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Peer reviewed

# Kidney insufficiency and nutrient-based modulation of inflammation

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## Purpose of review

Patients with chronic kidney disease have a high cardiovascular mortality rate. Despite recent advances in dialysis techniques, over 20% of US dialysis patients die every year. Protein–energy malnutrition and inflammation are common and usually concurrent in chronic kidney disease patients, and have been implicated as the main cause of high mortality. We reviewed the pathophysiology of the malnutrition–inflammation complex syndrome and its potential modulation by dietary and other nutritional interventions in chronic kidney disease patients.

## Recent findings

The malnutrition–inflammation complex syndrome is a main cause of the atherosclerotic cardiovascular disease epidemic in chronic kidney disease. This may be by virtue of the syndrome's inflammatory components. Malnutrition and inflammation lead to weight loss over time, i.e. cachexia in slow motion, and result in decreased serum cholesterol and homocysteine levels. A 'reverse epidemiology' of cardiovascular risk factors is observed in chronic kidney disease, in that obesity, hypercholesterolemia and hyperhomocysteinemia are paradoxically associated with better survival. Among the possible etiologies of the malnutrition–inflammation complex syndrome, anorexia, low nutrient intake and oxidative stress are theoretically amenable to dietary modulation; however, the bulk of findings are epidemiological.

## Summary

There is no consensus as to how to correct the malnutrition–inflammation complex syndrome in chronic kidney disease patients. Because the malnutrition–inflammation complex syndrome is multifactorial, its correction probably requires a battery of simultaneous interventions, rather than one single modality. Clinical trials focusing on the syndrome are currently non-existent and are therefore urgently required to improve poor clinical outcome in chronic kidney disease patients.

## Keywords

atherosclerosis, cardiovascular disease, dialysis, malnutrition–inflammation complex syndrome, outcome, protein–energy malnutrition, reverse epidemiology

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**Abbreviations**

| | |
|---|---|
| **CKD** | chronic kidney disease |
| **CRP** | C-reactive protein |
| **ESRD** | end-stage renal disease |
| **IDPN** | intradialytic parenteral nutrition |
| **MA** | megestrol acetate |
| **MIA** | malnutrition–inflammation–atherosclerosis |
| **MICS** | malnutrition–inflammation complex syndrome |

## Introduction

In the United States, approximately 20 million individuals have chronic kidney disease (CKD), i.e. irreversible damage to the kidney with progression over time to end-stage renal disease (ESRD) [1]. There are currently approximately 300 000 ESRD patients in the USA, whose renal replacement therapy consists of maintenance hemodialysis (over 90%) or chronic peritoneal dialysis treatment (8–10%) [1]. According to the estimates of the United States Renal Data System, the number of maintenance dialysis patients will approach one-half million by the year 2010 [2]. These patients experience a lower quality of life, greater morbidity, higher hospitalization rates and increased mortality, currently still approximately 20% annually. The incidence and prevalence of cardiovascular disease are markedly elevated in these individuals, despite many recent improvements in dialysis treatment [2]. Several recent multicenter clinical trials, including the HEMO [3] and ADAMEX [4] studies failed to show any survival advantage of increasing dialysis dose or membrane in ESRD patients. The recent Deutsche Diabetes Dialyse Studie (4D Study) in 1255

dialysis patients, randomly assigned to receive either atorvastatin 20 mg or placebo, did not show any significant advantage of using statins in improving survival [5]. Modulating other cardiovascular risk factors such as hyperhomocysteinemia in dialysis patients has not led to major improvements in survival in this population either [6••,7•,8]. Therefore, the question as to how to improve the poor clinical outcomes, especially the high rate of cardiovascular disease and mortality, in dialysis and other CKD patients remains unanswered.

