

Malnutrition, inflammation, atherosclerosis syndrome in chronic kidney disease – implications for anaemia management

Peter Bárány

Division of Renal Medicine,
Department of Clinical Science, Intervention and Technology, Karolinska Institutet,
and
Department of Renal Medicine,
Karolinska University Hospital, Stockholm, Sweden

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■ INTRODUCTION

The concept of the malnutrition-inflammation-atherosclerosis (MIA) syndrome in chronic kidney disease (CKD) is based on the notion that these factors are strongly interrelated and associated with an exceedingly high mortality rate¹⁻³. The main features of wasting and high levels of pro-inflammatory cytokines in CKD patients with cardiovascular disease are common in the elderly dialysis population in most industrialised countries. The hypothesis that the disease process is driven by activation of the immune system and its cytokine-producing cells in various tissues is supported by experimental evidence but has not been fully established in the clinical setting^{3,4}. This editorial focuses on the relationship between the MIA syndrome and the implications for anaemia severity and management.

■ INFLAMMATION

Inflammation and activation of acute phase responses are common in CKD and are observed also in the early stages of CKD⁵. The prevalence of inflammation increases with deterioration of renal function⁶ and, depending on the methods used to

detect inflammatory activity, up to two thirds of dialysis patients have signs of an acute phase response^{7,8}. While several specific causes of inflammation, such as acute and chronic infectious diseases or peripheral vascular disease with gangrene, may be obvious in CKD patients, in many instances the underlying condition cannot readily be identified³. Contributing factors can be divided into comorbid factors and dialysis-related factors. The first set includes cardiovascular disease, especially congestive heart failure; systemic inflammatory disease; uraemic factors, such as metabolic and hormonal imbalances and retention of pro-inflammatory mediators and cytokines. The latter factors include access-related infections, bioincompatibility and catabolic effects of the dialysis procedure.

Inflammation and associated oxidative stress interact with erythropoiesis at several levels^{9,10}. Pro-inflammatory cytokines and inflammatory mediators suppress native erythropoietin production and blunt response to erythropoietin at the receptor level¹⁰. They also inhibit erythroid progenitor proliferation and differentiation¹¹⁻¹³ and accelerate destruction of erythrocytes in the circulation¹⁴. Inflammation has profound effects on iron traffic by diverting iron from erythropoiesis to storage sites within the reticuloendothelial system¹⁰.

Pro-inflammatory cytokines such as interferon- γ (IFN-gamma) and tumour necrosis factor- α (TNF-alpha) have marked inhibitory effects on erythroid progenitor cells¹⁰⁻¹³. It has been suggested that the suppressive effect is related to the ability of these cytokines to generate nitric oxide (NO)¹⁵.

Both pro-inflammatory and anti-inflammatory cytokines play major roles in the regulation of intracellular iron homeostasis¹⁶. Anti-inflammatory cytokines are able to increase iron sequestration in activated macrophages and may, under certain conditions, contribute to the development of anaemia¹⁶. Pro-inflammatory cytokines provoke both hypoferraemia and anaemia in animal experiments where recombinant TNF-alpha and recombinant IL-1 cause a significant decrease in serum iron levels^{10,13,17}. Similarly, administration of TNF-alpha or IFN-gamma in humans results in hypoferraemia accompanied by an increase in circulating ferritin concentration and a decrease in soluble transferrin receptor levels^{10,18,19}.

There is evidence that oxidative stress during inflammation alters the expression of ferritin synthesis at a translational level and that transcriptional mechanisms may also be affected²⁰. Cytokine-mediated alteration in the iron response element-binding activity of iron regulatory proteins, and the diminished availability of apotransferrin during inflammation, leads to reduced iron transport from the gut into the portal circulation. Indeed, impaired mucosal absorption of iron is seen in haemodialysis patients with increased CRP levels²¹. A key factor may be the IL-6-induced production of the peptide hepcidin in the liver. Hepcidin is a negative regulator of iron absorption in the small intestine and iron release from macrophages and increased activity is implicated in the development of functional iron deficiency²². High levels of hepcidin have been found in patients with anaemia of chronic diseases and in CKD patients with anaemia²³⁻²⁷.

■ WASTING

The prevalence of wasting has been reported to be up to 65 % in dialysis patients⁸. The causes are multifactorial, but comorbidity and inflammation are two major underlying factors in CKD patients. Metabolic factors such as acidosis and other uraemic syndrome

imbalances have been identified as contributing factors, as has the catabolic effect of the haemodialysis procedure. Attention should also be paid to previous or ongoing treatment with corticosteroids and other medications with catabolic effects.

