Nephrology
Dialysis
Transplantation

Anaemia and inflammation: what are the implications for the nephrologist?

Peter Stenvinkel

Department of Renal Medicine K56, Huddinge University Hospital, Stockholm, Sweden

Abstract

End-stage renal disease (ESRD) is characterized by a high mortality rate, which is mainly caused by cardiovascular disease. In patients with ESRD, high levels of pro-inflammatory cytokines and increased oxidative stress are common features and may contribute to the development of malnutrition, anaemia, resistance to recombinant human erythropoietin (epoetin) and atherosclerosis. The onset of inflammation is multi-factorial and is a predictor of poor outcome in ESRD. Although the inflammation may reflect the underlying cardiovascular disease, the acute-phase response may also contribute to both oxidative stress and progressive vascular injury. The acute-phase response in these patients may be influenced by a number of factors, and possibly the dialysis procedure itself. Inflammation and the acute-phase response interact with the haematopoietic system at several levels, resulting in reduced erythropoiesis, accelerated destruction of erythrocytes and blunting of the reactive increase in erythropoietin in response to reduced haemoglobin levels. In patients with ESRD, epoetin resistance has been linked with inflammation, which is often associated with a state of functional iron deficiency. Patients with ESRD are thought to have a reduced capacity in their control of oxidative stress and there is evidence that suggests that a relationship may exist between inflammation, oxidative stress and the treatment of anaemia with epoetin. Controlled trials are needed before evidence-based recommendations for the management of inflammation-induced anaemia and resistance to epoetin can be defined.

Keywords: anaemia; end-stage renal disease; inflammation; oxidative stress; recombinant human erythropoietin

Introduction

One of the most intriguing questions in modern nephrology is why the absolute risk of cardiovascular events in a 30-year-old patient receiving dialysis is similar to that of a 70–80-year-old patient from the general population [1]. This question is becoming increasingly important because the prevalence of chronic kidney disease is currently on the increase in North America, as well as in Western Europe and Japan [2]. The prevalence of chronic kidney disease in the elderly population in the USA is, at present, 11% [3], which means that almost 20 million Americans could have this condition. In fact, in the USA, kidney disease has been included for the first time as a 'focus area' in a report published by the Surgeon General [4].

The level of kidney function is an independent predictor of cardiovascular outcomes and all-cause mortality. Indeed, recent evidence suggests that advanced atherosclerosis is present before dialysis treatment has begun [5]. In general, patients with end-stage renal disease (ESRD) have a range of traditional cardiovascular risk factors, including old age, hypertension, diabetes mellitus and dyslipidaemia. In addition, many patients are smokers. These factors alone, however, cannot account for the very high risk of cardiovascular disease, and thus recent interest has focused on non-traditional risk factors, such as inflammation, anaemia, oxidative stress, endothelial dysfunction, vascular calcification, homocysteine and advanced glycation end-products.

Inflammation

Numerous studies have shown that inflammatory markers are strong predictors of outcome in patients with ESRD. In a recent study of about 25 000 US patients on haemodialysis, neutrophil count was a strong independent predictor, particularly when combined with a low lymphocyte count [6]. C-reactive protein (CRP) is also a strong predictor of outcome,