## Reverse epidemiology

Many reports have indicated that in advanced CKD and dialysis patients there is a high prevalence of protein–energy malnutrition, up to 40% or more, and a strong association between malnutrition and greater morbidity and mortality [9]. In highly industrialized, affluent countries, malnutrition is an uncommon cause of poor outcome in the general population, whereas 'overnutrition' is associated with a greater risk of cardiovascular disease, and has an immense epidemiological impact on the burden of this disease and on shortened survival [10]. In contrast, in dialysis patients 'undernutrition' is one of the most common risk factors for adverse cardiovascular events and death [11,12•]. The terms 'reverse epidemiology' or 'risk factor paradox' underscore this paradoxical observation [11]. These terms indicate that certain markers which predict a low likelihood of cardiovascular events and indeed an improved survival in the general population, such as decreased body mass index and lower serum cholesterol, become paradoxically strong risk factors for increased cardiovascular morbidity and death in hemodialysis patients. Moreover, some indicators of overnutrition actually predict improved outcome in hemodialysis patients [11,12•,13]. The reverse epidemiology phenomenon is not quite unique to the hemodialysis population. Elderly individuals such as octogenarians, patients with congestive heart failure, AIDS, or malignancy, and possibly other vulnerable populations may have a similar risk factor paradox [11,14,15] (see Table 1). Therefore, the key to improved survival in over 20 million Americans (and many millions throughout the world) may lie in interventions to modify

**Table 1. Populations with a 'reverse epidemiology' or 'risk factor paradox'**

| Population | Estimated census in the USA |
| --- | --- |
| ESRD undergoing dialysis | 0.3–0.4 millions |
| Chronic heart failure | 4–5 millions |
| Advanced age (> 75 years) | 15–20 millions |
| Nursing home residency | 0.3–0.5 millions |
| Advanced malignancies | 0.4–0.8 millions |
| AIDS | 0.1–0.3 millions |
| Total | 20–30 millions |

ESRD, End-stage renal disease, hemodialysis was maintenance dialysis. Adapted from Kalantar-Zadeh *et al.* [14], with permission from S. Karger AG, Basel.

**Table 2. Causes of wasting ('cachexia in slow motion') and protein–energy malnutrition in chronic kidney disease patients**

| | |
| --- | --- |
| A. | Inadequate nutrient intake |
| | 1. Anorexia[a] |
| |   (a) Caused by uremic toxicity |
| |   (b) Caused by impaired gastric emptying |
| |   (c) Caused by inflammation with or without co-morbid conditions[a] |
| |   (d) Caused by emotional and/or psychological disorders |
| | 2. Dietary restrictions |
| |   (a) Prescribed restrictions: low-potassium, low-phosphate dietary regimens |
| |   (b) Social constraints: poverty, inadequate dietary support |
| |   (c) Physical incapacity: inability to acquire or prepare food or to eat |
| B. | Sources of nutrient losses in dialysis patients |
| | 1. Loss through hemodialysis membrane into hemodialysate |
| | 2. Adherence to hemodialysis membrane or tubing |
| | 3. Loss into peritoneal dialysate |
| C. | Hypercatabolism caused by co-morbid illnesses |
| | 1. Cardiovascular diseases[a] |
| | 2. Diabetic complications |
| | 3. Infection and/or sepsis[a] |
| | 4. Other co-morbid conditions[a] |
| D. | Hypercatabolism associated with dialysis treatment |
| | 1. Negative protein balance |
| | 2. Negative energy balance |
| E. | Endocrine disorders of uremia |
| | 1. Resistance to insulin |
| | 2. Resistance to growth hormone and/or IGF-1 |
| | 3. Increased serum level of or sensitivity to glucagons |
| | 4. Hyperparathyroidism |
| | 5. Other endocrine disorders |
| F. | Acidemia with metabolic acidosis |
| G. | Concurrent nutrient loss with frequent blood losses |

IGF-1, Insulin-like growth factor 1. [a] The given condition may also be associated with inflammation. Adapted from Kalantar-Zadeh *et al.* [9].

non-conventional cardiovascular risk factors, including inflammation and malnutrition, which lead to reverse epidemiology in such distinct populations [14].

