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C-reactive protein and other markers of inflammation in hemodialysis patients

Abstract

Background: Hemodialysis patients are at greater risk of cardiovascular disease. Higher than expected cardiovascular morbidity and mortality in this population has been attributed to dislipidemia as well as inflammation. The causes of inflammation in hemodialysis patients are multifactorial. Several markers were used for the detection of inflammatory reaction in patients with chronic renal disease.

These markers can be used for the prediction of future cardiovascular events. Among the several parameters of inflammatory markers, serum, CRP is well known and its advantages for the detection of inflammation and its predictor ability has been evaluated in several studies. This review addressed the associated factors and markers of inflammation in hemodialysis patients. In addition, their ability in predicting future atherosclerosis and effect of treatment has been reviewed. However, this context particularly in using CRP as a prediction marker of inflammation and morbidity requires further studies.

Keywords: Hemodialysis, Inflammation, C-reactive protein, Statin

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Patients with end stage renal disease (ESRD) have higher than expected mortality which can not only be explained by traditional risk factors of atherosclerosis like diabetes, hypertension, dislipidemia but also the other factors like inflammation, malnutrition, and predisposition to infection are also believed to have substantial contribution in the development of cardiovascular diseases as well as morbidity and mortality (1-6). Patients on chronic hemodialysis are at greater risk of morbidity and mortality as compared with the general populations (3, 5). Among the several associated factors of atherosclerosis, more attention has been given to the contribution of inflammation and its consequence in hemodialysis patients. The impact and the adverse effects of inflammatory response has been also investigated in several organs and this issue is used to explain a number of symptoms and signs of apparently non-inflammatory and inflammatory conditions such as osteoarthritis and chronic obstructive pulmonary disease (7-9).

Inflammation in hemodialysis patients: The causes of inflammation in hemodialysis patients are multifactorial. While inflammation may directly result in cardiovascular injuries but the underlying cardiovascular complications in these patients may be also associated with inflammatory response (2, 5). Inflammatory reaction may originate from several sites including graft or fistula infections, bioincompatible dialysis membrane, dialysate, endotoxin exposure, back filtration, chronic infections, and malnutrition (10-12).

Poor oral, dental and periodontal health in hemodialysis patients can be a source of inflammatory reactions (11, 13). One study showed that 63% of hemodialysis patients had periodontal infection. Periodontitis and the presence of *p. gingivalis* are associated with an enhanced inflammatory response expressed by higher CRP levels. In hemodialysis patients

with periodontitis, the proportion of patients with high CRP is significantly greater than those without periodontitis.

In one study of hemodialysis patients, 41.7 % of patients with periodontitis versus 27.1% without periodontitis had serum CRP greater than 0.3 gr/dl (11, 12, 14). In patients with periodontal disease, serum CRP is higher than control and increases positively in correlation with the extent of periodontitis, while serum HDL-cholesterol concentration is lower than control (15). These findings indicate that both conditions have a common pathway for the development or progression of cardiovascular diseases (11, 12). The association of periodontitis with CRP levels indicate that periodontitis is a contributing factor for cardiovascular diseases and might be a possible intermediate pathway in this association (12, 14).

The positive correlation between CRP and periodontal disease might be a possible underlying pathway in the association between periodontal disease and the observed higher risk for cardiovascular diseases in these patients (11). This role has been emphasized in recent investigations. However, a proportion of patients with periodontal disease may be unrecognized or overlooked (10, 12, 16, 17).

In patients on long-term chronic hemodialysis, superimposed malnutrition provides greater risk of development or progression of atherosclerotic cardiovascular disease, by several pathogenetic mechanisms (1, 18-20). In the early stage of nondiabetic kidney diseases, inflammatory process is greater resulting in malnutrition, and consequent increased risk of cardiovascular diseases (21).

The available data suggest that pro-inflammatory cytokines play a central role in the genesis of both malnutrition and cardiovascular disease in ESRD (1, 22). The dental/periodontal health in hemodialysis patients is poor and becomes worse with increasing time on dialysis. Thus, oral health maintenance is of utmost importance in this patient group (11, 12, 19).