Correspondence and offprint requests to: Peter Stenvinkel, MD, PhD, Department of Renal Medicine K56, Huddinge University Hospital, Karolinska Institutet, Stockholm, Sweden. Email: peter.stenvinkel@klinvet.ki.se
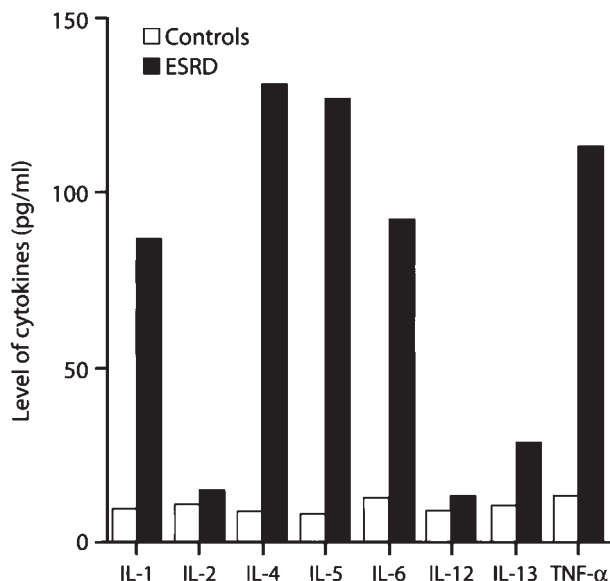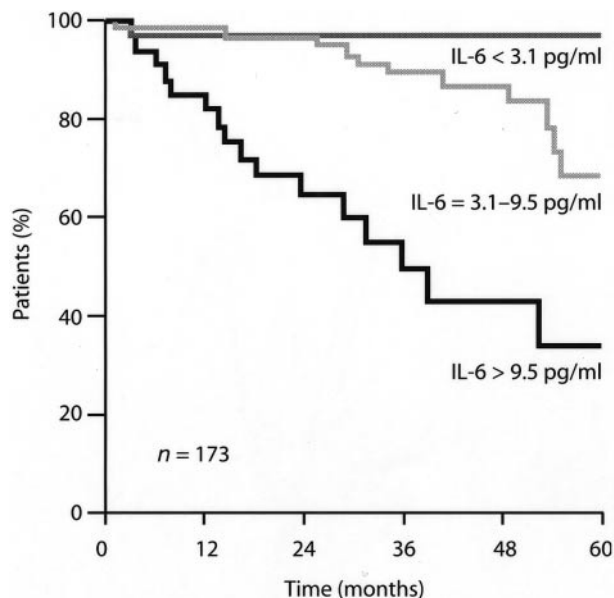
Fig. 1. Levels of pro-inflammatory cytokines in patients with ESRD and matched controls. Reproduced, with permission, from Kimmel *et al.* [8].

Fig. 2. Proportion of patients surviving during dialysis treatment, categorized in quartiles according to IL-6 level. Reproduced, with permission, from Stenvinkel *et al.* [9].

with elevated CRP levels corresponding to a higher mortality rate [7]. Inflammation is a common feature of the uraemic syndrome. In a European study using a variety of cut-off points for CRP, ~50% of patients had CRP levels >8 mg/l and almost 75% of patients had CRP levels >3.4 mg/l [7].

The evidence available suggests that ESRD is a state of increased pro-inflammatory cytokine activity. In patients with ESRD, plasma levels of pro-inflammatory cytokines such as interleukins (IL) 1, 4 and 6, and tumour necrosis factor-α (TNF-α) were shown to be 8–10-fold higher compared with a matched group of controls (Figure 1) [8]. Moreover, increased levels of pro-inflammatory cytokines predict poor outcome in patients starting renal replacement therapy (Figure 2). In fact, the quartiles of patients with the highest levels of IL-6 have mortality rates that are similar to those observed in patients with metastatic malignancies [9]. Possible causes of increased inflammation in patients with ESRD are listed in Table 1.

Table 1. Potential causes of inflammation in patients with ESRD

Intrinsic to ESRD	Linked to dialysis
Reduced renal clearance of cytokines	Graft and fistula infections (haemodialysis)
Accumulation of advanced glycation end-products	Peritonitis (peritoneal dialysis)
Sedentary lifestyle	Bio-incompatibility
Genetic factors	Contaminated dialysate
Obesity	Backfiltration (haemodialysis)
Oxidative stress	
Chronic heart failure	
Atherosclerosis	
Inflammatory disease	
Unrecognized persistent infections	

whom none of the three components is present (P. Stenvinkel *et al.*, unpublished data).