## Malnutrition–inflammation complex syndrome

CKD-associated malnutrition is a multifactorial condition (see Table 2) [9]. CKD patients not only have a high prevalence of malnutrition but also a higher occurrence rate of inflammatory processes [16–18,19•]. As evident from Table 2, many conditions leading to malnutrition and wasting may also cause inflammation. As both malnutrition and inflammation are strongly associated with each other and can change many nutritional measures and outcomes in the same direction, and because the relative contributions of the measures of these two conditions to each other and to poor outcomes in CKD patients are not yet well defined, the term 'malnutrition–inflammation complex syndrome' (MICS) has been suggested to denote the important contribution of both of these conditions to ESRD outcome (see Fig. 1) [9]. Alternatively, it has been called the 'malnutrition–inflammation–atherosclerosis' (MIA) syndrome to underscore the strong association of MICS with atherosclerotic cardiovascular disease and high morbidity and mortality
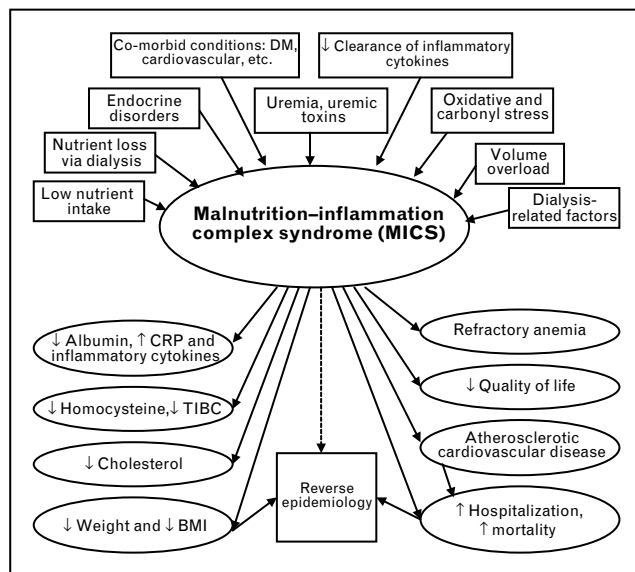
BMI, Body mass index; CRP, C-reactive protein; DM, diabetes mellitus, TIBC, total iron-binding capacity. Adapted from Kalantar-Zadeh et al. [9].

in CKD [20]. The MICS/MIA appears to be a plausible cause of the above-mentioned reverse epidemiology and poor dialysis outcome [9,11,12•,13,14]. Moreover, unlike cancer cachexia, the wasting syndrome in CKD usually does not lead to immediate death as a result of the direct consequences of malnutrition but acts over time to promote atherosclerotic cardiovascular disease [21], hence the term 'cachexia in slow motion' may be more appropriate to identify this syndrome.

## Exploring new interventions to improve outcomes in chronic kidney disease patients

CKD and ESRD patients continue to have an unacceptably poor survival rate [2,22]. Efforts so far to improve survival by focusing on conventional cardiovascular risk factors or dialysis techniques have practically failed [3,5,6••]. Ironically, although some traditional risk factors, such as hypertension, are highly prevalent in CKD patients, the evidence showing a significant link between hypertension and poor clinical outcome in these patients is not convincing, and indeed the association is reversed in hemodialysis patients, which is another component of the reverse epidemiology [23••]. The combination of poor outcomes and inverse risk factor–outcome association demonstrates that there is a great need to test the benefit of therapeutic interventions that modulate such non-traditional risk factors as malnutrition and inflammation.

