

Malnutrition and Chronic Inflammation as Risk Factors for Cardiovascular Disease in Chronic Renal Failure

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Introduction

Despite the recent considerable improvements in dialysis technology, cardiovascular disease (CVD) still remains the main cause of morbidity and mortality in maintenance hemodialysis (HD) patients. It is obvious that 'traditional' risk factors, such as hypertension, chronic heart failure, dyslipidemia, tobacco smoking and diabetes mellitus, may account for a large part of the increased cardiovascular mortality rate observed in these patients. However, based on recent research it is evident that also other, 'nontraditional', risk factors, such as inflammation, oxidative stress and malnutrition, may contribute to an increased cardiovascular mortality among dialysis patients. Chronic inflammation, as evidenced by increased levels of various acute phase reactants such as C-reactive protein (CRP), fibrinogen, serum amyloid A (SAA), transferrin, serum albumin and prealbumin, is a common feature in dialysis patients. Various pro-inflammatory cytokines are the major mediators of acute phase protein induction and interleukin (IL)-6 is felt to be the principal cytokine influencing CRP changes. Although the association between inflammation and atherosclerotic CVD by now is well established, the mechanism(s) by which inflammation may accelerate atherosclerosis are not well

understood. It has been proposed that various acute phase reactants promote atherogenesis by directly affecting different parts of the atherosclerotic process. On the other hand, recent evidence suggests that inflammation may rather be a marker of an atherogenic milieu and that the association is merely indirect. Indeed, inflammation has been proven to be associated with endothelial dysfunction, insulin resistance and oxidative stress, all of which may accelerate atherosclerosis.

Traditional Risk Factors Are Inadequate as Predictors of Cardiovascular Mortality in Dialysis Patients

CVD remains the main cause of morbidity and mortality in maintenance HD patients. The annual mortality rate due to CVD is approximately 9%, which is 10- to 20-fold higher than the general population, even when adjusted for age, gender, race and diabetes mellitus [1]. It is evident that the atherosclerotic process is accelerated in CRF patients [2, 3] and it has recently been demonstrated that coronary artery calcification is common and progressive also in young HD patients [4]. The causes of atherosclerotic CVD in the general population are multifactorial

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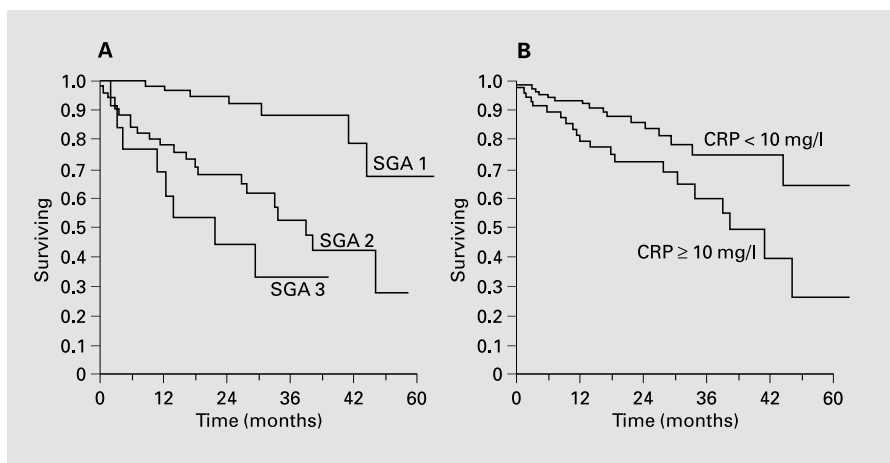
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Fig. 1. A Survival by Kaplan-Meier plot of 173 patients followed during dialysis treatment divided according to subjective global assessment (SGA). SGA 1 = Well-nourished, SGA 2 = mild malnutrition and SGA 3 = moderate malnutrition before start of dialysis treatment (χ^2 30.1; $p < 0.0001$). **B** Survival by Kaplan-Meier plot of 176 patients followed during dialysis treatment divided according to CRP levels (< 10 mg/l or ≥ 10 mg/l, respectively) before start of dialysis treatment (χ^2 6.7; $p < 0.01$).



