Cardiac effects of chronic inflammation in dialysis patients

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Abstract
Cardiovascular pathology is the major cause of death in uraemia. There is evidence that a chronic inflammation with activation of C-reactive protein, interleukin-6, tumour necrosis factor-α and other cytokines is associated with vascular pathology, both in the general population and in dialysis patients. The cardiovascular system, and particularly the vascular wall, is the main target of the inflammatory process. Inflammation of the coronary arteries could be involved in the development of atherosclerosis and its related clinical syndromes. In the uraemic state, an increased production of pro-inflammatory cytokines may trigger the onset and progression of atherosclerosis and favour the subsequent complications, such as plaque fissuration and rupture. However, inflammatory cytokines also have a depressant action on the myocardium, thus inducing myocardial dysfunction. Together, these conditions may ultimately enhance the risk of myocardial infarction and death. From this standpoint, cardiovascular disease should also be investigated with the traditional biochemical inflammation markers and the evaluation of the circulating cytokine level, although new reliable markers could provide further diagnostic help. New therapeutic approaches should also be considered.

Keywords: acute phase reaction; atherosclerosis; haemodialysis; inflammation; myocardiopathy; uraemia

Introduction
The incidence of cardiac death is 5–10 times greater in uraemic patients than in the age-matched general population [1]. Cardiovascular mortality is related prevalently to myocardial ischaemia (40% of cardiac deaths are related to myocardial infarction), but also to a high incidence of heart failure and sudden death [1,2]. The prevalence of cardiac diseases is high in uraemic patients just beginning dialysis and even more so in cases of late referral. In the Canadian multicentre study [3] comprising 432 patients starting dialysis and prospectively followed for a mean duration of 41 months, clinical signs of cardiac and vascular involvement were very frequent: coronary insufficiency 15%, angina 19%, heart failure 31%, arrhythmias 7% and peripheral vascular diseases 8% [1].

The excessive risk of cardiac diseases and atherosclerosis in chronic uraemic patients is the result of a complex interplay between renal and non-renal factors as well as co-morbidities (Figure 1). In uraemic patients, traditional vascular risk factors are added to specific uraemia and dialysis-related factors. Moreover, the prevalence of the conditions that are recognized as risk factors for cardiovascular disease in the general population, such as older age, hypertension, hyperlipidaemia, diabetes and physical inactivity, is higher in dialysis patients. Furthermore, uraemia and dialysis have per se further specific risk factors including oxidized low-density lipoprotein (LDL), free radicals, hyperhomocysteinaemia, infections, acidosis and bioincompatibility. Most of these factors may induce close interdependent links between atherosclerosis and chronic low-grade inflammation. The compromised metabolic milieu and a chronic state of inflammation, in moderate to severe chronic renal failure and in dialysis, seem to favour strongly an increased rate of atherosclerotic lesions and thrombotic events in these patients [3].

In this review, we will evaluate the cardiac effects of microinflammation in uraemic patients and the potential mechanisms responsible for these effects.

Inflammatory response in uraemia
Several studies have reported the association of acute-phase reactant proteins (indicators of inflammation) with ischaemic heart diseases and cerebrovascular disease [4,5]. C-reactive protein (CRP) and other acute-phase reactants may be altered in uraemia without an
apparent current inflammatory process [4]. The serum concentration of CRP reflects the activity of cytokine-mediated acute-phase processes and is roughly proportional to the extent of tissue injury. Owen et al. [2] reported on the serum CRP levels in 845 haemodialysis patients: 35% of the values measured in these patients exceeded the upper limit of the laboratory reference range. The logistic regression analysis described a strongly interdependent inverse relationship between the serum albumin and creatinine concentration and the odds risk of death. In a study by Zimmermann et al. [4], a clear concentration-dependent relationship was noted between actuarial survival over 24 months on the one hand, and CRP concentration on the other. These observations have also been confirmed by others [5,6]. Instead, the relationship between CRP and cardiovascular death is not confined to uraemic patients. Elevated concentrations of acute-phase proteins predict the development of coronary heart disease over many years [7]. Close interdependent links between chronic low-grade inflammation on the one hand, and malnutrition and atherosclerosis on the other seem wholly consistent with the epidemiology of these specific parameters [5]. In this context, two studies, one from Stockholm [8] and the other from Wurzburg [4], confirm that both serum albumin and high CRP predicted death in the dialysis patients by univariate analysis, but only CRP emerged as an independent predictor by multivariate analysis. These considerations led Stevinkel et al. [9] to distinguish two types of malnutrition, ‘pure malnutrition’ (type 1) and ‘inflammatory malnutrition’ (type 2). The latter is closely linked to the presence of an inflammatory state, markedly elevated oxidative stress, increased protein catabolism, cardiac and vascular co-morbidities and an inability to reverse the malnutrition.