## Short-term versus long-term survival

In contrast to the conventional cardiovascular risk factors and overnutrition that require several years to decades to exert their deleterious effect, the impact of undernutrition is fast, with decreased survival ensuing within a much shorter period of time. This 'time discrepancy' may explain the reverse epidemiology phenomenon observed in vulnerable populations, in whom undernutrition overwhelms the presence of overnutrition, leading to poor short-term survival (Table 1) [9,11,12•,13,14]. Therefore, no matter how strongly such cardiovascular risk factors as hypertension, hyperhomocysteinemia or obesity are present, dialysis patients will continue to die excessively and fast as long as the short-term impact of MICS-associated undernutrition and anorexia prevails. In other words, malnourished or inflamed dialysis patients will not live long enough to die of obesity or hypertension, because they die much faster of MICS [14]. This explanation of reverse epidemiology may have major clinical implications in the management of CKD patients. If the main issue is indeed the high rate of short-term mortality (20% per year), it is also expected that a short-term intervention that can correct the underlying condition (i.e. MICS) can also improve short-term survival.

## Malnutrition–inflammation complex syndrome as the major cause of poor outcome in end-stage renal disease patients

At present, the preponderance of evidence is epidemiological and counterfactual. However, the consistency of the studies is impressive. The salient implication for the possible role of MICS in causing poor outcomes in ESRD patients lies in its short-term effect and its overwhelming impact, leading to the reversal of the associations between traditional cardiovascular risk factors and clinical outcomes, as discussed above. A large number of observational studies have demonstrated repeatedly and consistently that a low serum albumin level and decreased protein intake, as demonstrated by low protein nitrogen appearance, are strongly associated with increased mortality in CKD patients [24,25]. Similarly, measures of inflammation such as increased serum C-reactive protein (CRP) or pro-inflammatory cytokines predict poor outcomes in ESRD patients [26••,27,28,29•]. Therefore, collectively, elements of MICS appear to be among the strongest risk factors for high morbidity and mortality and low quality of life in CKD patients [26••]. It is quite probable, although not yet clearly proved, that an improvement in nutritional status or inflammation can substantially improve clinical outcomes in dialysis patients. Moreover, as the deleterious effect of malnutrition is usually exerted within a short period of time (see above), it is quite possible that a short-term intervention would suffice to reverse MICS and improve survival.

## Interventions to correct malnutrition–inflammation complex syndrome

As inflammation may indeed be secondary to malnutrition, as recently shown in animal models [30••], dietary

**Table 3. Classification of nutritional/anti-inflammatory interventions in dialysis patients**

1. Oral interventions
   Increasing food intake
   Oral supplements
2. Enteral interventions
   Tube feeding
3. Parenteral interventions
   IDPN
   Other parenteral interventions
4. Hormonal interventions
   Androgens
   Growth factors/hormones
5. Non-hormonal medications
   Anti-inflammatory agents (see Table 4)
   Anti-oxidants (see Table 4)
   Appetite stimulators (see Table 5)
   Carnitine
   Bicarbonate
6. Dietary counseling
   In-center supervision/counseling
7. Dialysis treatment related
   Dialysis dose and frequency
   Membrane compatibility

IDPN, Itradialytic parenteral nutrition.

interventions may mitigate inflammation, as shown in several recent clinical trials [31,32•]. A number of different modalities have been employed to improve the nutritional or inflammatory status in dialysis patients, as shown in Table 3. Among more intensive interventions, tube feeding has been reported to be an effective modality, particularly in pediatric, elderly or disabled individuals [33–36]. However, this modality is a cumbersome option that cannot be used in the average (stable and functional) CKD outpatient. Parenteral interventions such as intradialytic parenteral nutrition (IDPN) are quite costly and can be employed only during dialysis treatment [37,38]. Several studies have examined the role of IDPN in improving nutritional status and outcomes in dialysis patients, and have shown inconsistent results. The complexity, cost, and technical demands of IDPN and tube feeding have restricted clinical access to these methods. Enthusiasm for providing such intensive nutrition modalities as tube feeding and IDPN is currently limited. There appears to be a strong suspicion that if the above-mentioned intensive dietary therapy were effective, we would already be using them. Among simple interventions, hormonal medications may be associated with many side-effects such as virilism and worsening atherosclerosis seen with androgens [39,40]. However, some other medications, especially appetite stimulants and anti-inflammatory/antioxidant agents, have shown some promise (see below). Moreover, a mere increase in energy or protein intake without the concurrent provision of anti-inflammatory or antioxidant nutrients may not be optimally effective, as we have recently shown that an increased protein intake above 1.4 g/kg a day was paradoxically associated with decreased survival in hemodialysis patients [25]. Therefore, it is unlikely, although not impossible, to find one single medication to correct MICS. On the contrary, oral supplements, especially if they contain a combination of several nutritional and anti-inflammatory agents, are the most practical and promising treatment modalities.

