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Short Communication

Correlation between MCP-1 (monocyte chemoattractant protein-1) and cardiovascular disease in patients on the end stage of renal disease

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ABSTRACT

Aim: MCP-1 (monocyte chemo attractant protein-1) plays an important role on atherosclerotic lessions. We studied the association of MCP-1 with left ventricular hypertrophy (LVH) and coronary artery disease (CAD) as manifestations of cardiovascular disease in patients on the end stage of renal disease.
Methods: We included 76 patients on on-line hemodiafiltration. The sodium removal and the ratio of LDL/HDL were calculated. Serum MCP-1 concentrations were measured using enzyme linked immunoabsorbed assay (ELISA).We performed a logistic-regression analysis to investigate the impact of MCP-1 on LVH and CAD after adjustment for the traditional and specific cardiovascular risk factors for dialysis patients.
Results: We found a positive correlation of MCP-1 with LDL/HDL ratio, but inverse association with sodium removal (r=0.315, p=0.04 and r=-0.288, p=0.01 respectively).The built logistic-regression analysis did not show significant impact of MCP-1 on CAD, but it was found as a significant independent predictor of LVH (B=0.004, p=0.04, OR=1.004, 1.000-1.008).
Conclusion: We observed a significant impact of MCP-1 serum concentrations on the LVH in patients on the end stage of renal disease, due may to its relationship with sodium retention and fluid overload, but we did not find a significant association with CAD. Pharmaceutical inhibition of this chemokine may be usefull for these patients, but more studies need to support such a conclusion.

Keywords: MCP-1; hemodiafiltration; atherosclerosis; cardiovascular disease.

INTRODUCTION

During hemodialysis modalities the circulating leukocytes of blood are activated and the production of proinflammatory cytokines including interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α) is elevated[1].Conservative hemodialysis results in phenotypic changes in adhesion molecules expression on monocytes, which is continued during interdialytic period and influences the adherence to endothelium[2]. However, convective dialysis, such as hemodiafiltration (HDF), has potential advantages than traditional dialysis, including the convective removal of medium molecular weight uremic toxins and the biocompatibility of dialysis membranes, which significantly contributes to reduction of the oxidative stress and inflammation.

Inflammatory procedure and oxidative stress are implicated in dialysis morbidity and mortality[3].

MCP-1 (monocyte chemoattractant protein-1), a monomeric polypeptide of a molecular weight of 9000 to 15,000 Da, acts as a chemoattractant specific for monocytes and may promote migration of monocytes into the atherosclerotic plaque after their initial adhesion to the endothelium, playing a particular role on the lessions of atherogenesis[4]. However, previous studies have not established its value as a biomarker of atherosclerosis.

In this study, we studied the association of MCP-1 with left ventricular hypertrophy (LVH) and coronary artery disease (CAD), as manifestations of cardiovascular disease in patients on the end stage of renal disease.

MATERIALS AND METHODS

Subjects

We studied 76 hemodialyzed patients (hemodialysis median duration =5.0, interquartile range 3-10 years), 47 men and 29 women on mean age 62.2 ±15 years and 24 healthy subjects. The treatment modality which was applied was on-line-predilution hemodiafiltration (on-l HDF) using exclusively high-flux synthetic dialysis membrane. Dialysis dose defined by Kt/V for urea was calculated according to the formula of Daugirdas[5].

Exclusion criteria from the study were the existence of multiple intradialytic hypotensive episodes, fibrillation and the interdialytic weight gain more than 5% of total body weight. Also, the patients with diabetes mellitus, autoimmune diseases, infections or malignancy and those without regular vascular hemodialysis access and who had dialysis catheter were not included in the study.

Inclusion criteria in the study were the absence of interdialytic peripheral edema, high BP or other characteristics of an inaccurate dry body weight.

However, patients with interdialytic blood pressure ≥160/90 (n=29, 38.2%) were considered hypertensive, as well as the patients who were receiving anti-hypertensive drugs.