Numerous potential pathomechanisms are responsible for chronic inflammation in renal failure. However, while many factors during dialysis may account for the elevation in cytokines, in pre-dialysis it is more difficult to detect pathophysiological evidence. Herbelin et al. [10] measured interleukin-6 (IL-6) and found an elevation even before the patients had been accepted for haemodialysis.

Advanced oxidation and glycation products may induce monocyte stimulation [11]. Subclinical infections by microorganisms, such as herpes virus or Chlamydia pneumoniae, and combinations of these and other factors, may induce a microinflammatory state [12]. Indeed, chlamydial antibodies are found more frequently in uraemic patients with coronary atherosclerosis [13]. Alternative explanations should not be excluded. Likewise, it occurs in congestive heart failure, in uraemic patients with circulatory overload: endotoxin penetrates the intestinal mucosa and gains access to the systemic circulation [14].

In dialysis patients, the factors in the development of an acute-phase reaction are easier to formulate, while water quality and membrane biocompatibility may be seen as the major culprits. During dialysis, transmembrane passage of intact endotoxins or low molecular weight bacterial products, including bacterial DNA, may account to some extent for the acute-phase reaction. In vivo studies have documented that trace concentrations of endotoxin in the dialysate have a clear effect on the CRP concentration [15].

Consequences of chronic inflammation on the cardiovascular system

Inflammation may play a key role in the development of cardiovascular damage by way of a number of different mechanisms: metabolic, endothelial and coagulative. Several epidemiological studies have demonstrated that inflammation per se may play an important role in the development of atherosclerosis.
and death from ischaemic heart and cerebrovascular disease. Thus one should also bear in mind that atherogenesis is an inflammatory process, as suggested by Ross [12].

Stimulation of atherogenesis may be due to modifications of lipids, such as Lp(a) and LDL, hypercoagulation [elevated fibrinogen and plasminogen activator inhibitor (PAI)], complement activation (enhancing the inflammatory response) and endothelial dysfunction (Figure 2). However, apart from the acceleration of atherosclerosis, other negative events mediated by inflammation may be expressed at the cardiac level, such as plaque instability, a decreased number of myocytes, an increased deposition of ground substance and fibrotic tissue, and an increase in heart size (Table 1).

Inflammation leads to the localized recruitment of neutrophils and monocytes. The presence of activated macrophages in the cap of the atherosclerotic plaque has led to the suggestion that they contribute to plaque rupture through effects on matrix metalloproteinases [16].

Cytokines, such as tumour necrosis factor-α (TNF-α) and IL-6, affect the endothelial function and also induce the endothelial expression of chemokines and adhesion molecules. The effects of these cytokines on triglyceride metabolism might impair further the endothelial generation of nitric oxide (NO), consequent to raised circulating concentrations of non-esterified fatty acids. Finally, the effects of IL-6 on platelets, fibrinogen and coagulation, and of TNF-α on the expression of PAI by hepatocytes, endothelial cells and adipose tissue will lead to a pro-coagulant state. The microvascularization abnormalities may favour the development of fibrosis at the level of the heart, with an increased deposition of ground substances, a decreased number of myocytes and an increment in left ventricular (LV) interstitial mass. On the other hand, these abnormalities reduce capillary density and this increases the distance of O₂ diffusion and could thus induce cellular ischaemia. The result is the high incidence of clinical signs of coronary heart diseases in uraemic patients without angiographic expression.

