, such as inflammation. Indeed, Kessler et al. [67] have reported in rabbits that pro-inflammatory mediators inhibit the formation of endothelium-dependent hyperpolarizing factor which may contribute to endothelial dysfunction. Moreover, an increased CRP is associated with endothelial dysfunction in patients with diabetes [68]. Altogether, available evidence suggests that inflammation can be associated with endothelial dysfunction, which may accelerate atherosclerosis.

CHF may cause wasting in dialysis patients

It has been well documented that CHF is associated with malnutrition (cardiac cachexia) and increased levels of pro-inflammatory cytokines. More than 50% of patients with CHF have signs of cardiac cachexia [69]. Evidence of muscle wasting is present even in mild CHF [70], and muscle wasting appears to be related to reduced exercise capacity [71]. The pathogenesis of cardiac cachexia is not understood, and no relationship between nutritional intake and cardiac cachexia has been established. However, elevated serum levels of TNF-α are related to cardiac cachexia [72]. The serum levels of IL-6 are also significantly higher even in mild or moderate CHF [73]. It has been suggested that pro-inflammatory cytokines, generated in response to factors such as reduced tissue perfusion, altered gut permeability and congestion, may play an important role in the loss of lean body mass in these patients. Indeed, cardiac cachexia is a strong independent risk factor for mortality in patients with CHF [74]. Since the prevalence of CHF is high among dialysis patients [75], CHF may contribute to wasting, elevated levels of pro-inflammatory cytokines and increased mortality even in dialysis patients.

Relationship between malnutrition, inflammation and cardiovascular disease

It may seem puzzling that whereas hypoalbuminaemia and inflammation have been shown to be important predictors of mortality in dialysis patients, complications from malnutrition as such are not common causes of mortality in dialysis patients [76]. In fact, malnutrition accounts for <5% of deaths in renal patients [77] while atherosclerotic cardiovascular disease is by far the most common cause of mortality in the dialysis population [78]. How can this finding be explained? A recent study suggests that strong interactions exist between cardiovascular disease and inflammatory as well as nutritional parameters in CRF patients [7]. We have therefore suggested the existence of a syndrome consisting of malnutrition, inflammation and athero-sclerosis (MIA syndrome) in some patients with CRF [79]. Indeed, inflammation is more common in malnourished HD patients [4], and Ikizler et al. [40] have shown that the nutritional status and inflammatory response are independent predictors of hospitalization in HD patients. Moreover, malnutrition [80] and inflammation [38] are associated with a higher cardiovascular mortality rate in HD patients. Taken together, available evidence suggests that nutritional and inflammatory markers are closely linked to cardiovascular disease in CRF. It therefore seems likely that elevated levels of pro-inflammatory cytokines could be the link between the high prevalence of inflammation, malnutrition and cardiovascular disease in patients with CRF (Figure 2).

Are there two types of malnutrition in dialysis patients?

On the basis of findings discussed above, it seems reasonable to conclude that the acute-phase response and malnutrition are closely linked and that both these conditions may contribute to the excessive atherosclerotic cardiovascular mortality observed in dialysis patients?
patients. Therefore, like Baltzan and Shoker [81], we believe that at least two types of malnutrition may occur in dialysis patients (Table 1). The first type (type 1) is associated with the uraemic syndrome per se or factors associated with uraemia (such as physical inactivity, underdialysis, dietary restrictions and psychosocial factors). It is characterized by a modest reduction in serum albumin levels, because of lower protein and energy intake due to uraemic toxicity. The first signs of protein and energy malnutrition begin early in the course of progressive renal failure [82] and the development of renal failure is associated with a spontaneous decrease in dietary protein intake [83]. Significant co-morbidity, such as CHF, and elevated levels of pro-inflammatory cytokines are usually not present in this type of malnutrition. The main feature is a low protein energy intake due to uraemic anorexia, with a corresponding decrease in protein catabolism. REE may be normal in this type of malnutrition. More marked hypoalbuminaemia, higher REE, markedly increased oxidative stress and increased protein catabolism, on the other hand, would characterize the other type of malnutrition (type 2). Significant co-morbid conditions, such as CHF, frequently are found in this type of malnutrition, and there is usually an inflammatory response, as evidenced by higher levels of CRP and pro-inflammatory cytokines. However, the spectrum of malnutrition in CRF may involve a continuous overlap between both types of malnutrition (Figure 3), and most dialysis patients probably have a mixed type of malnutrition. It is of interest that if one uses either normalized protein catabolic rate in HD patients, or subjective global assessment in pre-dialysis patients as markers of nutrition, reduction in serum albumin concentration below values of 3.5 g/dl is only encountered when CRP levels are increased (Figure 1). Thus, hypoalbuminaemia in these patient populations may well reflect this combination between malnutrition and inflammation. It seems likely that ‘cytokine-driven’ type 2 malnutrition occurs not only in CRF patients but also in those with wasting disorders, e.g. CHF, chronic inflammatory diseases (e.g. rheumatoid arthritis and AIDS), advanced cancer and chronic respiratory insufficiency.