The presence of left ventricular hypertrophy (LVH, n=45, 59.2%) and coronary arterial disease (CAD, n=25, 32.9%) were noted as manifestations of cardiovascular disease, which, however, were not inclusion criterion in the study, but the enrollement of patients was randomized.The coronary syndrome was documented by history of myocardial infarction, coronary artery angioplasty or bypass surgery, or clinical signs of angina pectoris.

The total of our patients was on long-term erythropoietin treatment and the one-half of them was in parenteral iron sucrose treatment. None of the enrolled patients received statin. Calcium channel blockers, beta-blockers or inhibitors of

angiotensin II receptors were included in the receiving medications by our patients.

Laboratory measurements

Albumin, cholesterol, triglycerides, high density lipoproteins (HDL) and low density lipoproteins (LDL) were measured by biochemical analysis and hemoglobin and monocytes blood cells values were also measured. The ratio of LDL / HDL were calculated. Sodium (Na^+) levels in the start and Na^+ levels in the end of the treatment session were measured by biochemical analysis. The sodium removal was determined as percent sodium removal (PSR) using the following formula:

(Na^+pre - Na^+ post / Na^+pre) x 100.

Serum MCP-1 concentrations were measured using ELISA (Alpco Diagnostics, Anachem, USA) according to manufacturer's specifications. High sensitivity C-reactive protein (hsCRP) and oxidized LDL (ox-LDL) serum concentrations were also measured by ELISA (Immundiagnostik AG., Germany, Immundiagnostik AG. Stubenwald-Allee, Bensheim respectively).

The concentrations of intact-parathormone (i-PTH) were measured by radioimmunoassay (CIS bio international /France).

Body mass index (BMI) was obtained from height and post-dialysis body weight.

Hemodynamic measurements

Predialysis peripheral systolic and diastolic blood pressures (SBP and DBP respectively) were calculated as the mean of 10 measurements during a treatment month using an automatic sphygmomanometer OMRON M4-I (Co Ltd Kyoto Japan). Mean peripheral pre-dialysis BP (MBP) was calculated as: MBP = DBP + 1/3 (SBP - DBP).

M-mode echocardiography was performed the day after dialysis with an Hewlett Packard SONOS 2500 using a 2.25 MHz transducer to estimate the existence of left ventricular hypertrophy according to the recommendations of the American Society of Echocardiography[6].

A 12-lead electrocardiographic examination was used to estimate the ischaemic findings.

APPROVAL AND CONSENT

The study was approved by the ethics committee of the Hospitals "Laiko, University General Hospital of Athens" and Renal Unit of "Diagnostic and Therapeutic Center of Athens Hygeia SA".Written consent was obtained from all participants in the study.

DATA ANALYSIS

Data were analyzed using SPSS 15.0 statistical package for Windows (SPSS Inc, Chicago, Illinois) and expressed as mean ± standard deviation or as median value (interquartile range) for data that showed skewed distribution; differences between mean values were assessed by using paired-t test and Mann-Whitney U test. Correlations between variables were defined by Pearson and Spearman coefficient and p values less than .05 were considered significant. x^2 analysis was used for the correlation between categorical variables.We performed a logistic-regression analysis to investigate serum MCP-1 concentrations as a possible independent predictor of the studied complications of cardiovascular disease (LVH and CAD) after adjustment for the traditional and specific cardiovascular risk factors for dialysis patients, such as age, hypertension, BMI, dyslipidemia, anemia, inflammation defined by hsCRP, oxidative stress defined by ox-LDL, mineral bone disease defined by

i-PTH and dialysis adequacy defined by Kt/V for urea.

RESULTS

The mean value of MCP-1 was not significantly different between patients and healthy subjects (274.1 ± 167.3 versus 276.4 ± 163.7, p=NS).

We observed a positive correlation of MCP-1 serum concentrations with LDL/HDL ratio and BMI (r=0.315, p=0.04 and r=0.228, p=0.04 respectively). Also, MCP-1 was inversely associated with sodium removal (r=-0.288, p=0.01).