Moreover, the chronic inflammatory status may be strongly associated with two major cardiac alterations, the coronary atheromatous vascular diseases and myocardial damage leading to uraemic cardiomyopathy.

**Table 1. Cardiac effects of chronic inflammation**

<table>
<thead>
<tr>
<th>Accelerated atherogenesis</th>
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<tbody>
<tr>
<td>Instability of the plaque</td>
</tr>
<tr>
<td>Direct myodepressant activity</td>
</tr>
<tr>
<td>Increased deposition of ground substance</td>
</tr>
<tr>
<td>Decreased number of myocytes</td>
</tr>
<tr>
<td>Cardiac fibrosis</td>
</tr>
<tr>
<td>Increased heart size</td>
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</tbody>
</table>

**Coronary artery disease**

There is a high prevalence of coronary artery disease (CAD) in end-stage renal disease (ESRD) patients. Half of the patients on maintenance haemodialysis have evidence of CAD before starting dialysis, and approximately half of the 40% of patients who develop evidence of coronary ischaemia subsequently do so in the first year of dialysis [17]. Ischaemic heart disease may present typical angina symptoms, particularly during dialysis, or cardiac heart failure without chest pain. Conversely, atherogenesis also could result in the decline of myocardial function due to ischaemia.
Ischaemic heart disease may be diagnosed by electrocardiographic or echocardiographic changes. The nature and distribution of coronary atherosclerotic lesions have not been studied intensively. However, there is a much greater frequency of complex-calcified atheroma in the coronary arteries of uraemic patients. Qualitative analyses show significantly calcified plaques of the coronary arteries in patients with end-stage renal failure (Table 2). The mean thickness of the coronary arteries is significantly higher in uraemic patients. Intravascular ultrasonography may be useful in evaluating the presence of arterial wall calcification. Inflammation may modify the arterial wall and plaque morphology. Raised plasma phosphate is associated with increased ectopic vascular and cardiac calcifications.

Cross-sectional studies have examined the relationship between normal conventional cardiovascular risk factors and the presence and severity of angiographic CAD in uraemic patients [18]. Inflammation may also be involved in the calcification of the atherosclerotic plaque (Figure 3), and apoptosis may occur in response to inflammatory cytokines [19]. In addition to soluble cytokines, which may trigger programmed cell death, the T cells in atheroma may be involved in eliminating some smooth muscle cells. In particular, certain T-cell populations, known to build up in plaques, can express Fas ligand on their surface. Fas ligand can engage Fas on the surface of smooth muscle cells and, in conjunction with soluble pro-inflammatory cytokines, lead to the death of the smooth muscle cells [20].

However, inflammation may have a crucial role in thrombus formation. The release of cytokines from the inflammatory cells may induce (Figure 4):

(i) endothelial activation with modification of the physiological properties of the endothelium, with pro-coagulant activity and vasoconstriction;
(ii) hyperactivity of the muscle cells to a vasoconstrictive stimulus;
(iii) increased release of metalloproteinases which induce degradation of the fibrous cap, fissuration and exposure of the thrombogenic component of the lipid nucleus.

Table 2. Angiographic characteristics of haemodialysis patients (HD) and non-haemodialysis (non-HD) patients

<table>
<thead>
<tr>
<th>Vessel affected</th>
<th>HD n=13</th>
<th>P</th>
<th>Non-HD n=35</th>
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<tbody>
<tr>
<td>Single (%)</td>
<td>13</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>Multiple (%)</td>
<td>87</td>
<td>0.05</td>
<td>62</td>
</tr>
<tr>
<td>Lesions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (%)</td>
<td>49</td>
<td>0.05</td>
<td>91</td>
</tr>
<tr>
<td>Calcified (%)</td>
<td>81</td>
<td>0.05</td>
<td>37</td>
</tr>
<tr>
<td>Score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atherosclerosis</td>
<td>18.3±8.1</td>
<td>ns</td>
<td>12.4±7.3</td>
</tr>
<tr>
<td>Calcification</td>
<td>5.1±2.0</td>
<td>0.05</td>
<td>3.1±2.3</td>
</tr>
</tbody>
</table>

Fig. 3. Intravascular echography showing several vascular arterial calcifications (at 6 and 8 hours, with the corresponding dark cone).

