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The malnutrition, inflammation, and atherosclerosis (MIA) syndrome – the heart of the matter

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Abstract

The majority of patients starting dialysis already have signs of advanced atherosclerosis, and the risk factors for cardiovascular morbidity and mortality seen in patients with end-stage renal disease (ESRD) develop with the disease progression. Therefore, the predialysis period is the ideal time to start therapeutic interventions. Traditional risk factors alone may not adequately predict cardiovascular disease (CVD) outcome in patients with ESRD. Inflammation has been identified as playing a key role in atherosclerotic CVD. Pro-inflammatory cytokines are pivotal to the inflammation that is associated with malnutrition and atherosclerosis in ESRD. Malnutrition may worsen patient outcome by aggravating existing inflammation and heart failure, accelerating atherosclerosis and increasing susceptibility to infection. Atherosclerosis is itself a major risk factor for CVD mortality. Moreover, inflammation is associated with congestive heart failure. Strong associations between malnutrition, inflammation and atherosclerosis in this patient population suggest the presence of a syndrome we have called malnutrition, inflammation, and atherosclerosis (MIA), which is associated with an exceptionally high mortality rate.

Keywords: atherosclerosis; chronic kidney disease; congestive heart failure; inflammation; malnutrition; MIA syndrome

Introduction

Patterns in end-stage renal disease (ESRD) pathophysiology, treatment, and complications have changed considerably over the past 40 years. Renal replacement therapy (RRT), introduced in the late 1950s, provides effective and well-tolerated treatment and has increased the life expectancy of patients with ESRD worldwide. Improvements in renal care and dialysis technology have added to this survival benefit. These advances have also changed the pattern of complications that nephrologists manage. Patients starting RRT today are older and have more co-morbidities. Cardiovascular disease (CVD) has replaced both electrolytic problems and infection as the main cause of morbidity and mortality. Annual CVD mortality is 10–20-fold higher for patients with ESRD than for the general population, even when adjusted for age, gender, race, and the presence of diabetes mellitus [1]. This high CVD mortality rate suggests that most patients with ESRD suffer accelerated atherogenesis [2] leading to peripheral, cerebral, and cardiac ischaemic disease.

The atherosclerotic burden must start long before the initiation of RRT, as the majority of patients starting dialysis already have signs of advanced atherosclerosis [3]. CVD risk factors are very common before the start of dialysis in patients with chronic kidney disease (CKD) [4]. Indeed, the prevalence of risk factors in mild CKD is similar to that in ESRD [5]. The time to intervene and prevent CVD is the predialysis phase.

Risk factors for CVD, such as hypertension, anaemia, insulin resistance, dyslipidaemia, and accumulation of uraemic toxins are aggravated in the progression to ESRD. Progression of renal disease *per se* may be associated with increased prevalence of inflammation [6], which is another risk factor for accelerated atherosclerosis [7]. Additionally, severe osteopathy usually found in patients with ESRD is often associated with reduced capacity of the bone to handle excess calcium loads. This may predispose deposition of overflow calcium and phosphate crystals in soft tissues, particularly those of the cardiovascular system. Vascular calcification is a risk factor for ischaemic heart disease in ESRD patients [8]. It is interesting that calcification of the cardiac valve is independently associated with the presence of inflammation and malnutrition in these patients [9].

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Indeed, the pro-inflammatory cytokine tumour necrosis factor-α (TNF-α) has been shown to promote vascular calcification *in vitro* [10], and an association between inflammation and a high calcium–phosphate product in patients with ESRD has recently been suggested [11].

Traditional risk factors do not predict outcome in ESRD adequately

Factors such as dyslipidaemia, left ventricular hypertrophy, diabetes mellitus, hypertension, and tobacco smoking, known to contribute to atherosclerosis in the general population, are highly prevalent in patients with CKD. It may be possible to extrapolate data from populations without CKD to patients with CKD. However, a recent study suggests that traditional risk factors alone may not account for the higher CVD morbidity and mortality in patients with ESRD [12]. Factors such as oxidative stress, endothelial dysfunction, and inflammation may have a greater effect on CVD mortality than other factors [13,14]. During the last few years, inflammation has been identified as playing a key role in atherosclerotic CVD, in populations both with [7] and without CKD [15]. In an ongoing prospective study we found that various markers of malnutrition and inflammation, such as subjective global assessment, C-reactive protein (CRP) and interleukin-6 (IL-6), are strong independent predictors of CVD and mortality in patients with ESRD. We also found strong associations between malnutrition, inflammation, and atherosclerosis in this patient population [14], suggesting the presence of a syndrome we have called malnutrition, inflammation, and atherosclerosis (MIA), which is associated with an exceptionally high mortality rate (Figure 1).