and ‘traditional’ risk factors, such as dyslipidemia, left ventricular hypertrophy, diabetes mellitus, hypertension, and tobacco smoking, have all been proven to contribute. Intuitively, it appears reasonable to assume that ‘traditional’ risk factors for the general population are also applicable to HD patients. However, in a recent study by Cheung et al. [5] performed in 936 HD patients, it was found that whereas ‘traditional’ risk factors, such as diabetes mellitus and smoking, were strongly associated with CVD, neither serum total cholesterol nor systolic blood pressure was associated with coronary heart disease. In an ongoing prospective study we have made similar preliminary findings and found that whereas ‘traditional’ risk factors such as age and diabetes mellitus do predict survival during dialysis treatment neither 24-hour ambulatory blood pressure nor serum cholesterol does. Indeed, already in 1982, Degoulet et al. [6] obtained a paradoxical result showing that the higher the serum cholesterol, the better the HD patient survival. Their finding was subsequently confirmed by others [7] and it is now widely appreciated that low cholesterol levels, as observed during malnutrition, may account for this paradoxical finding.

Nontraditional Risk Factors in Chronic Renal Failure

A number of ‘nontraditional’ risk factors for CVD, such as hyperhomocysteinemia, oxidative stress, vascular calcification, malnutrition and inflammation are commonly found in chronic renal failure (CRF) patients. Thus, it could be speculated that they might provide a rationale for the remarkable prevalence of atherosclerotic

CVD observed in these patients. In an ongoing prospective study, we have found that various markers of malnutrition and inflammation are strong independent predictors of mortality in dialysis patients (fig. 1). Thus, it could be speculated that the impact of ‘nontraditional’ risk factors, such as inflammation and malnutrition, on cardiovascular mortality are so strong in dialysis patients that it obscures the impact of common ‘traditional’ risk factors, such as hypertension, tobacco smoking and dyslipidemia.

It may seem puzzling that whereas hypoalbuminemia [7, 8] and inflammation [9, 10] have been shown to be important predictors of mortality, complications from malnutrition and inflammation as such are not common causes of mortality in dialysis patients [11]. In fact, malnutrition accounts for less than 5% of deaths in renal patients while atherosclerotic CVD is by far the commonest cause of mortality in the dialysis population [1]. How can this paradox best be explained? One possible explanation may be the strong documented interactions between CVD and inflammatory as well as nutritional parameters in CRF patients [3]. Based on these findings, a syndrome (MIA) consisting of malnutrition, inflammation and atherosclerosis has been suggested [12].

Are There Two Types of Malnutrition in Dialysis Patients?

Malnutrition is a common feature in patients with CRF and is commonly associated with decreased body weight, depleted energy (fat tissue) stores, loss of somatic protein (low muscle mass). Moreover, it has been stated

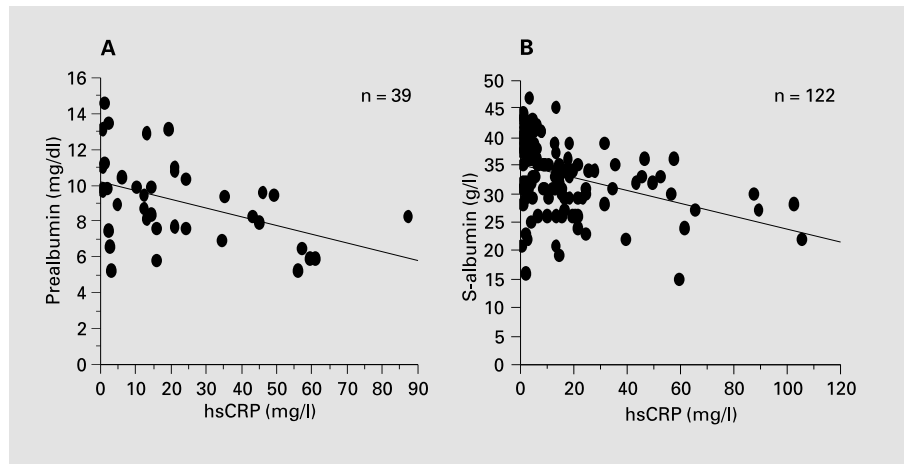


Fig. 2. Association between high-sensitivity CRP and **A** prealbumin ($R = -0.45$; $p < 0.01$) and **B** serum albumin ($R = -0.37$; $p < 0.0001$) levels in predialysis patients.