Malnutrition, inflammation and atherosclerosis

Inflammation appears to be closely associated with atherosclerotic events and malnutrition, and a number of factors could play a central role, including pro-inflammatory cytokines, as well as increased oxidative stress, carbonyl stress and uraemic toxins. The common association of inflammation and atherosclerosis with malnutrition has led us to suggest that together they represent a specific condition, known as the malnutrition–inflammation–atherosclerosis (MIA) syndrome [10]. As expected, patients with two or three components of the MIA syndrome have higher mortality rates than those who have only one, or in

Inflammation, anaemia and oxidative stress

One link between elevated levels of pro-inflammatory cytokines and poor treatment outcomes in patients with ESRD may be the presence of anaemia. For example, low haematocrit levels (i.e. <30%) are associated with a significantly increased relative risk of death in patients with ESRD (Figure 3) [11]. Moreover, there are relationships between anaemia, inflammation and levels of oxidative stress. After an inflammatory response to an infection, there is usually a sharp fall in haemoglobin (Hb) levels within 2–3 days, which mainly results from a decrease in erythrocyte survival. Inflammation also causes activated macrophages to remove senescent erythrocytes as well as red cells
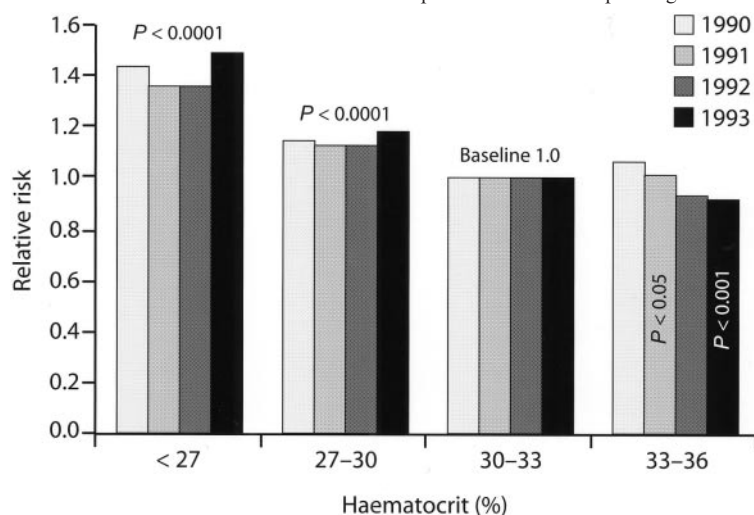
Fig. 3. Relative risk of death in patients with ESRD in relation to the haematocrit level. Reproduced, with permission, from Collins *et al.* [11]. © 1998 National Kidney Foundation.

coated with immunoglobulins and immune complexes from the circulation [12]. In addition, pro-inflammatory cytokines may have some anaemic effects *per se*.

Suppression of bone marrow erythropoiesis

Many investigators have shown that cytokines can suppress stem cell proliferation. For example, IL-1 prevents the erythropoietin-induced stimulation of bone marrow erythrocyte precursors *in vitro* [13], while serum from uraemic patients can inhibit erythroid colony formation and response to erythropoietin, a process, which can be restored by the addition of antibodies to TNF-α and interferon-γ (IFN-γ) [14]. Some studies, however, have failed to show a cytokine-mediated suppression of stem cell proliferation. In mice, daily injections of IL-6 produce an increase in the number of progenitor cells in bone marrow [15]. It is possible that the cytokine concentrations used may vary across the studies, which may account for the different findings in the literature. In addition, other cytokines, such as IL-12, are known to stimulate the growth of bone marrow progenitor cells [16].

Suppression of erythropoietin production

Erythropoietin levels in patients with anaemia related to chronic disorders such as cancer may be inappropriately low for the degree of anaemia [17], while IL-1α, IL-1β and TNF-α inhibit erythropoietin production in cultures of human hepatoma cell lines [18]. These same cytokines also cause dose-dependent inhibition of hypoxia-induced erythropoietin production in Hep3b cells [19]. One study has shown, however, that the erythropoietin response did not differ between rats with acute inflammation and anaemia, and control animals with a comparable degree of anaemia [20].

