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Recent Advances in Understanding the Malnutrition-Inflammation-Cachexia Syndrome in Chronic Kidney Disease Patients: What is Next?

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ABSTRACT

Several recent clinical trials using single modalities to correct the conventional cardiovascular risk factors in patients with chronic kidney disease (CKD) or to improve dialysis dose and techniques in maintenance dialysis patients have failed despite the high rate of cardiovascular mortality in these individuals. Protein-energy malnutrition and inflammation, two relatively common and concurrent conditions in CKD patients, have been implicated as the main cause of poor short-term survival in this population. The “malnutrition-inflammation-cachexia syndrome” (MICS) appears to be the main cause of worsening atherosclerotic cardiovascular disease in the CKD population. The MICS is associated with low serum cholesterol and homocysteine levels and leads to “cachexia in slow motion.” Hence a

reverse epidemiology of cardiovascular risk factors is observed in dialysis patients with a paradoxical association of obesity, hypercholesterolemia, and hyperhomocysteinemia with better survival. Correction of MICS can potentially ameliorate the cardiovascular epidemic in CKD patients. Because MICS is multifactorial, its correction will require an integral approach rather than a single intervention. The ongoing obsession with conventional cardiovascular risk factors largely reflecting overnutrition in a population that suffers from the short-term consequences of undernutrition and excessive inflammation may well be fruitless. Clinical trials focusing on the causes and consequences of MICS and its modulation using nutritional interventions may be the key to improving survival in these individuals.

Individuals with chronic kidney disease (CKD) continue to have an unacceptably poor survival (1,2). Efforts thus far to improve survival by focusing on conventional cardiovascular risk factors or dialysis technique have largely failed (3–6). Ironically, although some traditional risk factors such as hypertension are highly prevalent in CKD patients, the evidence showing a significant link between them and poor clinical outcome in these patients is not convincing; indeed, the association is reversed in hemodialysis patients (7). Several recent multicenter clinical trials including the Hemodialysis (HEMO) (3) and Adequacy of Peritoneal Dialysis in Mexico (ADEMEX) (5) studies have failed to show any survival advantage of increasing dialysis dose or membrane permeability in CKD patients undergoing maintenance dialysis treatment. The recent Deutsche Diabetes Dialyse Studie (4D study) in 1255 dialysis patients, randomized to either atorvastatin 20 mg or placebo, did not show any significant advantage of statin use in improving survival (4). Similarly, modulating other cardiovascular risk factors such as hyperhomocysteinemia in

dialysis patients have failed to decrease mortality (6,8,9). Thus the question of how to improve the poor clinical outcomes, especially the high rate of cardiovascular disease and mortality, in dialysis and other CKD patients remains unanswered.

Malnutrition-Inflammation-Cachexia Syndrome

Many reports indicate that in patients with advanced CKD and those on dialysis 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 (10). CKD patients not only have a high prevalence of malnutrition, but also a higher occurrence rate of inflammatory processes (11–14). Many conditions leading to malnutrition and wasting may also cause inflammation. Oxidative stress may be a major underlying cause for both conditions (15). Since both malnutrition and inflammation are strongly associated with each other and can change many nutritional measures and clinical outcomes in the same direction, and because the relative contributions of 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 (10). Alternatively,

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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 in CKD (16). The MICS may also be defined as the “malnutrition-inflammation-cachexia syndrome” to better indicate the presence of the wasting syndrome pointed out recently (17). However, unlike cancer cachexia, the wasting syndrome in CKD usually does not lead to immediate death from the direct consequences of malnutrition, but acts over time to promote atherosclerotic cardiovascular disease (17). Hence the term “cachexia in slow motion” may be more appropriate to identify this syndrome (18).

One of the most important consequences of MICS in dialysis patients is the development of a so-called reverse epidemiology phenomenon (19), in that markers that predict a low likelihood of cardiovascular events and an improved survival in the general population, such as decreased weight and low serum cholesterol, become paradoxically strong risk factors for increased cardiovascular morbidity and death in hemodialysis patients. Moreover, some indicators of overnutrition, such as increased weight or hypercholesterolemia, actually predict improved outcome in hemodialysis patients (19–22). Hence the key to improved survival in almost half a million American dialysis patients (and many millions throughout the world) may lie in interventions to modify nonconventional cardiovascular risk factors, mainly inflammation and malnutrition, which lead to the reverse epidemiology in dialysis patients and several other populations, such as individuals with heart failure and other chronic disease states (23,24). The combination of poor outcome and the inverse risk factor-outcome association demonstrates that there is a great need to test the benefit of therapeutic interventions that modulate such nontraditional risk factors as malnutrition and inflammation.