The association of higher or lower serum MCP-1 concentrations with LVH was found statistically significant by x^2 analysis (x^2 =6.6, p=0.009, figure 1), although the correlation with CAD was not found significant. Also, the built logistic-regression analysis did not show significant impact of serum MCP-1 concentrations on CAD, but it was found as a significant independent predictor of LVH (B=0.004, p=0.04, OR=1.004, 1.000-1.008), after adjustment for the traditional and specific risk factors for these patients.

DISCUSSION

The present study did not show increased circulating MCP-1 serum concentrations in studied hemodialyzed patients in comparison to healthy subjects.

Different approaches have been reported of whether the uremic state affects MCP-1 concentrations. Previous study using an *in vitro* method, reported significantly lower spontaneous production of MCP-1 from mononuclear cells of uremic patients, compared to healthy subjects and that hemodialysis using synthetic dialysis membranes normalized MCP-1 release from mononuclear cells which had been reduced by cuprophane treatment[7].Other previous studies observed a significant increase in circulating MCP-1 levels in hemodialyzed patients treated either cellulosic or synthetic membranes, compared with healthy subjects[1]. The different findings for MCP-1 data in patients with uremia, may suggest that the methods used for chemokines analysis have to be taken into consideration.

It has been already supported that the kidney plays an important role in the catabolism of molecules such as MCP-1.However, the comparable levels reported in hemodialysis, peritoneal dialysis and pre-dialysis patients probably show that dialysis itself does not affect significantly their elimination.

In the mean time, previous study reported significantly increased levels of MCP-1 in patients treated with erythropoietin[8]. In contrast, other study reported that the treatment with erythropoietin in these patients decreased the levels of chemokines including MCP-1, when the patients were not in iron therapy[9,10]. This may explain, at least partially, our finding for the similar MCP-1 levels in the patients and in healthy subjects, as the total of our patients was on long-term erythropoietin treatment, although the half of them was in parenteral iron sucrose treatment.

Additionally, the increase of molecules as MCP-1 is mainly observed in increased oxidative stress conditions and inflammatory diseases.In this study, the enrolled patients were in a good status excluding the patients with active infections.

However, we observed significantly positive relationship between MCP-1 serum concentrations and dyslipidemia defined by the ratio of LDL/HDL. Previous studies provided opposite results for the association between MCP-1 and lipids, even if it has been reported that the link of cells with LDL causes the release of chemokines, such as MCP-1[11].

Moreover, in this study we noted that MCP-1 was positively associated with BMI. Indeed, previously it has been shown that the large cells of adipose tissue in obesity produce high MCP-1, which, on the other hand, promotes migration of monocytes in adipose tissue of obese subjects[12].

On the other hand, in present study MCP-1 was inversely associated with sodium removal and higher MCP-1 serum concentrations were combined with retention of sodium, than lower MCP-1 values.

Inadequate sodium and fluid removal result in fluid overload, increased extracellular volume (ECV), increased blood pressure (BP) and increased mortality. LVH, which is the most frequent cardiac abnormality in dialyzed patients, is influenced by fluids and sodium balance. LVH is mainly caused by an increased demand in left ventricular work related to fluid overload and it usually coexists with hypertension. Even if the presence of hypertension in dialyzed patients implies volume overload, previous study reported discrepancies between BP values and the degree of LVH in dialysis patients[13].

In present study, we found significant correlation between the existence of LVH and increased MCP-1 concentrations and MCP-1 was shown as a potential independent risk factor of LVH after adjustment for tranditional and specific risk factors in these patients. The explanation for this finding should be the above also explored relationship of MCP-1 with sodium retention.

However, even if LVH may be the underlying disease that leads to heart failure, myocardial infarction and ischaemia, we and other previous reports did not find a significant correlation between the increased MCP-1 values and coronary disease[14]. Despite chemoattractants, including MCP-1, stimulate leukocyte transmigration through the endothelium and may induce directional locomotion to atherosclerotic lesions, it is not available to be determined the relationship of MCP-1 serum concentrations with atherosclerosis. This difficulty may explain the found difference regarding its association with LVH or CAD in this study. Controversially, another previous study reported significant correlation between MCP-1 and coronary disease and MCP-1 may be a biomarker of acute coronary syndromes[15].