Increased intestinal bleeding

IL-6, when given intraperitoneally to rats, is associated with intestinal blood loss, as well as a marked decrease in haemoglobin levels, which is not related to suppression of bone marrow or erythropoietin [21]. Several studies have shown that TNF-α can cause acute inflammatory responses, haemorrhage and necrosis [18,22], and might also play a critical role in the pathophysiology of vascular injury induced by non-steroidal anti-inflammatory drugs [23]. Indeed, inhibition of TNF-α by pentoxyfylline reduces gastric damage in a dose-dependent fashion [23].

Modulation of iron metabolism

Serum ferritin is an acute-phase reactant — ferritin levels are usually very high in inflammatory disorders [24] and there also appears to be a positive correlation between ferritin levels and inflammatory markers such as CRP in patients with ESRD [25]. In general, cytokines may impair iron metabolism, leading to 'functional iron deficiency' in one of two ways. First, high doses of erythropoietin may over-stimulate erythropoiesis to exceed the maximum capacity of liver iron stores. Secondly, increased ferritin and decreased transferrin production shunt iron to the reticulo-endothelial storage pool, preventing delivery to erythrocyte precursors. Mucosal uptake and mucosal transfer of iron are also significantly decreased in dialysis patients with increased CRP levels [26]. Thus, it is possible that decreased synthesis of transferrin during inflammation leads to less apo-transferrin being delivered to the gut, resulting in reduced delivery of iron to the transferrin receptors of the mucosal cells.

Oxidative stress and anaemia

In healthy individuals, there is a finely tuned balance between causative and protective factors for oxidative stress. In the uraemic syndrome, however, factors such as inflammation, anaemia and uraemic toxins lead to an increase in reactive oxygen species. There is also a decrease in anti-oxidative defences, notably serum albumin levels. Thus, in the uraemic state, there is an increase in oxidative stress.

Unfortunately, only few published data are available on the relationship between anaemia and oxidative stress in ESRD. Peroxidation of lipids in cell membranes may reduce erythrocyte life span [27], and anaemia is associated with increased plasma concentrations of markers of oxidative stress, including 4-hydroxynonenal and malonyldialdehyde (Figure 4) [28,29]. The mechanisms by which anaemia contributes to oxidative stress are not fully understood, but factors such as hypoxia and alterations in catecholamine metabolism may play a significant role. It could also be speculated that treatment of anaemia may be associated with increased availability of antioxidants such as glutathione.

Antioxidant strategies as treatments for anaemia

Vitamin E supplementation or the use of vitamin E-modified dialysis membranes appear to have a sparing effect on erythropoietin dose requirement and can also improve the therapeutic effect of erythropoietin [30–32]. Erythropoietin itself may also have an anti-oxidant effect, reducing the susceptibility of plasma lipids and erythrocytes to oxidation [31,33,34]. More-over, a study by Roob et al. [35] has shown that a single oral dose of vitamin E attenuates lipid peroxidation in patients on haemodialysis receiving i.v. iron.

Associations between inflammation and oxidative stress

It is well known that inflammatory stimuli such as lipopolysaccharide injections may cause oxidative stress, and there is also evidence that oxidative stress can lead to an inflammatory response. In haemodialysis patients, inflammation and duration of dialysis are the most important factors leading to increased oxidative stress [36]. The presence of other markers of oxidative stress, such as advanced oxidation protein products (AOPP) and plasma F_2 isoprostanes, is also strongly correlated with markers of inflammation [37,38]. We examined levels of 8-hydroxy-2-deoxyguanine, a marker of DNA oxidative stress, in patients on haemodialysis who had had elevated CRP levels for at least 6 months, and compared the results with those from a group of matched patients with no signs of chronic inflammation for at least 6 months. Preliminary results showed a significant difference between these two groups, confirming that there is an association between inflammation and increased oxidative stress in dialysis patients (P. Stenvinkel et al., unpublished data).