Is MICS the Major Cause of the High Death Rate in CKD Patients?

At present, the preponderance of evidence is epidemiologic and observational. However, the consistency of the studies is impressive. We have recently shown that an increase in serum albumin over time, especially to values greater than 3.8 g/dl, is the strongest correlate of prospective survival and can potentially save 15,000–20,000 lives per year among dialysis patients in the US (25). Low serum albumin level and decreased protein intake, as demonstrated by low protein nitrogen appearance, are strongly associated with increased mortality in CKD patients (26,27). Similarly, measures of inflammation, such as increased serum C-reactive protein (CRP) or proinflammatory cytokines, predict poor outcome in CKD patients (28–31). Although yet unproved, interventions that improve nutritional status or inflammation can potentially improve clinical outcome in dialysis patients. Moreover, since the deleterious effect of malnutrition is usually exerted within a short period of time (see below), it is quite possible that even short-term interventions would improve survival.

Short-Term or Long-Term Survival, that is the Question!

In contrast to conventional cardiovascular risk factors and overnutrition, which require several years to decades to exert their deleterious effects, the adverse impact of undernutrition occurs rapidly. This “time discrepancy” may explain the reverse epidemiology phenomenon observed in vulnerable populations, in whom the short-term impact of MICS overwhelms the long-term adverse impact of traditional cardiovascular risk factors such as hypertension, hyperhomocysteinemia, and obesity. Dialysis patients will continue to die at an excessive rate 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 (23). The foregoing hypothesis may have major clinical implications in the management of CKD patients. If the main issue is indeed the high rate of short-term mortality (currently greater than 20% per year in the United States), it is also expected that a short-term intervention that can correct the underlying condition (i.e., MICS) can also improve short-term survival.

How can MICS be Corrected?

Inflammation may be secondary to the malnutrition, as recently shown in animal models (32). Hence dietary interventions may mitigate chronic inflammation, as shown in several recent clinical trials (33,34). A number of methods have been tried to improve nutritional status in dialysis patients (Table 1). Tube feeding, which has been employed especially among pediatric, elderly, and disabled individuals (35–38), is a cumbersome modality and cannot be imposed on the average (stable and functional) CKD outpatient. Parenteral interventions, including intradialytic parenteral nutrition (IDPN), are quite costly

TABLE 1. Classification of nutritional/anti-inflammatory interventions in dialysis patients (adapted from Kalantar-Zadeh et al. (18))

Oral interventions
Increasing food intake
Oral supplements
Enteral interventions
Tube feeding
Parenteral interventions
IDPN
Other parenteral interventions
Hormonal interventions
Androgens
Growth factors/hormones
Nonhormonal medications
Anti-inflammatory agents
Antioxidants
Appetite stimulators
Carnitine
Bicarbonate
Dietary counseling
In-center supervision/counseling
Dialysis treatment related
Dialysis dose and frequency
Membrane compatibility

and can be utilized only during dialysis treatment (39,40). The complexity, cost, and technical demands of IDPN and tube feeding have restricted clinical access to these methods (18). Enthusiasm for providing such intensive nutrition modalities is currently limited, although their role in improving survival and other clinical outcomes in dialysis patients should be reexamined in the postnegative trials (HEMO/ADEMEX/4D) era (3–5).

An increase in energy or protein intake without concurrent provision of anti-inflammatory or antioxidant nutrients may not be optimally effective; we have recently shown that increasing protein intake to more than 1.4 g/kg/day was paradoxically associated with decreased survival in hemodialysis patients (27). Among simple interventions, hormonal medications may be associated with many side effects, such as virilism and worsening atherosclerosis seen with androgens (41,42). However, some other medications, especially appetite stimulants and anti-inflammatory/antioxidant agents, might be promising. It is unlikely, although not impossible, that one single medication or intervention will be found to correct MICS and improve survival. This may be the reason why clinical trials that focus on a single intervention, such as the HEMO study or 4D trial, have all failed (3,4). On the other hand, oral supplements, especially if they contain a combination of several nutritional and anti-inflammatory agents, are the most practical and promising treatment modalities (18). Thus large-scale, prospective randomized interventional studies are urgently needed to ascertain the potential benefits of correcting MICS in hypoalbuminemic dialysis patients using combination therapy.