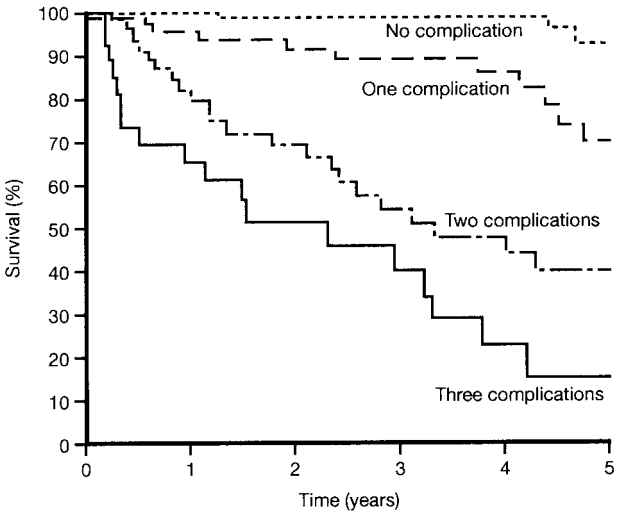

Fig. 1. Survival, represented by Kaplan–Meier survival curves (Log Rank 84.2; $P < 0.00001$), in 204 ESRD patients with none, one, two, or all three of the complications malnutrition, inflammation and atherosclerosis.

Inflammation is associated with malnutrition and atherosclerosis in ESRD

Studies conducted in Europe and in the USA show serological evidence of an activated inflammatory response in 30–50% of patients with ESRD [16]. RRT is unlikely to be solely responsible for this, as raised CRP levels are also common in patients with CKD prior to initiation of dialysis [3]. CRP levels may also be raised by chronic inflammation. Persistent infections (e.g. *Chlamydia pneumoniae* and dental infections), comorbidity (e.g. chronic heart failure), accumulation of advanced glycation products (AGEs), and pro-inflammatory cytokines may all contribute to a state of chronic inflammation [16].

Malnutrition

Protein-energy malnutrition and wasting are common in patients with ESRD. Although various factors associated with the dialysis procedure, such as bio-incompatibility and nutrient losses, may contribute to malnutrition, recent studies have shown that malnutrition is common even before the start of RRT [3]. A low serum albumin (S-albumin) level has been used as a marker for malnutrition for many years and is considered to be an important risk factor for mortality [17]. However, S-albumin may not be a valid nutritional marker as it is affected by inflammation and external losses. As both inflammation and inadequate nutritional intake can decrease the concentration of S-albumin [18], much of the previously reported relationship between S-albumin, malnutrition, and mortality in patients undergoing RRT may be due to an inflammatory process rather than poor nutritional intake. Indeed, inflammatory markers, such as CRP and IL-6, are strong predictors of both poor outcome [15] and malnutrition [19,20] in patients on dialysis. Elevated levels of pro-inflammatory cytokines may cause malnutrition by acting directly on the gastrointestinal system or indirectly through affecting appetite and resting energy expenditure. Cytokines may also cause malnutrition by mediating increased protein hydrolysis and muscle protein breakdown [14].

Atherosclerosis

Chronic inflammation may contribute to accelerated atherosclerosis [7]. Pro-inflammatory cytokines (such as IL-6 and TNF-α), and acute-phase reactants (such as CRP and fibrinogen) have all been suggested to contribute directly [16]. IL-6 may be particularly important in this process, as elevated IL-6 levels predict myocardial infarction in healthy men [21] and progression of carotid atherosclerosis in patients starting dialysis [20]. Although acute-phase reactants and cytokines may promote atherogenesis directly, there also may be indirect associations between chronic inflammation and CVD. Normal endothelial function

is important for maintaining cardiovascular homeostasis; therefore, endothelial injury may result in lipid accumulation, smooth muscle proliferation, and vasospasm. Moreover, it is interesting that endothelial dysfunction (prominent in patients with ESRD) is associated with inflammation [22]. Inflammation and accelerated atherosclerosis may also be indirectly associated via oxidative stress, which has recently been recognized as an important factor in the development of both endothelial dysfunction and atherogenesis. Indeed, recent studies suggest that ESRD patients are subject to increased oxidative stress, which appears to be closely associated with inflammation [23,24].

Inflammation is associated with congestive heart failure

Although accelerated atherosclerosis is a major cause of CVD in patients with ESRD, there may also be other causes [25]. The majority of patients receiving dialysis experience cardiomyopathy. Left ventricular hypertrophy and systolic dysfunction both lead to congestive heart failure (CHF) and reduced life expectancy [26,27]. Patients with left ventricular systolic dysfunction (dilated left ventricle) are at a higher risk of CHF than those with a normal resting ejection fraction (non-dilated left ventricle). Anaemia, often associated with inflammation in patients with ESRD [28], is an important risk factor for cardiomyopathy, as well as increased morbidity and mortality rates in these patients [29].