Dialysis and inflammation

Bio-incompatibility may be one factor contributing to inflammation in haemodialysis patients. Studies
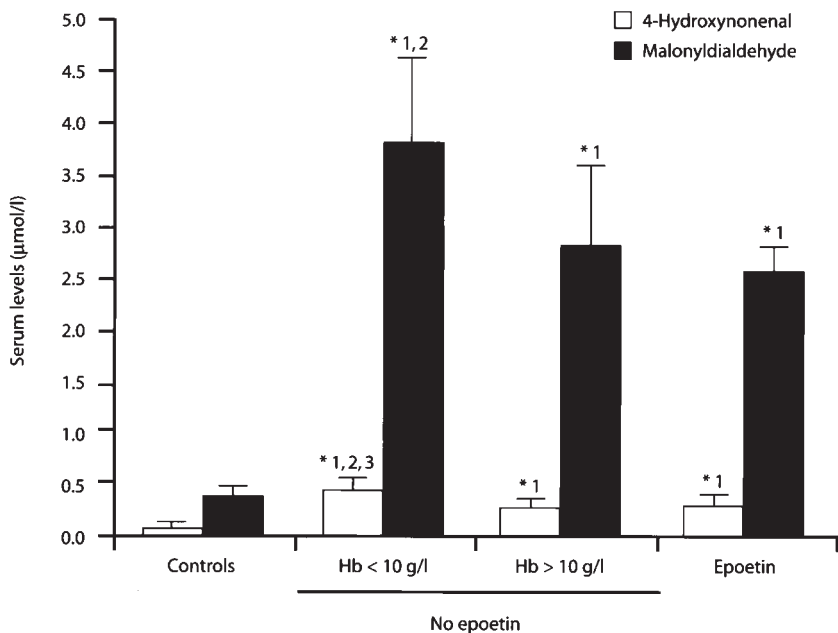
Fig. 4. Serum levels of 4-hydroxynonenal (HNE) and malonyldialdehyde (MDA) in patients with chronic renal failure and controls. *1 $P < 0.0001$ vs controls; *2 $P = 0.039$ (HNE) and $P = 0.042$ (MDA) vs epoetin only; *3 $P = 0.042$ (HNE) vs no epoetin with Hb > 10 g/l. Reproduced, with permission from Oxford University Press, from Sommerburg et al. [28].

have shown that cuprophane dialysis membranes lead to higher levels of markers, such as CRP and IL-6, than membranes made of polymethylmethacrylate, polyamide or polycarbonate [39,40]. The quality of dialysis water and incidence of back-filtration may also be related to inflammation during haemodialysis [41,42]. It is important to note that although ultra-pure dialysate and biocompatible membranes can decrease inflammation, markers such as CRP are not reduced to normal levels [39]. Thus, non-dialysis-related factors, such as co-morbidity and residual renal function, may be the most important causes of the inflammatory state in patients treated by haemodialysis.

A strong correlation between circulating IL-6 levels and the need for erythropoietin treatment has been observed in patients on haemodialysis [43]. In addition, patients who have high IL-6 and TNF-α levels need higher weekly doses of epoetin than patients with lower cytokine levels [44]. Conversely, a negative correlation has been observed between IL-12 levels and epoetin dose [44]. It is notable that the use of ultra-pure dialysate is associated with reduced levels of IL-6 and CRP and leads to better responses to epoetin treatment [43].

Management of inflammation-induced epoetin hyporesponsiveness

A treatment strategy for patients who are iron replete is simply to increase the dose of erythropoietin administered. Any existing chronic infections and inflammatory disorders should be adequately treated, and patients should receive dialysis using ultra-pure membranes and bio-compatible membranes. It could be speculated that in the future, treatment with anti-cytokine therapies, such as anti-TNF-α antibodies, soluble TNF receptors, and IL-1 and IL-6 receptor antagonists, may become available in this patient group.

