Inflammation Markers as Cardiovascular Prognostic Factors in Hemodialyis Patients

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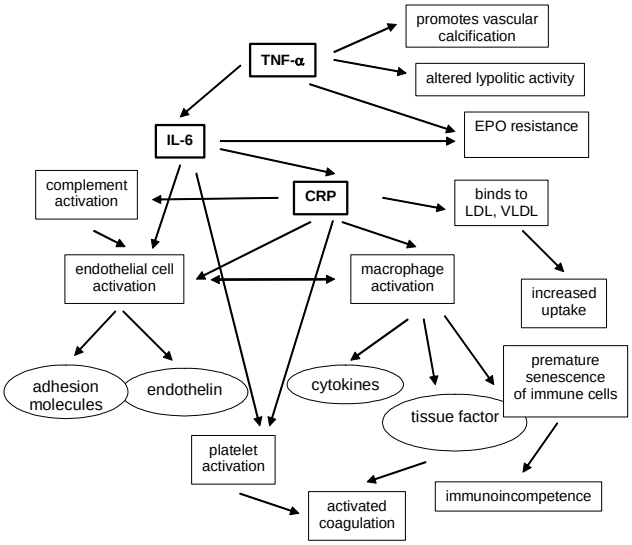
Mortality in dialysis patients remains 10-20 times higher than in general population[1] despite advances in dialytic techniques. Cardiovascular (CV) causes, mainly atherosclerosis, account for 40-50% of deaths, the second cause of mortality being infectious complications (15%). Atherosclerosis is currently regarded as an inflammatory state, while dialysis patients have disturbed immune response and high incidence of infection. A better understanding of the pathophysiological mechanisms leading to this associated pathology might improve prevention and treatment, thus the patients outcome. The excess CV mortality and morbidity of dialysis patients cannot be entirely explained by traditional risk factors: age, sex, race, family history, diabetes mellitus, dyslipidemia, hypertension, obesity, cigarette smoking. Non-traditional risk factors: hyperhomocysteinemia, impaired NO synthesis, increased oxidative stress, infections, volume overload, hyperparathyroidism, anemia, increased angiotensin II and aldosterone levels and chronic inflammation play an important role. The current presentation focuses on the role of chronic inflammation on excess morbidity and mortality of hemodialysis patients.

Inflammation markers are strong predictors of CV risk in general population[2]. It is now established that the same holds true for dialysis patients; high levels of C-reactive protein (CRP)[3], IL-6[4], serum amiloid A[5], fibrinogen[6] or $\alpha_2$macroglobulin[7], and low levels of anti-inflammatory cytokines such as IL-10[8] and fetuin-A[9] predict CV as well as all cause morbidity and mortality. A single cross-sectional measurement of an inflammation marker can predict morbidity and mortality for long periods of time, although these markers have relatively short half life and intraindividual variability in time. It is not clear what is the cause for the chronic inflammatory status, present in 30-50% of chronic renal failure (CRF) patients. Discussed are both non-dialysis as well as dialysis related causes. Non-dialysis related causes are present before dialysis is innitiated, early in the course of CRF: genetic factors, altered metabolism and excretion of immunologically active proteins, increased oxidative stress, plasma volume expansion, hypertension, infections (with high incidence in CRF, including those thought to play a role in the pathophysiology of atherosclerosis, such as chlamidia pneumoniae, helicobacter pylori, cytomegalovirus). On the other hand, dialysis related causes expose patients to supplemental inflammatory stimuli: contact of blood with dialysis membranes, dialysate contaminants, vascular access infections, all result in complement as well as monocyte and granulocyte activation, cytokine release and increased oxidative stress. The result is a status of chronic inflammation; liver synthesis of acute phase proteins (CRP, serum amilod A, fibrinogen, α1acid glycoprotein and $\alpha_2$macroglobulin) is increased while negative acute phase proteins synthesis (albumin, prealbumin, transferrin) is decreased. The low-range increase in CRP and other inflammation markers might be either a sensor of chronic inflammatory state, or directly implicated in the pathophysiology. TNF-α, IL-6 and CRP can promote complement, macrophage and endothelial cell activation, alter coagulation processes, lipid metabolism and lead to premature senescence of immune cells (Fig 1). Indeed, complement activation by the alternative pathway[10] and endothelial activation have been demonstrated in dialysis patients. CRP is present in human atheromatous plaque, demonstrated for the first time by Vlaicu R. et al in 1985[11], colocalised with complement components.