that low plasma levels of serum albumin, transferrin, prealbumin and other visceral proteins accompany malnutrition. Various studies show signs of malnutrition in 23–76% of HD and 18–50% of peritoneal dialysis (PD) patients [13, 14] and there has been a growing body of evidence linking poor nutritional status in CRF patients with increasing morbidity and mortality. A number of factors directly associated with the dialytic procedure per se, such as bioincompatibility, nutrient losses in the dialysate and, during PD, poor appetite due to abdominal discomfort and uptake of glucose, may be important contributors to malnutrition in dialysis patients. However, as malnutrition is also prevalent in predialysis patients [3, 15] it is obvious that non-dialysis-related factors also contribute.

It was recently, in a large number of patients, demonstrated that as glomerular filtration rate declines, <20–25 ml/min signs of nutritional deterioration develop with declining levels of serum albumin [15]. One component of this decline in the nutritional status may be due to a spontaneous reduction in dietary caloric intake [16]. However, since most malnourished CRF patients also have evidence of inflammation and CVD (table 1) it is possible that dialysis-unrelated factors, such as co-morbidity associated with inflammation and elevated serum levels of pro-inflammatory cytokines, also contribute to malnutrition in CRF. Indeed, Kaizu et al. [17] has demonstrated that the nutritional status in HD patients is affected, at least partly, by circulating IL-6 levels. Moreover, a Japanese group has demonstrated that infusion of recombinant IL-6 lowers serum albumin levels and that IL-6 transgenic mice have a muscle-wasting syndrome [18].

Table 1. Nutritional and inflammatory parameters and prevalence of CVD in predialysis patients grouped as well-nourished (SGA 1) or malnourished (SGA > 1), respectively

	SGA 1 (n = 95)	SGA > 1 (n = 63)	Significance p <
Age, years	48 ± 1	56 ± 1	0.0001
Weight, kg	76.3 ± 1.4	66.9 ± 1.7	0.0001
Lean body mass, kg	51.8 ± 1.2	45.7 ± 1.2	0.001
Serum albumin, g/l	34.6 ± 0.6	32.4 ± 0.8	0.05
Serum creatinine, µmol/l	758 ± 24	582 ± 22	0.0001
Hand-grip strength, kg	37.2 ± 1.3	25.7 ± 1.4	0.0001
Prevalence CVD, %	19	57	0.0001
hsCRP, mg/l	8.2 ± 1.2	25.7 ± 3.6	0.0001
IL-6, pg/ml	6.6 ± 0.8	11.7 ± 1.6	0.01
Serum hyaluronan ng/ml	81.3 ± 6.9	148.8 ± 21.5	0.001
VCAM-1, ng/ml	1,105 ± 53	1,436 ± 94	0.01

The synthetic rate of various serum proteins used as markers of malnutrition, such as serum albumin, prealbumin, retinol binding protein and SAA, are vulnerable to the effects of inflammation (fig. 2). Consequently, their use as nutritional markers in dialysis patients may be problematic. In fact, in healthy subjects subjected to semi-starvation [19], or in patients with anorexia nervosa [20], serum albumin levels decline only modestly. Moreover, Bistrian et al. [21] have shown that adult marasmus (protein-calorie malnutrition without inflammation) is associated with preserved serum albumin levels. In fact, the only direct dietary cause for severe hypoalbuminemia seems to be adequate or excessive energy intake when the protein intake is severely limited [22]. Indeed, Heimbü-

Table 2. Proposed features of pure malnutrition (type 1) and inflammatory-associated malnutrition (type 2) [adapted from 12]