Inflammation and atherosclerosis: Formation of atherosclerotic plaque is balanced by local pro-inflammatory and anti-inflammatory cytokines. The prognostic value of these cytokines for cardiovascular events is greater than the traditional risk factors (23). Cytokines along with CRP and serum albumin can be also considered for prognosis of long-term mortality in ESRD (4, 22). Inflammatory process is evident at certain sites of atherosclerotic lesions in the arterial tree such as branch points and flow dividers (23). CRP has a role in developing inflammation through binding

with lipoproteins and activation of complement system (24, 25). In addition to inflammatory marker, CRP as a mediator for developing atherosclerosis, directly affect endothelial cells, monocytes-macrophages and smooth muscle cells and contribute to atherogenesis (26, 27).

Markers of inflammation: In addition to CRP which seems to be the important marker for the identification and control of inflammation in clinical practice, many other markers are also available for the evaluation of inflammatory state. Serum levels of high sensitive CRP (hs-CRP), TNF- α , albumin, adiponectin also increase in patients with chronic renal failure (13, 28).

In addition, high levels of other related parameters of inflammation like ESR, hepcidine, and ferritin may be seen in patients with ESRD whereas, by contrast, serum albumin, LDL and HDL cholesterol levels decrease with inflammation (4, 21, 22, 29-31). A number of these markers may be used for the prediction of kidney function variations. For example, higher levels of CRP and soluble tumor necrosis factor receptor 2, were shown to be associated with faster kidney function loss (14, 32).

Cardiac troponin and hs-CRP may be used in predicting future mortality. In hemodialysis patients with history of coronary artery disease, higher troponin levels were associated with higher mortality as compared with those without coronary disease. While in patients without history of coronary artery disease hs-CRP>3 mg/L was associated with significantly higher mortality (13, 33). However, IL-6 may be a more reliable predictor of cardiovascular diseases and mortality in patients with ESRD (4).

Serum CRP: Apparently, in healthy subjects higher levels of serum CRP are associated with greater risk of atherosclerosis and cardiovascular complications (34). The advantages of CRP test are, lower cost and availability particularly in developing countries (21). Serum CRP concentration does not change with the changes in kidney function but in the early stage of kidney disease, serum CRP may be related to serum albumin levels which is affected by inflammatory response (2, 35).

It appears that elevated serum CRP may be more associated with thrombotic risk rather than the degree of atherosclerosis (14). Because serum CRP changes in response to the development of cardiovascular complications ; so it can not be considered as an independent factor of

atherosclerosis (24). However, hs-CRP has greater predictive ability for primary prevention of cardiovascular risk. The risk prediction role of hs-CRP has been advocated in several studies. In general, serum blood levels at 1, 1-3, and >3 mg/ml corresponds to low, moderate, and high vascular risk across all levels of LDL-C (24). The association between inflammatory markers and cardiovascular events, coronary artery disease and its complications occur with high frequency in patients with ESRD; and substantially is contributing to cardiovascular morbidity and mortality in this population (3, 24). Elevated levels of serum CRP is linked to the development of coronary artery disease even in the absence of dyslipidemia. Serum CRP level measured by conventional method is a predictor of mortality in hemodialysis patients (16, 31, 27, 36, 37).

Serum CRP has shown as a strong independent risk factor for cardiovascular disease (34, 16, 35). Patients with higher baseline CRP will have significantly a greater risk of coronary artery event one year later (38). In one study of hemodialysis patients, serum CRP levels greater than 0.6mg/dL increased the odds of cardiovascular diseases by 1.73 times (35). In a study of hemodialysis patients, CRP level determined the outcome more than LDL-cholesterol (31). Other cytokines alone or in combination with CRP may be also considered for predicting future cardiovascular or noncardiac complications (17, 22, 29, 35).