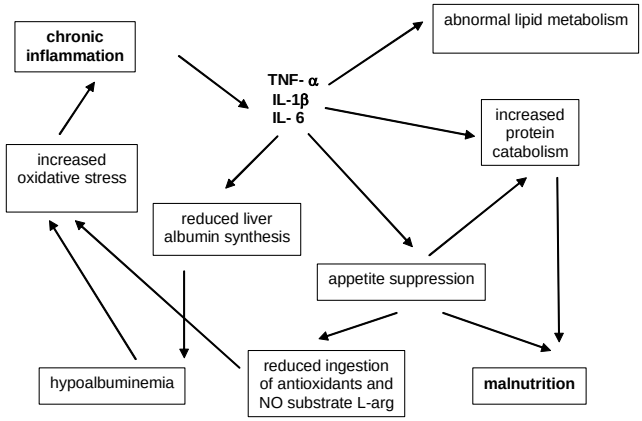
Thus, inflammation markers can be used as screening test in order to identify high risk patients. Particularly CRP is suitable for this purpose; its determination is less expensive and equally reliable to other inflammation markers, it is the most sensitive acute phase protein in humans, liver synthesis is the only determinant of CRP level, which does not depend on storage, fasting, sex, age or diurnal moment. In a group of 74 hemodialysis patients, we found significantly higher values of CRP (9.6±1.7 vs. 0.4±0.2 mg/l) and α1acid glycoprotein (125.2±5.4 vs. 91.4±3.2 mg/dl) than in controls. During a 12 months follow-up period, survival rate was only 83% in the subgroup with CRP higher than 1 mg/l, while it was 97% in the subgroup with CRP below this value. In 40 dialysis patients we found significantly increased levels of IL-18 as compared to controls (611.9±90.8 vs. 193.9±10.7 pg/ml). It is yet not clear if IL-18 has the same prognostic value for CV morbidity in dialysis patients, although increased levels have been previously described[12], as in the general population, where this association has been demonstrated[13]. Importantly, in previous epidemiological studies in non-renal patients, IL-18 showed only a weak correlation with other inflammation markers, and it has been suggested that it might be part of a novel pathway involved in atherosclerotic plaque instability[13].

Figure 1. The pathophysiological role of the chronic inflammatory state



Malnutrition, assessed by anthropometric as well as biochemical values (albumin, prealbumin, transferrin, protein catabolic rate) is frequent in dialysis patients, and low serum albumin is a strong risk factor of mortality in dialysis patients[14]. Serum albumin is a negative acute phase protein and has been repeatedly shown to inversely correlate with positive acute phase proteins[5]. Stenvinkel has described the association between chronic inflammation, malnutrition and high mortality as the MIA (malnutrition, inflammation and atherosclerosis) syndrome[15]. There is interplay between chronic inflammation and poor nutritional status in dialysis patients (Fig. 2). In 99 dialysis patients, we found a statistically significant negative correlation between CRP and serum albumin (R 0.337, $p<0.001$), transferrin (R 0.218, $p<0.05$), predialitic serum creatinine (R 0.229, $p<0.05$) and total cholesterol (R 0.248, $p<0.05$). The patients that had died after 12 months follow-up had higher CRP values, and lower albumin, transferrin and predialitic serum creatinine and urea as compared to survivors, an example of the previously described "reverse epidemiology"[16] in CRF patients. It is not yet clear if the presence of increased inflammation markers is a cause or a consequence of CV disease in the general population and in CRF patients. In either case, chronic inflammation creates a vicious cycle comprising increased oxidative stress and malnutrition. On the other hand, the immunoincompetence of dialysis patients, manifested as increased rate of infection and malignancies, might be related to chronic immune activation.

Figure 2. The interplay between chronic inflammation and malnutrition



The therapeutic approach includes measures considered to be effective in general population (diet, smoking cessation and especially blood pressure control) as well as measures specific for the dialysis population, such as identification and treatment of all infection sources (involving vascular access, dental, gingival). Additionally, there are a series of therapeutic interventions that in different studies seem to have a beneficial effect on the chronic inflammatory status in dialysis patients. Concerning the dialysis technique, utilization of more biocompatible membranes and increased dialysis dose[17], vitamin E-coated membranes[18], haemolipodialysis[19] and ultrapure dialysate[20] have been proposed. Antihypertensive treatment with angiotensin converting-enzyme inhibitors or angiotensin receptor blockers[21] as well as HMG-CoA reductase inhibitors[22], antioxidants such as vitamin E or selenium[23], better correction of anemia or aspirin have been advocated. A series of anti-cytokine therapies: anti-TNF-α antibodies, soluble TNF-α receptors, IL-1 antagonist, thalidomide, pentoxifylline and regulators of the complement cascade are now under evaluation in patients with non-renal diseases. Direct anti-inflammatory treatment is not recommended, due to the fact that no clinical trials prove its benefits and there is increased risk of unmasking infections in this population of immunoincompetent patients.

In conclusion, inflammation markers and especially CRP are important predictors of mortality in dialysis patients as well as in the general population. Given the possibility that these molecules have a pathogenetic role in the CV morbidity, interventions that reduce the levels of inflammatory cytokines might prove beneficial in the prevention of CV disease in dialysis patients. So far, even though some of the above-mentioned therapeutic approaches have been successfull in reducing the level of pro-inflammatory molecules in dialysis patients there is as yet no proof that a beneficial effect on morbidity and mortality is present. More prospective studies are needed, and indeed a series of studies concerning the effect of HMG-CoA reductase inhibitors, like CHORUS (Cerivastatin in Heart Outcomes in Renal Disease: Understanding Survival), a multicenter study in North America[24] and Die Deutsche Diabetes Dialyse Studie

Investigators (4D) a multicenter study in Germany using atorvastatin[25] are currently under way. More in-depth knowledge on the mechanisms underlying the activated inflammatory response will undoubtely lead to new therapeutic strategies that might improve the prognostic of hemodialysis patients.

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