The influence of nutrition on inflammation requires further evaluation, and the role of vitamin E remains to be clarified in large-scale, prospective studies. Interestingly, Asian patients on haemodialysis have a lower prevalence of inflammation and atherosclerosis than haemodialysis patients from Europe and North America. It has been suggested that the high intake of soy protein in the Asian diet may contribute to this observation [45], and *in vitro* research has shown that soy has potent anti-inflammatory effects and contains large amounts of phytoestrogens, which appear to inhibit the transcription factor, nuclear factor κB (NF-κB) [46]. Also, widely used drugs such as statins, angiotensin-converting enzyme inhibitors and glitazones inhibit NF-κB, and large trials are now needed to confirm the anti-inflammatory properties of these agents in patients with ESRD.

Recently, it has been suggested that there is an association between TNF activity and the need for erythropoietin [47]. Patients with persistently low haemoglobin levels who were treated with the anti-TNF agent pentoxifylline for 6–8 weeks, showed a marked increase in haemoglobin levels. This increase in haemoglobin was accompanied by a decrease in TNF-α and IFN-γ levels in circulating T-cells (Cooper *et al.*, submitted for publication). These results are consistent with those observed in other patient groups such as patients with rheumatoid arthritis, showing that treatment with an anti-TNF antibody led to increased haemoglobin levels compared with those receiving placebo [48].

Summary

Chronic inflammation is associated with increased morbidity and mortality in patients with ESRD, and may be one of the most common causes of erythropoietin resistance in patients receiving dialysis. Inflammation can be caused by a number of factors, some of which are related to dialysis, and is strongly associated with malnutrition and atherosclerosis. Increased levels of pro-inflammatory cytokines may cause anaemia in patients with ESRD by several mechanisms, and inhibition of these cytokines may have beneficial effects on the anaemia seen in chronic kidney disease.

References

1. Foley RN, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. *Am J Kidney Dis* 1998; 32: S112–S119
2. Bommer J. Prevalence and socio-economic aspects of chronic kidney disease. *Nephrol Dial Transplant* 2002; 17 [Suppl 11]: 8–12
3. Coresh J, Astor BC, Greene T, Eknoyan G, Levey AS. Prevalence of chronic kidney disease and decreased kidney function in the adult US population: Third National Health and Nutrition Examination Survey. *Am J Kidney Dis* 2003; 41: 1–12
4. US Department of Health and Human Services. Chronic kidney disease. In: *Healthy People 2010*. Government Printing Office, Washington, DC, 2000
5. Shoji T, Emoto M, Tabata T *et al*. Advanced atherosclerosis in predialysis patients with chronic renal failure. *Kidney Int* 2002; 61: 2187–2192
6. Reddan DN, Klassen PS, Szczech LA *et al*. White blood cells as a novel mortality predictor in haemodialysis patients. *Nephrol Dial Transplant* 2003; 18: 1167–1173
7. Stenvinkel P, Wanner C, Metzger T *et al*. Inflammation and outcome in end-stage renal failure: does female gender constitute a survival advantage? *Kidney Int* 2002; 62: 1791–1798
8. Kimmel PL, Phillips TM, Simmens SJ *et al*. Immunologic function and survival in hemodialysis patients. *Kidney Int* 1998; 54: 236–244
9. Stenvinkel P, Barany P, Heimbürger O *et al*. Mortality, malnutrition, and atherosclerosis in ESRD: what is the role of interleukin-6. *Kidney Int* 2002; 61: S103–S108
10. Stenvinkel P, Heimbürger O, Lindholm B, Kaysen GA, Bergström J. Are there two types of malnutrition in chronic renal failure? Evidence for relationships between malnutrition, inflammation and atherosclerosis (MIA syndrome). *Nephrol Dial Transplant* 2000; 15: 953–960
11. Collins AJ, Ma JZ, Xia A, Ebben J. Trends in anemia treatment with erythropoietin usage and patient outcomes. *Am J Kidney Dis* 1998; 32: S133–S141
12. Leb L, Snyder LM, Fortier NL, Andersen M. Antiglobulin serum mediated phagocytosis of normal senescent and oxidized

RBC: role of anti-IgM immunoglobulins in phagocytic recognition. *Br J Haematol* 1987; 66: 565–570