In a study of 757 hemodialysis patients followed up for 30 months, the relationship between hs-CRP, IL-6, IL-8, and serum albumin with mortality and morbidity was determined by multivariate analysis. In this study, CRP was considered as the most powerful predictive factor of cardiovascular events. The predictive ability of CRP increases by using it together with proinflammatory cytokines (5). Serum CRP was also shown as a predictor for severity of pruritus and mortality (30). Furthermore, the serum CRP levels were shown to be independently associated with serum albumin level and cardiovascular disease prevalence (39). The levels of adiponectin and TNF-alpha in hemodialysis patients were shown to be higher than controls and these parameters are also considered as inflammatory markers (40).

The level of serum CRP increases with declining serum albumin concentration. The reduction of serum albumin in early stage of nondiabetic kidney diseases is associated with inflammation and increased risk of cardiovascular diseases. In one study, serum CRP level >0.6 mg/dl was associated

with decrease in serum albumin level by 70 mg/dl (95%CI, 0.03 to 0.12). In diabetes type 2, CRP and tumor necrosis factor-alpha may be considered as independent risk factors for progression of chronic kidney disease (40).

However, serum CRP may rise without any change in serum albumin or creatinine (17). At the beginning of hemodialysis, serum or CRP albumin levels may be useful in predicting the future risk of long-term mortality (4). However, serum CRP elevation is not specific but may change due to several inflammatory or noninflammatory responses. Whether, rising CRP should be considered as an important prognostic marker or not requires further studies (16).

Treatment: Owing to the high prevalence of inflammation in hemodialysis patients and the potent anti-inflammatory effect of statins among individuals with elevated levels of C-reactive protein, these drugs should be especially effective in patients with hemodialysis (41). It is not clear whether the reduction of inflammatory markers improves prognosis. In a number of studies, improvement of dyslipidemia with statins was associated with the reduction of inflammatory markers (24, 29, 42-46). In hyperlipidemic hemodialysis patients, treatment with simvastatin significantly decreased inflammatory markers (47).

Similar effects on both dyslipidemia and inflammatory markers have been shown by atorvastatin. Atorvastatin affects markers of endothelial dysfunction, inflammation, oxidative stress, endothelial cell apoptosis and peripheral blood monocyte stimulation (44, 48). Reduction in CRP has been attributed to the lipid-lowering effects of simvastatin (47). Large observational studies demonstrated that statin treatment is independently associated with a 30%-50% mortality reduction in patients with dialysis-dependent chronic kidney disease (29). Therefore, statin therapy may be effective in the primary prevention of coronary events among the subjects with relatively low lipid levels but with elevated levels of C-reactive protein (38, 49).

However, the results of various published studies were not similar (45, 46, 42). In a study of patients with chronic renal disease, the high levels of inflammatory parameters and t-PA as compared with age-matched healthy control subjects were not reduced with simvastatin (42). In another study, atorvastatin treatment was associated with improvement of cholesterol as well as inflammatory state (44). Pravastatin appears to have greater efficacy on inflammation and in patients with higher inflammation seem

to exert additional preventive effect on kidney function (46). Patients with chronic inflammation who have higher baseline inflammatory state are expected to respond more rapidly and effectively to the treatment (50).

In conclusion, the patients on chronic hemodialysis are at greater risk of inflammatory reaction against factors originating from graft, fistula, dialysis membrane, infection sites. These reactions are associated with increased levels inflammatory markers such as serum CRP, cytokines, and especially hs-CRP. Serum CRP seems to have a contribution in the development of cardiovascular complications in hemodialysis patients.

In addition, this marker and other markers of inflammation can be used as predictors of cardiovascular diseases. The ability of CRP and hs-CRP in predicting future cardiovascular morbidity and mortality was shown in several studies. Many studies have shown the reduction of inflammatory markers during treatment of dislipidemic hemodialysis patients with statins.

Although the results of previous studies are not similar, but the capability of statins in combined improvement of cholesterol and reduction of serum CRP is shown in several studies. It is possible that the reduction of inflammatory markers with statins is associated with reduction of future cardiovascular events.

Conflict of Interest: There is no conflict of interest.

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