	Type 1	Type 2
S-albumin	Normal/low	Low
Co-morbidity	Uncommon	Common
Presence of inflammation	No	Yes
Food intake	Low	Low/normal
Resting energy expenditure	Normal	Elevated
Oxidative stress	Increased	Markedly increased
Protein catabolism	Decreased	Increased
Reversed by dialysis and nutritional support	Yes	No

ger et al. [23] have reported that serum albumin levels did not differ significantly between well-nourished and malnourished predialysis patients whereas the presence of inflammation was associated with much lower serum albumin levels. Based on these findings, we have proposed that at least two types of malnutrition may be present in CRF patients [12]. Whereas type 1 malnutrition is associated with the uremic syndrome per se, the other cytokine-driven type of malnutrition (type 2) is often associated with significant co-morbidity as outlined in table 2. It is obvious that in the clinical setting these two types of malnutrition may often be combined.

Inflammation Is a Common Feature of Chronic Renal Failure

As inflammation may cause the same changes in the concentration of commonly used biochemical markers of malnutrition, as does inadequate nutritional intake, much of the previously reported relations between serum albumin and total and cardiovascular mortality in HD [7] and PD [8] patients may have been caused by an ongoing inflammatory process rather than poor nutritional intake. Recently, it has been recognized that about 30–50% of predialysis [3], HD [9, 10, 13, 24], and PD [25] patients have serologic evidence of an activated inflammatory response as evidenced by elevated CRP levels. It should be emphasized that CRP measurements in these cross-sectional studies were made at a single time point, which may complicate interpretation as it is well recognized that CRP may be a 'moving target'. Longitudinal studies with repetitive CRP measurements are therefore warranted as Kaysen et al. [26] recently showed that the acute phase

Table 3. Potential causes of inflammation in patients with CRF

<i>Chronic renal failure</i>
Reduced renal clearance of cytokines
Reduced renal clearance of advanced glycation end products (AGEs)
Chronic heart failure
The atherosclerotic process per se
Various inflammatory diseases
Unrecognized persistent infections, e.g., <i>C. pneumoniae</i> , <i>H. pylori</i> , dental and/or gingival infections
<i>Additional causes in HD</i>
Graft and fistula infections
Bioincompatibility
Exposure to endotoxins and other cytokine-inducing substances from contaminated dialysate, e.g., backfiltration
<i>Additional causes in PD</i>
Peritonitis
Peritoneal access
Bioincompatibility
Exposure to endotoxins, plasticizers and other cytokine-inducing substances from contaminated dialysate

response is intermittent and varies significantly in time with no change in dialyzer type or treatment. The observation by Kaysen et al., together with the high prevalence of elevated CRP documented in predialysis patients [3], suggest that factors unrelated to dialysis therapy, such as co-morbidity, might be the most important causes of elevated CRP in CRF patients (table 3).

However, several lines of evidence suggest that also factors associated with the dialysis procedure per se might contribute to an inflammatory response (table 3). At first, Haubitz et al. [27] have demonstrated that acute phase proteins are induced during HD, probably due to cytokine release, and Schindler et al. [28] suggest that the dialyzer membrane may play a role in the induction of an inflammatory reaction during the dialysis procedure. Moreover, data by Memoli et al. [29] suggest an important role of poor dialysis bioincompatibility of cuprophane on enhancing the inflammatory effects of IL-6. Available evidence also suggests that the quality of water used to prepare the dialysate might contribute to inflammation [30]. Indeed, Schindler et al. [28] could recently demonstrate that optimized HD therapy using ultrapure dialysate and biocompatible dialyzer membranes was able to reduce, but not to normalize, elevated CRP levels in HD patients again suggesting that non-dialysis-related factors contribute to inflammation in CRF.