## Can oral interventions correct malnutrition–inflammation complex syndrome in chronic kidney disease patients?

To date no large-scale, randomized prospective interventional studies have examined this question. However, aggressive attempts to increase nutritional intake appear to improve the nutritional status in CKD patients according to some studies [41,42]. On the basis of such studies, there is good reason to believe that nutritional therapy will improve nutritional status in ESRD patients with malnutrition. However, virtually all previous studies have serious methodological flaws. Many investigators of such studies used small sample sizes, did not randomize at all or randomized unconventionally, failed to restrict study subjects to those with hypoalbuminemia, did not control for concurrent food intake, did not define or adjust appropriately for co-morbid conditions, performed nutritional interventions for very short periods of time and followed patients for only short intervals, did not adhere to intent-to-treat principles, and did not examine the inflammatory status in study subjects. Therefore, large-scale, prospective randomized interventional studies are urgently needed to ascertain the potential benefits of correcting MICS in hypoalbuminemic maintenance dialysis patients.

## Anti-inflammatory and antioxidant modalities

Although epidemiological evidence strongly links inflammation and oxidative stress to each other and to poor outcome in CKD patients [43•,44–46], there have not yet been randomized trials that indicate an improvement of outcomes by anti-inflammatory or antioxidant approaches. However, a number of treatment modalities (Table 4) have been implicated to target inflammation or oxidative stress in dialysis patients. Some examples include the administration of vitamin E, which may be associated with a decreased risk of cardiovascular mortality in dialysis patients according to some [47,48] but not all [49] reports. In the general population, epidemiological studies indicated that a vitamin E-rich diet may be associated with a better cardiovascular outcome [50,51], but clinical trials such as the HOPE study did not confirm such results [52]. Therefore, it is possible that purified vitamin E supplement does not show the benefits of dietary vitamin E combined with other nutrients. Statins have been shown to decrease CRP levels irrespective of their effects on lipids, and may be associated with reduced mortality in hemodialysis patients [53,54,55•]. However, the issue of worsening hypocholesterolemia in hemodialysis patients as a result of statins

**Table 4. Potential anti-inflammatory and antioxidant agents for chronic kidney disease patients**

Antioxidant vitamins
    Vitamin E
    Vitamin C
    Vitamin A/carotenoids
    Other antioxidants
Eicosanoids (fish oil)
$\gamma$-Linolenic (borage oil)
Megestrol acetate
Pentoxifylline
Steroids/adrenocorticotrophic hormone
Non-steroidal anti-inflammatory drugs
Anti-TNF-$\alpha$ agents
Thalidomide
Statins
Angiotensin-converting enzyme inhibitors
Erythropoietin
Acetyl cysteine
Glitazones
Others: dialysis technique

is not resolved [56,57]. Moreover, as mentioned above, the 4D trial has been reported to be negative [5]. Angiotensin-converting enzyme inhibitors may have anti-inflammatory properties in both the general population and hemodialysis patients [58,59]. However, many hemodialysis patients who are already on these agents continue to have poor outcomes. Acetyl cysteine may improve cardiovascular events in dialysis patients [60]. Glitazones are another group of drugs that have been shown to inhibit the activation of inflammatory response genes, and promote an immune deviation away from T helper type 1 to T helper type 2 cytokine production [19•]. The optimization of dialysis treatment, ultrapure dialysate fluid, and more biocompatible dialysis membranes may improve the inflammatory status in hemodialysis patients [61,62]. However, the HEMO Study did not confirm such effects [3,63••]. Therefore, as discussed above, it is possible that one single agent cannot correct MICS, whereas a combination of interventions may be able to do so.