Anti-inflammatory and Antioxidant Interventions

A number of treatment modalities have been suggested to correct the inflammation and oxidative stress seen in dialysis patients (Table 2). Although the risks and benefits of these interventions are not entirely clear, the choice should be based on weighing the risks and benefits against each other. Some examples of interventions that are more realistic and more likely to correct MICS and improve survival in CKD patients include vitamin E administration, which may improve outcomes according to some (43,44) but not all studies (45,46). Statins may have anti-inflammatory properties in dialysis patients (47–49), but worsening hypocholesterolemia may indeed compromise survival according to the “endotoxin-lipoprotein” hypothesis (50,51); this may explain why the 4D trial was negative (4). Acetylcysteine may reduce cardiovascular events in dialysis patients (52). Glitazones are another group of drugs that have been shown to inhibit the activation of inflammatory response genes and modulate the immune system (14).

Correction of MICS by Nutritional Intervention

Since oral nutritional intake is the most convenient and preferred route, a focus on the development of interventions that reverse inflammation-induced anorexia and

TABLE 2. Potential anti-inflammatory and antioxidant agents for CKD patients

Intervention	Benefits	Risks
Antioxidant vitamins		
Vitamin E	++	+?
Vitamin C	+?	+?
Vitamin A/carotenoids	+?	+?
Other antioxidants	+	+?
Eicosanoids (fish oil)	+++	+
α -linolenic (borage oil)	+++	+?
Megestrol acetate	++	++
Pentoxifylline	++	+
Steroids/ACTH	+	++
NSAIDs	+	+
Anti-TNF- α agents	+?	++++
Thalidomide	+?	+++
Statins	++	+
ACE inhibitors	++	+
Erythropoietin	+++	+
Acetylcysteine	+?	+?
Glitazones	+?	+
Others: dialysis technique	++	+?

ACE, angiotensin-converting enzyme; ACTH, adrenocorticotropic hormone; NSAIDs, nonsteroidal anti-inflammatory drugs; TNF, tumor necrosis factor.

promote oral intake is warranted (53). However, evidence that inflammation may be ameliorated by nutritional interventions is less clear, even though animal models have recently shown that malnutrition may lead to inflammation (32). Two recent studies based on nutritional interventions using an unconventional vegetarian (33) or Mediterranean-style (34) diet showed that diet might be effective in correcting inflammation and associated cardiovascular risk in non-CKD populations. Similar studies are urgently needed in the CKD population. A list of possible nutritional interventions to mitigate inflammation in CKD patients have recently been presented elsewhere (18,54).

Conclusion

Malnutrition, inflammation, and wasting, together known as MICS, are among the most common conditions in CKD patients. They are probably the greatest correlates of the high mortality rate in these individuals. However, since MICS is multifactorial, single therapeutic strategies are not likely to be successful. Integrated interventions that target several aspects of MICS in the form of combined nutritional treatment strategies with novel micronutrient components that have antioxidant and anti-inflammatory properties should be tested.

The ongoing obsession with treating such traditional risk factors as hypertension, hypercholesterolemia, obesity, and hyperhomocysteinemia may not lead to any immediate improvement in the high mortality rate in CKD patients, as long as short-term survival is the issue at hand. CKD patients, especially those undergoing maintenance dialysis, are very different than the general population. The characteristics of a surviving dialysis patient stand in clear contradiction to those predicted by traditional cardiovascular risk factors. Hence focusing on managing

these risk factors in dialysis patients would be similar to screening for cancer among patients who already have a malignant disease with a poor prognosis. The MICS is such a “disease.” It may be time to abandon the obsession with Framingham risk factors and try to explore modalities that can correct specific risk factors in CKD patients, namely malnutrition, inflammation, and oxidative stress.

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