Causes of Inflammation in Chronic Renal Failure

Serum levels of CRP appear to reflect generation of pro-inflammatory cytokines (IL-1, IL-6 and TNF- α) which have been reported to be markedly elevated in CRF patients [31, 32] and also to predict mortality [31, 33]. The cause(s) of elevated serum levels of pro-inflammatory cytokines in CRF patients are not well understood. However, available evidence suggests that both decreased renal clearance [34] as well as increased synthesis of cytokines might contribute. In this respect it is of interest that reduced renal function may affect both TNF [35] and IL-1 [36] clearance in nephrectomized rats. The importance of the kidney in cytokine handling is further underscored by Hession et al. [37] who demonstrated that the Tamm-Horsfall glycoprotein might function as a unique renal regulatory glycoprotein that regulates the activity of potent cytokines, such as IL-1 and TNF. As not all dialysis patients have elevated CRP levels it has been proposed that a polymorphism in the genes encoding pro-inflammatory cytokines contribute to the observed differences in the prevalence of elevated CRP. However, a recent preliminary study, in a small patient material, concluded that TNF and interferon gene polymorphism do not play a role in determining CRP levels in dialysis patients [38].

The kidney may play an important role in the metabolism of advanced glycation end products (AGEs), which may be another factor that play a role in activating mononuclear cells and stimulate an inflammatory response. Conversely, inflammation may also play a role in the production of AGEs [39]. Other non-dialysis-related causes of elevated CRP might include factors such as chronic heart failure with edema [40] and the atherosclerotic process per se. In fact, by virtue of its acute phase behavior it has been suggested that CRP may be a marker for severity and progression of atherosclerotic processes in the vessels [41]. However, as many patients with stable and unstable angina pectoris have normal levels of acute phase proteins, this implies that coronary atherosclerosis itself does not always induce a full-blown acute phase response. Whereas noninfectious causes may be the most common cause of an inflammatory response in CRF patients, it should be recognized that also various chronic persistent infections such as *Chlamydia pneumoniae* [42, 43], *Helicobacter pylori* and dental or gingival infections may contribute. In fact, in a recent preliminary study of 104 HD patients, it was demonstrated that CRP levels correlated with the titer of periodontal pathogens suggesting that poor dental status may contribute to inflammation [44].

Does Chronic Inflammation Cause Atherosclerotic Cardiovascular Disease?

There is no doubt that the most significant process that correlates with inflammation is atherosclerotic CVD, although the relationship between these two processes is complex. Recent studies have established that even small increases in the levels of pro-inflammatory cytokines, such as IL-6 [45], or acute phase proteins such as CRP [46], predict CVD in otherwise healthy adults. Moreover, in non-renal patient populations, elevated levels of CRP are associated with ischemic stroke [47] and mortality in nondisabled older people [48]. In a recent updated meta-analysis including 2,557 cases, Danesh et al. [49] reported that the combined risk ratio for coronary heart disease was 1.9 times higher in the patients that had the highest CRP compared to those in the bottom third.

Several groups have by now reported that increased CRP is a strong risk factor for death also among HD [9, 10, 50, 51] and PD [52] patients. Moreover, elevated CRP has been shown to predict cardiovascular mortality [9, 10] and hospitalization [53] in dialysis patients. In fact, available data suggest that the association between inflammation and atherosclerosis is particularly strong in dialysis patients. A strong relation between malnutrition, elevated CRP levels and atherosclerosis has also been documented in predialysis patients [3] and serum hyaluronan, another inflammatory marker generated in response to pro-inflammatory cytokines, is a powerful predictor of mortality in CRF patients commencing renal replacement therapy [54].

Although the association between CVD and inflammation in the dialysis patient population is well documented, we do not know if the acute phase response merely reflects an epiphenomenon accompanying established atherosclerotic disease or whether different acute phase reactants are involved in the initiation and/or progression of atherosclerosis (table 4). In fact, several lines of evidence suggest that different acute phase reactants actually may be directly involved as causative factors in atherogenesis. At first, Torzewski et al. [55] have demonstrated that CRP deposit in the arterial wall of early atherosclerotic lesions. Secondly, as CRP has been shown to localize in heart tissue it has been hypothesized that CRP may directly cause tissue damage [56]. Moreover, during inflammation, SAA is incorporated into HDL and the interaction between acute inflammation and lipoprotein structure could provide one possible link between accelerated vascular disease and inflammation, as recently reviewed by Kaysen [57]. Finally, other acute phase reactants, such as Lp(a)