## Can nutritional interventions correct inflammation in chronic kidney disease?
Evidence that inflammation may be ameliorated by nutritional interventions is less clear, although animal models have shown that malnutrition may lead to inflammation [30••]. Because body protein has no inactive storage form, the loss of protein during inflammation translates into the loss of functional tissue [64]. Therefore, the provision of supplemental nutritional support is a reasonable approach to limit the negative nutritional consequences associated with systemic inflammation. As oral nutrition intake is the most convenient and preferred route, attention focused on the development of interventions that reverse inflammation-induced anorexia and promote oral intake is warranted [65]. Two recent studies based on nutritional interventions using an

unconventional vegetarian [31] or Mediterranean-style [32•] diet showed that diet might be effective in correcting inflammation and the associated cardiovascular risk in non-ESRD populations. Similar studies are urgently needed in the CKD population.

Many foods contain factors that can modulate the synthesis or activity of pro-inflammatory mediators, e.g. the synthesis of prostaglandin E2 from arachidonic acid [65,66]. These factors and foods are sometimes called nutraceuticals [65,67]. The efficacy of fish oil in the diet has been demonstrated in several clinical trials, animal feeding experiments and in-vitro models [67,68]. Fish oil is an abundant source of eicosapentaenoic acid, a precursor of certain prostaglandins and leukotrienes that have been shown to have anti-inflammatory properties [69,70]. Kutner et al. [71] found that dialysis patients who consumed fish more often were less likely to die compared with others. In addition, there is some evidence that borage oil, a plant seed (Borago officinalis) oil with a high concentration of gamma linolenic acid has anti-inflammatory, antioxidant and vasoprotective properties [72–74]. Gamma linolenic acid is efficiently and quickly elongated to dihomo-gamma-linolenic acid, the fatty acid precursor to prostaglandin E1, known to have vasodilator and anti-aggregator properties [75]. Antioxidant-rich nutrients are the focus of intense research, because oxidative stress is believed to be a main cause of chronic inflammation, especially in maintenance dialysis patients [76,77]. Carnitine is another nutraceutical that has been reported to mitigate pro-inflammatory cytokine levels in liver patients [78], heart failure patients [79] and CKD patients [79–81]. One of the commercial products we have recently studied (Oxepa, Ross Laboratories, Columbus, OH, USA) contains relatively large amounts of fish oil, borage oil, carnitine and antioxidants, and is designed for critically ill patients with inflammation and oxidative stress [69,70,82]. Therefore, this and similar dietary formulae may be promising in CKD patients [83].

## Anorexia
It has been argued that inflammation-induced anorexia is an integrated component of the systemic inflammatory response [64,65,84••]. This argument implies that anorexia, like fever, is actively regulated centrally during inflammation [65]. Moreover, anorexia has been shown to be closely related to pro-inflammatory cytokines such as IL-6 and TNF-$\alpha$ and predicts all-cause and cardiovascular mortality in dialysis patients [84••]. Consequently, an exploration of the interaction between energy and protein-regulatory mechanisms and pro-inflammatory cytokines may lead to an effective treatment for MICS-associated anorexia.

Several appetite stimulants have been studied clinically (Table 5). Megestrol acetate (MA) is by far the most

**Table 5. Potential appetite stimulants (orexigenic agents) for chronic kidney disease patients**

1. Steroids:
   Corticosteroids
   Anabolic steroids
2. Megestrol acetate
3. Medroxyprogesterone
4. Cyproheptadine
5. Pentoxifylline
6. Dronabinol
7. Melanocortin blocker
8. Cannaboids