The final result is a greater tendency to plaque instability and thrombus formation.

However, a recent study by Schwarz et al. [21] examined post-mortem coronary disease in dialysis and control patients. Coronary plaques in patients with ESRD were characterized by increased mean thickness and marked calcification. However, the plaque area was comparable in both groups, and cellular infiltrate in coronary arteries showed no major differences in the advanced plaques of uraemic and non-uraemic subjects.

Inflammation promotes platelet aggregation, intravascular thrombosis or particulate embolism. Furthermore, inflammation, fostering degradation of the matrix covering patients’ atheromatous plaques, makes them prone or ‘vulnerable’ to rupture. The state of impaired fibrogenesis in uraemia could enhance this process. More instability may be present in the plaques of uraemic patients than in controls [17].

**Myocardial damage**

Inflammatory cytokines, including TNF-α and IL-1β, may play an important role in the pathogenesis of myocardial failure [22]. These and other inflammatory cytokines can regulate growth and gene expression in cardiac myocytes and other cells present in the myocardium. The circulating levels of TNF-α and IL-6 are increased in patients with heart failure [23], and may promote apoptosis. An acute reduction in cardiac contractility mediated by NO is induced by TNF-α [24]. On the other hand, the failing myocardium itself may be a source of inflammatory
cytokines, which might thus be present in high local concentrations [23]. In cultured cardiac myocytes, TNF-α and IL-1β can stimulate hypertrophy and re-expression of the fetal gene programme [25], and both can cause apoptosis [26].

Transgenic mice overexpressing TNF-α in the heart developed dilated cardiomyopathy associated with a reduced survival [27].

Pilot clinical trials with soluble TNF-α receptors that reduce the level of TNF-α available to the tissue have suggested that this may be a therapeutic tool [28].

In uraemia, mechanical and neuro-hormonal stimuli may induce cardiac remodelling that involves myocytes and non-monocyte cells (Figure 5).

Inflammatory cytokines along with other substances, such as endothelial NO, catecholamines and angiotensin, may promote the death of the myocytes. Such cell death in the presence of LV hypertrophy and continuous pressure and volume overload may be catastrophic, leading to further LV dilatation and eventually systolic dysfunction [3].

Conclusions

There is growing evidence that a persistent state of systemic inflammation exists in a broad spectrum of chronic diseases, including ESRD.
Inappropriate activation of inflammatory and immune response can have devastating pathological sequences. Activation of the immune response results in the release of IL-1β, IL-6 and TNF-α, as well as numerous other cytokines from peripheral blood mononuclear cells and tissue macrophages. One result of this response is the induction of an acute-phase reaction characterized by elevated CRP, complement, fibrinogen and haptoglobin, as well as hypoalbuminaemia and decreased pre-albumin, retinol-binding protein and transferrin concentrations. The cytokine cascade can itself account for anorexia, decreased skeletal muscle protein synthesis, increased protein catabolism and diminished physical activity. However, the cardiovascular system is one of the most important targets of the inflammatory activation. Inflammation in the vascular wall plays an essential part not only in the onset and progression of atherosclerosis but also in the erosion or fissuration of plaques and essentially in the rupture of the plaques. Increased pro-inflammatory cytokine production may be the first of the factors leading to atherosclerosis, high risk of myocardial infarction and death from myocardial ischaemia in uraemic patients [29].

On the other hand, inflammatory cytokines have a depressive effect on the myocardium and can induce myocardial dysfunction. TNF-α and IL-1β can regulate growth and gene expression in cardiac myocytes.

Viewing atherosclerosis coronary disease in uraemic patients also as a consequence of an inflammatory disease provides a basis for developing new insights into the pathogenesis of uraemic vascular and cardiac damage. The discovery of reliable markers would be a major advance in the pre-morbid diagnosis of atherosclerosis and could provide a potential therapeutic end point for disease activity.

Conversely, if the hypothesis that the elimination of the arterial inflammatory response reduces the cardiovascular risk is confirmed, then new therapeutic approaches may involve direct anti-inflammatory strategies.

References