In the general population, CHF is associated with both malnutrition (cardiac cachexia) and increased levels of pro-inflammatory cytokines [30]. The failing heart produces large quantities of TNF-α. A direct relationship has been shown between the level of TNF-α expression and the severity of CHF [31]. An association between cytokines and the autonomic dysfunction that characterizes CHF has also been documented [32]. It is clear from advances in cardiology that many features of CHF can be explained by known biological effects of inflammatory mediators. Notably, TNF-α administered to animal models at concentrations observed in CHF produced effects parallel to those seen in patients with CRF [31]. Development of CHF was averted by anticytokine therapy [31]. Thus, it could be hypothesized that the pro-inflammatory cytokines play an important pathogenic role in CHF. Changes in pro-inflammatory cytokines and acute-phase reactants in CHF are dynamic (i.e. increased levels occur mainly with decompensation). Therefore, it is important to distinguish between compensated and decompensated CHF when evaluating serum parameters of inflammation [33]. Normalization of volume status is associated with significantly decreased endotoxin levels [34], which further supports the possible association between CHF and inflammation. Less is known about the relationship between CHF and inflammation in patients with

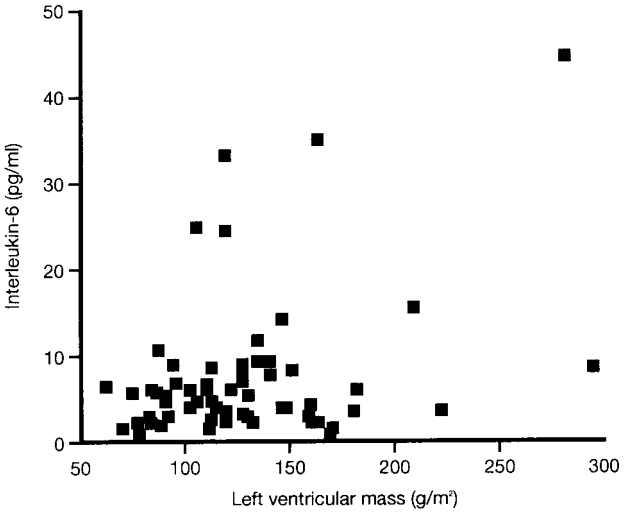

Fig. 2. Association ($P < 0.01$) between left ventricular mass and plasma IL-6 levels in 60 ESRD patients close to start of dialysis treatment.

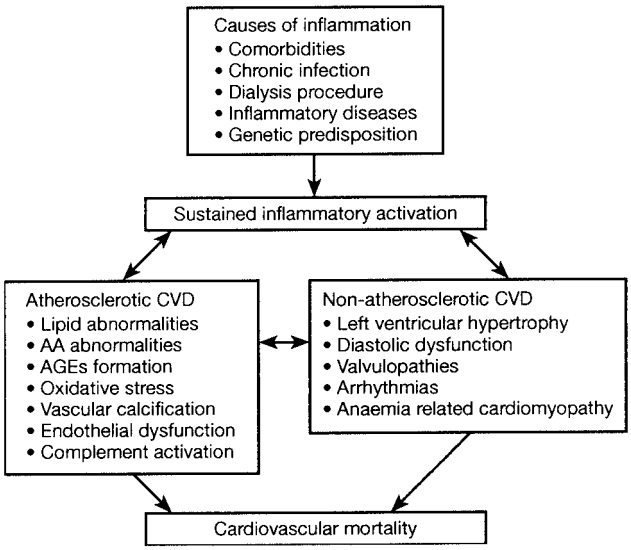

Fig. 3. Hypothetical relationships between inflammation, atherosclerotic and non-atherosclerotic causes of CVD in ESRD patients.

ESRD. However, we have identified a relationship between plasma levels of IL-6 and left ventricular mass in patients with ESRD about to start dialysis (Figure 2). Further studies are needed to investigate the associations between CHF and cytokines in ESRD. Moreover, as renal failure *per se* may be associated with elevated levels of pro-inflammatory cytokines, additional investigation is warranted to verify if hypercytokinaemia *per se* leads to depressed myocardial function in patients with ESRD.

Conclusions

Available literature suggests that CVD in patients with ESRD is influenced by sustained inflammatory

activation (Figure 3). Inflammation has many causes but pro-inflammatory cytokines generated in response to CHF and/or fluid overload, chronic infections, and other inflammatory stimuli have a pivotal role. Chronic inflammation may cause muscle wasting, hypoalbuminaemia and anorexia, as well as reduced cardiac contractility and atherosclerotic vascular disease. In contrast, malnutrition is rarely a direct cause of death. However, it may worsen patient outcome by aggravating existing inflammation and heart failure, accelerating atherosclerosis and increasing susceptibility to infection. There are many missing pieces in the puzzle. More research is needed before the interrelationship between malnutrition, inflammation, cytokines, oxidative stress, endothelial dysfunction, and heart disease in patients with ESRD can be established more precisely. We hope that a better understanding of the pathogenetic processes involved will help to reduce the unacceptably high morbidity and mortality rate in patients with ESRD.

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