Table 4.

a Possible *direct* atherogenic mechanisms by which various acute phase reactants may cause atherosclerotic CVD

CRP deposits in the arterial wall
 CRP causes direct tissue damage
 SAA affect lipoprotein structure
 Lp(a) promotes athero- and thrombogenesis
 Fibrinogen promotes athero- and thrombogenesis and increases plasma, viscosity

b Possible *indirect* mechanisms by which an acute phase reaction may be associated with atherosclerotic CVD

Endothelial dysfunction, e.g., nitric oxide, soluble adhesion molecules
 Insulin resistance
 Increased oxidative stress
 Stimulation of advanced glycation end products (AGEs)
 Persistent atherogenic infections, e.g., *C. pneumoniae*, *H. pylori*

[58] and fibrinogen [59], may have direct atherogenic and/or thrombogenic properties that may accelerate atherogenesis. On the other hand, several lines of evidence suggest that the association between chronic inflammation and CVD is indirect. It is documented that chronic inflammation is associated with features, such as endothelial dysfunction, insulin resistance and increased oxidative stress, all of which may accelerate atherogenesis.

Does Inflammation Cause Endothelial Dysfunction?

Recent evidence suggests that endothelial dysfunction, which is thought to be associated with early atherosclerotic CVD, may be more prevalent in conditions associated with malnutrition and inflammation. As inflammation has been shown to be associated with reduced bioavailability of nitric oxide, this suggests that endothelial dysfunction may be a critical intermediate phenotype in the relationship between inflammation and CVD [60]. In this respect it is of interest that although Kim et al. [61] showed correlations between serum albumin, CRP and serum markers of endothelial function, an infusion of albumin did not normalize endothelial function. Consequently, their findings suggest that the relationship between low serum albumin levels and endothelial dysfunction may be secondary to other factors, such as inflamma-

tion. Indeed, recent observations have shown correlations between inflammation and various circulating markers of endothelial activation in both type 1 diabetic [62] and CRF [63] patients. Bhagat and Vallance [64] have showed that infusion of endotoxins or pro-inflammatory cytokines in healthy volunteers caused a selective impairment of endothelium-dependent relaxation. Moreover, Sinisalo et al. [65] and Cleland et al. [60] recently showed a relationship between low-grade chronic inflammation and endothelial dysfunction. Finally, long-term exposure of vascular endothelium to IL-1 β and TNF- α causes endothelial dysfunction, intimal thickening and coronary vasospasm in pigs [66]. Taken together, these findings suggest that a synergy exists between the presence of chronic inflammation and the development of malnutrition contributing to cardiovascular risk via an endothelial dysfunction.

Inflammation may also affect endothelial function by altering the expression of soluble adhesion molecules (sICAM-1, sVCAM-1 and E-selectin) which has been shown to promote monocyte binding to endothelial cells. In this respect it is of interest that elevated levels of ICAM-1 have been shown to be a prognostic risk factor for future cardiovascular events in both men [67] and women [68]. It is therefore of interest that markedly elevated serum levels of soluble adhesion molecules have been documented in both predialysis [69, 70] and dialysis [70] patients. Bonomini et al. [70] suggested that inadequate clearance contributes to elevated serum levels of adhesion molecules in CRF. However, as it has repeatedly been demonstrated that pro-inflammatory cytokines can upregulate the expression of adhesion molecules from endothelial cells [71], increased synthesis may also contribute to elevated serum levels of adhesion molecules in CRF patients. As ICAM-1 has recently been shown to be an independent predictor of death in dialysis patients [63], further studies are needed to investigate if inflammation may cause accelerated atherogenesis via effects on soluble adhesion molecules.