### Table 1. Proposed features of type 1 and type 2 malnutrition

<table>
<thead>
<tr>
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<th>Type 1</th>
<th>Type 2</th>
</tr>
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<tbody>
<tr>
<td>Serum albumin</td>
<td>Normal/low</td>
<td>Low</td>
</tr>
<tr>
<td>Co-morbidity</td>
<td>Uncommon</td>
<td>Common</td>
</tr>
<tr>
<td>Presence of inflammation</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Food intake</td>
<td>Low</td>
<td>Low/normal</td>
</tr>
<tr>
<td>Resting energy expenditure</td>
<td>Normal</td>
<td>Elevated</td>
</tr>
<tr>
<td>Oxidative stress</td>
<td>Increased</td>
<td>Markedly increased</td>
</tr>
<tr>
<td>Protein catabolism</td>
<td>Decreased</td>
<td>Increased</td>
</tr>
<tr>
<td>Reversed by dialysis and nutritional support</td>
<td>Yes</td>
<td>No</td>
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**Nutritional support in uraemic patients with malnutrition**

To date, >20 studies have investigated the effects of intradialytic nutritional support in patients with CRF [84]. Overall, the findings have been difficult to interpret usually because of the lack of control groups. A recent review indicated that the data supporting the use of intradialytic parenteral nutrition are weak [84].

**Fig. 3. Proposed relative contribution of non-inflammatory components (such as low intake of protein and energy due to uraemic anorexia, underdialysis, physical inactivity, etc.) and the inflammatory components of malnutrition in patients with type 1 and type 2 malnutrition, respectively.**

**New treatment strategies are needed**

Despite the considerable improvement in dialysis technology, the mortality rate from cardiovascular disease
is still unacceptably high in dialysis patients [78] and new treatments obviously are needed for the next century. Indeed, several new strategies may be of interest and should be tested in prospective interventional trials in patients having malnutrition associated with MIA syndrome. In view of the strong associations between CHF, muscle wasting and elevated levels of pro-inflammatory cytokines, we believe that it is very important to optimize cardiac performance in dialysis patients. In this respect, treatment with angiotensin-converting enzyme inhibitors (ACEIs) may be of particular interest. This class of drugs has been shown not only to improve cardiac function and reduce the mortality rate in patients with cardiovascular disease [88,89], but also to be associated with a better nutritional status and lower levels of TNF-α in CRF patients [90]. Anker et al. [91] recently found that treatment with ACEIs reduced the risk of developing weight loss in patients with CHF. It is thus possible that ACEIs, in addition to their favourable haemodynamic effects, may also improve the response to metabolic and immunological abnormalities in CRF. In view of the documented association between increased oxidative stress and endothelial dysfunction [60], we speculate that anti-oxidant supplementation may improve endothelial function in malnourished dialysis patients. Indeed, vitamin C improves endothelial dysfunction of the pericardial coronary arteries in hypertensive patients [92].

Since there is now mounting evidence suggesting that certain persistent bacterial and viral infections may play a role in the pathogenesis of cardiovascular disease [93], prospective studies are needed to determine whether anti-bacterial or anti-viral treatment may improve the cardiovascular and nutritional status of dialysis patients. Finally, anti-cytokine therapy (e.g. anti-TNF-α antibodies, soluble TNF-α receptors and IL-1 receptor antagonists) in other patient groups with wasting disorders [94] has been found to be associated with a rapid improvement not only in clinical findings but also in inflammatory parameters. It should also be noted that thalidomide (which selectively inhibits the degradation of TNF-α mRNA transcripts) reverses the wasting syndrome associated with HIV [95] and tuberculosis [96]. Prospective studies are therefore needed to investigate whether anti-cytokine therapies are safe and may have a beneficial effect on cardiovascular and nutritional status and mortality rate in CRF patients with signs of wasting and inflammation.

Conclusions

Chronic inflammation, as evidenced by increased levels of pro-inflammatory cytokines and CRP, is common in CRF patients and may cause malnutrition and progressive atherosclerotic cardiovascular disease by several pathogenetic mechanisms. We therefore propose that at least two types of malnutrition exist in CRF: one without (type 1) and one with (type 2) a concomitant inflammatory response and significant co-morbidity. It is likely that the treatment strategies for these types of malnutrition should be very different. We suggest that in future prospective studies, in which the effects of various interventions on nutritional and/or cardiovascular status are evaluated in CRF patients, an appropriate assessment of inflammatory status and distinction between the two types of malnutrition should be made.

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References

17. Avram MM, Fein PA, Bonomini L et al. Predictors of survival in continuous ambulatory peritoneal dialysis patients: a five year
prospective study. *Peritoneal Dial Int* 1996; 16 [Suppl. 1]: S190–S194


41. Owen WF, Lowrie EG. C-reactive protein as an outcome predictor for maintenance hemodialysis patients. *Kidney Int* 1998; 54: 627–634


73. Munger MA, Johnsson B, Amber IJ, Callahan KS, Bil bert EM. Circulating concentrations of proinflammatory cytokines in mild or moderate heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. *Am J Cardiol* 1996; 77: 723–727.


91. Anker SD, Negassa A, Coats AJ, Poole-Wilson PA, Yusuf S. Weight loss in chronic heart failure (CHF) and the impact of treatment with ACE inhibitors. Results from the SOLVD treatment trial. *Circulation* 1999; 100: 1781.