13. Schooley JC, Kullgren B, Allison AC. Inhibition by interleukin-1 of the action of erythropoietin on erythroid precursors and its possible role in the pathogenesis of hypoplastic anaemias. *Br J Haematol* 1987; 67: 11–17

14. Allen DA, Breen C, Yaqoob MM, Macdougall IC. Inhibition of CFU-E colony formation in uremic patients with inflammatory disease: role of IFN-gamma and TNF-alpha. *J Invest Med* 1999; 47: 204–211

15. Pojda Z, Tsuboi A. *In vivo* effects of human recombinant interleukin 6 on hemopoietic stem and progenitor cells and circulating blood cells in normal mice. *Exp Hematol* 1990; 18: 1034–1037

16. Dybedal I, Larsen S, Jacobsen SE. IL-12 directly enhances *in vitro* murine erythropoiesis in combination with IL-4 and stem cell factor. *J Immunol* 1995; 154: 4950–4955

17. Miller CB, Jones RJ, Piantadosi S, Abeloff MD, Spivak JL. Decreased erythropoietin response in patients with the anemia of cancer. *N Engl J Med* 1990; 322: 1689–1692

18. Patton JS, Peters PM, McCabe J *et al*. Development of partial tolerance to the gastrointestinal effects of high doses of recombinant tumor necrosis factor-alpha in rodents. *J Clin Invest* 1987; 80: 1587–1596

19. Faquin WC, Schneider TJ, Goldberg MA. Effect of inflammatory cytokines on hypoxia-induced erythropoietin production. *Blood* 1992; 79: 1987–1994

20. Leng HM, Folb PI. Erythropoiesis and erythropoietin synthesis during aseptic acute inflammation. *Inflamm Res* 1996; 45: 541–545

21. Jongen-Lavrencic M, Peeters HR, Rozemuller H *et al*. IL-6-induced anaemia in rats: possible pathogenetic implications for anemia observed in chronic inflammations. *Clin Exp Immunol* 1996; 103: 328–334

22. Remick DG, Kunkel RG, Larrick JW, Kunkel SL. Acute *in vivo* effects of human recombinant tumor necrosis factor. *Lab Invest* 1987; 6: 583–590

23. Appleyard CB, McCafferty DM, Tigley AW, Swain MG, Wallace JL. Tumor necrosis factor mediation of NSAID-induced gastric damage: role of leukocyte adherence. *Am J Physiol* 1996; 270: G42–G48

24. Lipschitz DA, Cook JD, Finch CA. A clinical evaluation of serum ferritin as an index of iron stores. *N Engl J Med* 1974; 290: 1213–1216

25. Fine A. Relevance of C-reactive protein levels in peritoneal dialysis patients. *Kidney Int* 2002; 61: 615–620

26. Kooistra MP, Niemantsverdriet EC, Van Es A, Mol-Beermann NM, Struyvenberg A, Marx JJ. Iron absorption in erythropoietin-treated haemodialysis patients: effects of iron availability, inflammation and aluminium. *Nephrol Dial Transplant* 1998; 13: 82–88

27. Cavdar C, Camsari T, Semin I, Gonenc S, Acikgoz O. Lipid peroxidation and antioxidant activity in chronic haemodialysis patients treated with recombinant human erythropoietin. *Scand J Urol Nephrol* 1997; 31: 371–375

28. Sommerburg O, Grune T, Hampl H *et al*. Does long-term treatment of renal anemia with recombinant erythropoietin influence oxidative stress in hemodialysis patients? *Nephrol Dial Transplant* 1998; 13: 2583–2587

29. Ludat K, Sommerburg O, Grune T, Siems WG, Riedel E, Hampl H. Oxidation parameters in complete correction of renal anemia. *Clin Nephrol* 2000; 53: S30–S35

30. Nemeth I, Turi S, Haszon I, Bereczki C. Vitamin E alleviates the oxidative stress of erythropoietin in uremic children on hemodialysis. *Pediatr Nephrol* 2000; 14: 13–17