Inflammation and Insulin Resistance

Insulin resistance is a well-documented feature of CRF [72] which is associated with a premature development of atherosclerosis. Several reports in nonrenal patient populations suggest that elevated CRP levels are associated with several different features of the insulin resistance syndrome including increased body mass index [73–75], serum lipids [73, 74], and fasting glucose [73]. Recently,

Festa et al. [76] demonstrated in 1,008 nondiabetic patients, of whom one third had impaired glucose tolerance, that there was a linear increase in CRP with an increase in the number of metabolic disorders. Consequently, chronic low-grade inflammation may be part of the insulin resistance syndrome. In this respect it is of interest that clamp studies in normal subjects have shown that insulin exerts selective effects on hepatic protein synthesis with an increase in serum albumin and decrease in fibrinogen synthesis [77]. It is therefore possible that decreased insulin sensitivity may lead to enhanced CRP expression by counteracting the physiological effects of insulin on hepatic acute phase synthesis [78]. However, other mechanisms may also be operative and it is possible that chronic inflammation may simply represent a triggering factor in the origin of insulin resistance as discussed by Festa et al. [76].

Does Inflammation Cause Increased Oxidative Stress?

Oxidative stress, which occurs when there is excessive free radical production or low antioxidant levels, has emerged as an important co-factor for the development of endothelial dysfunction and atherogenesis [79]. Free radicals are involved in the development of atherosclerosis by generating oxidized low-density lipoprotein (LDL), which by various mechanisms, damage the vascular wall and cause atherosclerotic lesions. Recent data support the hypothesis that increased oxidative stress is present in HD patients [80] and it is probable that loss of antioxidants, such as vitamins C and E, occurs in CRF or as a consequence of the dialysis treatment per se.

Plasmalogen phospholipids have been demonstrated to play a significant role in the defense of LDL particles against oxidative stress [81]. As we have found lower levels of erythrocyte plasmalogen phospholipids in malnourished compared to well-nourished predialysis patients, one could speculate that an increased oxidative stress might be a contributing factor to the high prevalence of CVD documented in malnourished and inflamed CRF patients [82]. The cause(s) of increased oxidative stress in malnourished patients are not well understood. However, in view of the documented strong relations between malnutrition and inflammation, is it possible that a chronic inflammatory response may be the primary cause of increased oxidative stress in malnourished CRF patients. Indeed, recent results by Memon et al. [83] have demonstrated that LDL isolated from animals treated with bac-

terial lipopolysaccharide (LPS) was significantly more susceptible to ex vivo oxidation with copper than LDL isolated from saline-treated animals. Unfortunately, data on the effect of inflammation on oxidative stress in CRF patients are scarce. However, recently Nguyen-Khoa et al. [84] found that the inflammatory status and duration of dialysis treatment are the most important factors relating to oxidative stress in HD patients.

Conclusions

CRF is characterized by an exceptionally high mortality rate, much of which is the result of CVD. Recent evidence demonstrates that chronic inflammation, as evidenced by increased levels of pro-inflammatory cytokines and CRP, is a common feature in CRF patients. Chronic inflammation may cause malnutrition and progressive atherosclerotic CVD by several pathogenetic mechanisms and could, thus, contribute to the high mortality rate. The cause(s) of inflammation is probably multifactorial and while it may reflect underlying CVD, it may also be a direct cause of vascular injury. As available data suggest that pro-inflammatory cytokines plays a central role in the genesis of both 'inflammatory-driven' malnutrition and CVD, it would be of obvious interest to study what effect anticytokine therapy (such as anti-TNF- α antibodies, soluble TNF- α receptors, IL-1 receptor antagonists and thalidomide) have on survival in dialysis patients. The impact of various anti-inflammatory and antibiotic treatment strategies may also be of interest to study in dialysis patients with signs of malnutrition, inflammation and atherosclerosis (MIA syndrome). In this respect it should be pointed out that Ridker et al. [85] recently demonstrated that whereas CRP levels tended to increase over 5 years in those patients that received placebo, randomization to pravastatin (a HMG-CoA reductase inhibitor) resulted in a significant reduction in CRP that was not related to the magnitude of lipid alterations observed.

Acknowledgements

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