utilized and best-studied agent. MA, at a dose of 800 mg/day, has been shown to increase appetite and food intake in cachectic patients with cancer or AIDS [85,86]. However, at this dose, it may be associated with side-effects, including venous thrombosis, vaginal bleeding, liver abnormalities and adrenal insufficiency. The pharmacokinetics of MA have not been evaluated in patients with renal impairment. In addition to improving appetite and food intake, MA has also been found to have significant anti-inflammatory properties (see Table 4) [87–89]. MA downregulates the synthesis and release of pro-inflammatory cytokines and relieves the symptoms of the anorexia–cachexia syndrome based on the modulation of cytokines [90]. MA reduces the in-vitro production of cytokines and serotonin in the peripheral blood mononuclear cells of cancer patients [87]. In addition, MA may mitigate oxidative stress [89,91]. Therefore, MA has both appetite-stimulating and anti-inflammatory properties, making it a potentially optimal agent to treat MICS. There are very few studies concerning MA in dialysis patients [92–94]. Our experience with a lower dose of MA (400 mg/day) has been encouraging [95].

Another potential orexigenic agent for CKD patients is pentoxifylline, which downregulates the local pro-inflammatory cytokine-mediated nitric oxide synthase pathway [96], inhibits TNF-$\alpha$ production [97], and decreases body weight loss and muscle protein wasting in acutely ill patients [98]. Cooper *et al*. [99••] showed that pentoxifylline, at a dose of 400 mg/day for 4 months, was safe and improved the response to erythropoietin in 16 anemic dialysis patients. Ex-vivo T-cell generation of TNF-$\alpha$ declined from 58 to 23% [99••]. We have recently shown that erythropoietin-resistant anemia is associated with MICS and increased inflammatory cytokines in hemodialysis patients [100]. Therefore, there is indirect evidence that pentoxifylline may be an effective treatment for MICS and its clinical consequences including anorexia and erythropoietin resistance. Although an ongoing randomized controlled trial (pentoxifylline versus placebo) is currently ongoing in 160 dialysis patients in England to study the effect of pentoxifylline on erythropoietin resistance and the TNF-$\alpha$ level [101],

the direct effect of pentoxifylline on anorexia and nutritional status in hemodialysis patients has not yet been tested.

## Can end-stage renal disease mortality be improved by nutritional modulation?

As malnutrition and inflammation are among the most powerful predictors of death in ESRD patients and because their deleterious effects are exerted within a short period of time, it is important to test whether interventions that can improve the nutritional and inflammatory status on a short-term basis will improve poor outcomes. Ample evidence suggests that maintaining an adequate nutritional intake in patients with a number of acute or chronic catabolic illnesses may improve their nutritional status and mitigate inflammation and cachexia irrespective of its etiology, leading to reduced morbidity and mortality and improved quality of life. However, such evidence in ESRD patients is quite limited. Moreover, given the multifactorial etiology of anorexia and MICS, it is unlikely that a single nutritional or anti-inflammatory or antioxidant agent can correct MICS or improve outcomes. Therefore, a combination of several interventions should be employed simultaneously [102]. Considering the extraordinarily high mortality rate and the high prevalence of this clinical dilemma, we believe that it is of immense importance to examine this question by means of a well-designed clinical trial based on several simultaneous interventions.

## Conclusion

Malnutrition and inflammation are common conditions in CKD and appear to be multifactorial. Therefore, single therapeutic strategies are not likely to be successful. Given the hitherto rather poor results of the exclusive provision of energy or protein supplementation, more inclusive nutritional treatment strategies with novel micronutrient components need to be tested. We believe that much can be learned from other malnourished and inflamed patient populations, such as heart failure, cancer and AIDS patients and elderly individuals with cachexia (Table 1). On the other hand, MICS in CKD may be significantly different from the foregoing populations, because its course appears to be rather indolent and its effects indirect. Therefore, the term 'cachexia in slow motion' may best describe the unique wasting syndrome observed in CKD patients with gradual deterioration over time [63••,103]. Because of the multifactorial pathophysiological mechanisms of MICS/MIA and its relative slow rate of progression, an integrated therapeutic approach consisting of both traditional (such as increased nutrient supply and nutraceuticals) and non-traditional (such as various anti-inflammatory supplements and antioxidants) components should be used to improve the quality of life and survival in CKD patients.

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