Body composition influences anaemia and sensitivity to erythropoiesis-stimulating agents (ESA) in CKD patients^{10,28}. Despite being associated with increased inflammatory activity, increased fat mass appears to decrease the need for ESA, hypothetically through a stimulatory effect of adipocyte-derived leptin or other adipokines on erythropoiesis. In non-renal populations, severe malnutrition is associated with anaemia, which can be reversed by nutritional intervention²⁹. CKD patients with the combination of wasting and inflammation are most likely to have more severe anaemia and to be hyporesponsive to epoetin^{9,13}.

■ CARDIOVASCULAR DISEASE

Of the multiple comorbidities encountered in CKD patients, cardiovascular disease has the strongest influence on mortality and overall morbidity. Accelerated arteriosclerosis was early described in haemodialysis patients³⁰ and recent interest in the vascular calcification process has shed new light on underlying mechanisms of this disorder³¹⁻³³. Apart from traditional risk factors calcium-phosphate metabolism, low levels of calcification inhibitors, oxidative stress and inflammation have been identified as playing a role in the disease process^{1,3,34}. Inflammation may have direct influence on the plaque formation, but also impacts on fetuin levels, an important circulating calcification inhibitor^{31,35}. In CKD patients, inflammation is associated with low fetuin levels, which adds up to a higher mortality risk for these patients than for patients without either of these risk factors³⁵.

Congestive heart failure is associated with elevated levels of pro-inflammatory cytokines which may contribute to wasting and anaemia³⁶. Anaemia and renal impairment, sometimes referred to as the “cardio-renal syndrome”, are associated with worse outcomes in such patients^{36,37}. Based on its impact on clinical outcomes in observational studies, anaemia has emerged as a possible treatment target in patients with heart failure.

■ IMPLICATIONS FOR TREATMENT OF ANAEMIA

Inflammation and comorbidity are associated with more severe anaemia and hyporesponse to ESA treatment^{9,10,13,38}. Unfortunately, there are very few controlled interventional studies of management of CKD patients with components of the MIA syndrome and there are as yet no evidence-based recommendations as to how anaemia should be managed in these patients. Inflammatory and other comorbid conditions such as infections, peripheral gangrene and congestive heart failure should obviously be adequately treated. Patients with comorbidity may obtain similar Hb levels but tend to require higher ESA doses than those without comorbidity (Bárány *et al*, poster ASN 2006). It is therefore not surprising that patients with high ESA requirements are at risk of complications and have a higher mortality than patients with good response to ESA. Patients with cardiovascular disease are obviously more vulnerable and it has been recommended that the target Hb interval for patients with congestive heart failure should be strictly between 110-120 g/L^{39,40}. Recent randomised trials in CKD patients not treated with dialysis confirm that no benefit is found in normal Hb targets and that aiming for high targets may be harmful, especially in patients with pre-existent cardiovascular disease⁴¹⁻⁴³. It has not been clarified if the negative effect is a direct consequence of the intensified anaemia treatment with ESA and iron or indirectly related to the higher Hb and secondary effects, such as aggravation of hypertension. The results of larger controlled clinical trials in patients with congestive heart failure as their primary diagnosis will soon be available and provide further information on the role of ESA treatment of anaemia in such patients⁴⁴.

Variations in inflammatory activity results in unstable Hb levels, which often drop below 100 g/L³⁸. The variation of inflammatory activity also affects iron availability and makes predicted response to both ESA and iron difficult. It has been shown that too frequent dose changes of ESA may contribute to further fluctuations in Hb levels⁴⁵. The recently published DRIVE study support a trial of intravenous iron in ESA hyporesponsive patients, even in those with high ferritin levels⁴⁶. Anti-inflammatory and anti-oxidative agents have been suggested for patients with inflammation^{9,10,13}. The experience is limited to a few studies comprising small groups of patients and the

results do not allow conclusions to be drawn as to the applicability of such strategies in the future^{9,10,13,39}.

In summary, the components of the MIA syndrome found in the late stages of CKD are a therapeutic challenge for nephrologists. Patients with these complications have exceedingly high morbidity and mortality and their anaemia is often hyporesponsive to treatment with ESA and parenteral iron. Further basic and clinical studies are necessary to improve our understanding of the disease process and to develop subsequent better treatment strategies for these patients.

Conflict of interest. None declared.

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Correspondence to:

Dr Peter Bárány
 Division of Renal Medicine K56
 Department of Clinical Science, Intervention and Technology
 Karolinska Institutet
 Karolinska University Hospital Huddinge
 14186 Stockholm
 Sweden
 e-mail: peter.barany@ki.se