31. Usberti M, Gerardi G, Micheli A *et al*. Effects of a vitamin E-bonded membrane and of glutathione on anemia and erythropoietin requirements in hemodialysis patients. *J Nephrol* 2002; 15: 558–564

32. Cristol JP, Bosc JY, Badiou S *et al*. Erythropoietin and oxidative stress in haemodialysis: beneficial effects of vitamin E supplementation. *Nephrol Dial Transplant* 1997; 12: 2312–2317

33. Mimic-Oka J, Simic T, Djukanovic L. Epoetin treatment improves red blood cell and plasma antioxidant capacity in hemodialysis patients. *Renal Fail* 2002; 24: 77–87

34. Inal M, Kanbak G, Sen S, Akyuz F, Sunal E. Antioxidant status and lipid peroxidation in hemodialysis patients undergoing erythropoietin and erythropoietin-vitamin E combined therapy. *Free Radic Res* 1999; 31: 211–216

35. Roob JM, Khoschsorur G, Tiran A *et al*. Vitamin E attenuates oxidative stress induced by intravenous iron in patients on haemodialysis. *J Am Soc Nephrol* 2000; 11: 539–549

36. Nguyen-Khoa T, Massy ZA, De Bandt JP *et al*. Oxidative stress and haemodialysis: role of inflammation and duration of dialysis treatment. *Nephrol Dial Transplant* 2001; 16: 335–340

37. Witko-Sarsat V, Friedlander M, Nguyen KT *et al*. Advanced oxidation protein products as novel mediators of inflammation and monocyte activation in chronic renal failure. *J Immunol* 1998; 161: 2524–2532

38. Handelman GJ, Walter MF, Adhikarla R *et al*. Elevated plasma F2-isoprostanes in patients on long-term hemodialysis. *Kidney Int* 2001; 59: 1960–1966

39. Schindler R, Boenisch O, Fischer C, Frei U. Effect of the hemodialysis membrane on the inflammatory reaction *in vivo*. *Clin Nephrol* 2000; 53: 452–459

40. Memoli B, Postiglione L, Cianciaruso B *et al*. Role of different dialysis membranes in the release of interleukin-6-soluble receptor in uremic patients. *Kidney Int* 2000; 58: 417–424

41. Panichi V, Migliori M, De Pietro S *et al*. The link of biocompatibility to cytokine production. *Kidney Int Suppl* 2000; 76: S96–S103

42. Tielemans C, Husson C, Schurmans T *et al*. Effects of ultrapure and non-sterile dialysate on the inflammatory response during *in vitro* hemodialysis. *Kidney Int* 1996; 49: 236–243

43. Sitter T, Bergner A, Schiffl H. Dialysate related cytokine induction and response to recombinant human erythropoietin in haemodialysis patients. *Nephrol Dial Transplant* 2000; 15: 1207–1211

44. Goicoechea M, Martin J, De Sequera P *et al*. Role of cytokines in the response to erythropoietin in hemodialysis patients. *Kidney Int* 1998; 54: 1337–1343

45. Velasquez MT, Bhathena SJ. Dietary phytoestrogens: a possible role in renal disease protection. *Am J Kidney Dis* 2001; 37: 1056–1068

46. Kang JL, Lee HW, Lee HS *et al*. Genistein prevents nuclear factor-kappa B activation and acute lung injury induced by lipopolysaccharide. *Am J Respir Crit Care Med* 2001; 164: 2206–2212

47. Kato A, Odamaki M, Takita T, Furuhashi M, Maruyama Y, Hishida A. High blood soluble receptor p80 for tumour necrosis factor-alpha is associated with erythropoietin resistance in haemodialysis patients. *Nephrol Dial Transplant* 2001; 16: 1838–1844

48. Davis D, Charles PJ, Potter A, Feldmann M, Maini RN, Elliott MJ. Anaemia of chronic disease in rheumatoid arthritis: *in vivo* effects of tumour necrosis factor alpha blockade. *Br J Rheumatol* 1997; 36: 950–956