Based on the findings of present study, we could suggest that MCP-1 serum concentrations could be connected to sodium retention and fluid overload in dialysis patients, as an additional role on cardiovascular disease manifestations in this population of patients, except of the migration of circulating leukocytes to sites of inflammation and atherosclerotic lesions. Pharmaceutical inhibition of this chemokine may be usefull for these patients.

CONCLUSION

We observed a significant impact of MCP-1 serum concentrations on the left ventricular hypertrophy in patients on the end stage of renal disease, due may to its relationship with sodium retention and fluid overload, but we did not find a significant association with coronary disease. However, more studies need to support such a conclusion.

ACKNOWLEDGEMENT

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LEGEND TO FIGURE

The association of higher or lower serum MCP-1 concentrations with left ventricular hypertrophy (x^2 =6.6, p=0.009).

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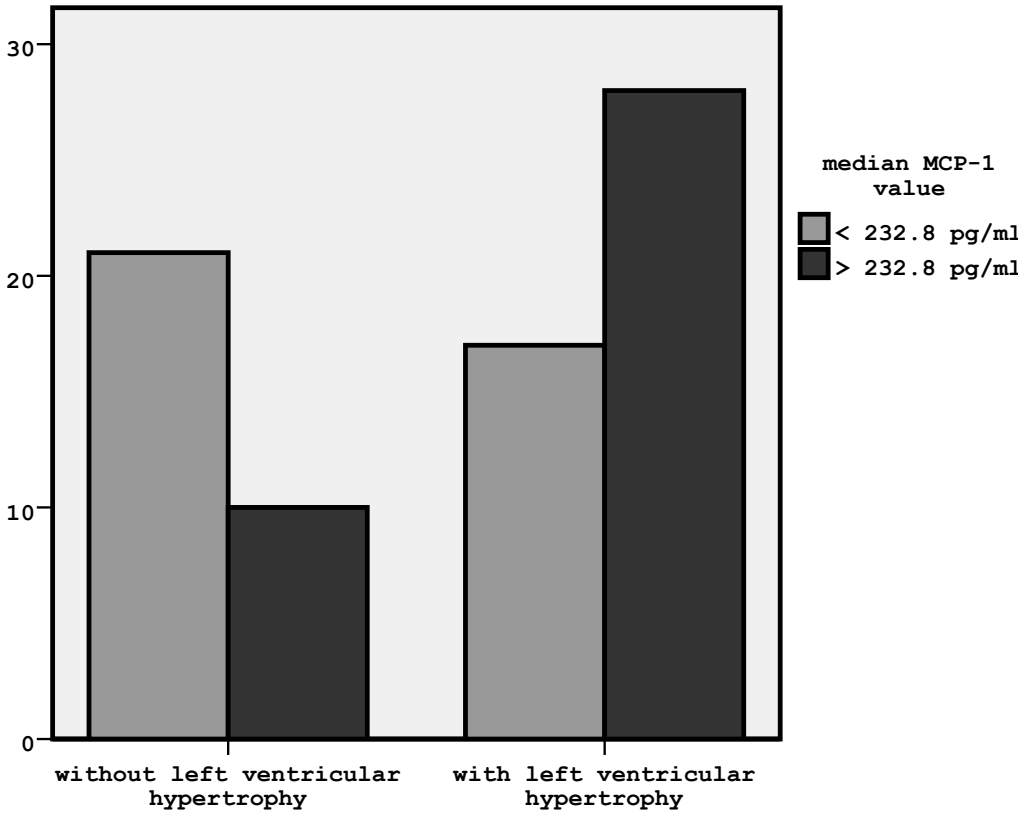

Figure No. 1: The association of higher or lower serum MCP-1 concentrations with left ventricular hypertrophy (x^2 =6.6, p=0.009).