Can chronic heart failure induce kidney function damage?

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ABSTRACT
Accelerated atherosclerosis and increased cardiovascular events have been extensively documented in patients with end stage chronic kidney disease. The aim of our work was to find evidence supporting the theory that chronic heart failure (CHF) induces renal function damage. In our work, lipids, apolipoprotein (apo)AI, NTproBNP, hs-CRP, lipid hydroperoxide (LPO) and creatinine levels were determined in patients with CHF. A total of 37 patients who were diagnosed with CHF, as well as 15 healthy persons, were recruited for the study. The patients were placed into 2 groups: patients with NYHA class 2 and NYHA class 3. Using routine laboratory methods, NT-proBNP level, and lipids were measured by way of employing a Cobas Integra analyser, while the concentration of hs-CRP was measured by immunonephelometric methods. Moreover, serum LPO concentration was measured using Cayman’s Assay Kit (LPO). The statistical analysis of the obtained results was performed using the nonparametric Kruskal-Wallis test and Spearman’s correlation analysis. Our work demonstrated that the CHF patients had significantly decrease concentration of HDL cholesterol and apoAI, but increased NT-pro-BNP, hs-CRP and LPO levels. In all CHF patients, a significant positive correlation between NTproBNP concentration and creatinine levels, and a significant negative correlation between NTproBNP concentration and apoAI levels, as well as between concentration of creatinine and apoAI levels, was shown. The study results suggest that variation in the concentration of NTproBNP, LPO, hs-CRP, apoAI, creatinine, in addition to chronic heart failure progression, gradually accompany the progress of chronic renal failure. What is more, the disorders may lead to the occurrence of cardiovascular events, consequently, to patient death.

Keywords: apoAI, NTproBNP, hs-CRP, lipid hydroperoxide, chronic heart and failure, chronic renal failure.

INTRODUCTION
Inflammation and oxidative stress play a critical role in the atherosclerotic process within various vascular beds, starting from endothelial dysfunction, through all stages of plaque build-up, until detrimental clinical ischemic complications [1]. Accelerated atherosclerosis and increased cardiovascular events have been extensively documented in patients with end stage chronic kidney disease (CKD) [1-3]. A graded association between glomerular filtration rate (GFR) and cardiovascular deaths begins with subtle decrease in GFR (<60-80ml/min/1.73m²). This imparts an independent risk of death, the occurrence of acute cardiovascular events, hospitalisation, and more cardiovascular complications following a myocardial infarct [4,5]. Even microalbuminuria, in the absence of an apparent decrease in renal function or diabetes, predicts more cardiovascular disease (CVD) and death [6]. The impact of CVD in CKD is illustrated by reports on the natural history of patients with early CKD. These indicate that the risk of premature CVD death is much higher than the risk of dialysis/transplantation progress [7,8]. Such observations are significant not only because of a high incidence and prevalence of end stage CKD, but because the number of patients with early CKD far exceeds those with end stage CKD. This trend is continuing to rise [9].

Patients with CKD, have the highest risk for atherosclerotic CVD. Current interventions have been insufficiently
effective in lessening excess incidence and mortality from CVD, in CKD patients, versus other high risk groups. The mechanisms underlying the heightened risk for CVD in CKD have been the focus of intense studies and may relate to the combined effects of traditional and CKD-specific risks involving inflammation and lipid metabolism, especially the perturbation of macrophage cholesterol homeostasis [2]. Unfortunately, there is no information in current literature about the association of chronic heart failure and chronic renal failure.

The aim of our work was to find evidence supporting the theory that chronic heart failure (CHF) induces renal function damage. Therefore, serum concentration of lipids, apoAI, NTproBNP, hsCRP, LPO and creatinine were determined in patients with cardiovascular disease.

**MATERIAL AND METHODS**

A total of 37 patients who were diagnosed with CHF according to ESC criteria, as well as 15 apparently normolipidemic healthy individuals as control, were recruited for the study. The CHF patients were hospitalized in the Department of Internal Diseases, Medical University of Lublin, Poland. Patients with liver diseases, active inflammatory diseases, acute and chronic kidney disease, malignancy, alcohol disease, thyroid diseases, unstable angina pectoris, and who had had myocardial infarction within the last three months, were excluded from the analysis. All CHF patients were on statin therapy. The patients were placed within 2 groups according to their NYHA class: patients with NYHA class 2 (n = 25), and NYHA class 3 (n = 12). This scale expresses the degree of severity of heart failure.

Written informed consents were obtained from all the participants. The study was approved by the Ethics Committee of the Medical University in Lublin, Poland, and conducted according to the principles outlined in the Helsinki Declaration.

Routine laboratory parameters were obtained in serum after 14-h overnight fasting. Blood was taken from a vein into commercial test tubes. The serum was immediately separated and stored in aliquots at -80°C until use. Using routine laboratory methods, the level of creatinine and NT-proBNP, and lipids were measured by way of a Cobas Integra analyser (Germany), while concentration of hs-CRP and apoAI was assessed by immunonephelometric methods, utilizing a Siemens Heath care Diagnostic Product. In addition, GmbH was measured on a Dade Behring nephelometer (BNII System, Germany), and Serum LPO concentration was measured using Cayman’s Lipid Hydroperoxide Assay Kit (LPO). This measures the hydroperoxides directly, utilizing the redox reactions with ferrous ions. Herein, it should be noted that hydroperoxides are highly unstable and react readily with ferrous ions to produce ferric ions. The resulting ferric ions are detected by using thiocyanate ions as chromogen.

The data were expressed as medians and minimum-maximum. Shapiro-Wilk’s test was used to investigate whether the variables had a normal distribution. The statistical analysis of the obtained results was performed using the nonparametric Kruskal-Wallis test. The relation between concentration of LPO and creatinine level, and between level of LPO and hs-CRP concentration, as well as between level of NTproBNP and apoAI concentration, and between the level of NTproBNP and creatinine level, was examined by Spearman’s correlation analysis. The statistical significance of all variables was established at p<0.05. Statistical analysis was performed using the STATISTICA program (Stat Soft, Krakow, Poland).

**RESULTS**

The age, and selected blood count (hemoglobin, white blood cells and platelets), BMI and eGFR in patients with CHF are presented in Table 1.

<table>
<thead>
<tr>
<th>Parametr</th>
<th>Controls n=15</th>
<th>Patients with NYHA 2 n=25</th>
<th>Patients with NYHA 3 n=13</th>
</tr>
</thead>
<tbody>
<tr>
<td>age (years)</td>
<td>Media±SD</td>
<td>Median min-max</td>
<td>Media±SD</td>
</tr>
<tr>
<td>Hb (g/dl)</td>
<td>12±1</td>
<td>10-13</td>
<td>13</td>
</tr>
<tr>
<td>WBC (109/l)</td>
<td>Media±SD</td>
<td>12±3.6</td>
<td>9.9±4.7</td>
</tr>
<tr>
<td>PLT (109/l)</td>
<td>Media±SD</td>
<td>18±3</td>
<td>183</td>
</tr>
<tr>
<td>BMI (m/</td>
<td>Media±SD</td>
<td>23.7±3.1</td>
<td>24.8±4.0</td>
</tr>
<tr>
<td>eGFR (m/min/</td>
<td>Media±SD</td>
<td>108±22</td>
<td>58±27.6</td>
</tr>
</tbody>
</table>
| **P < 0.01**

Here, it can be seen that in patients with CHF, their lipid profiles had a significant concentration decrease of HDL cholesterol: in all patients (HDL-C 37(8-81) mg/dl, p = 0.01), in patients with NYHA 2 (HDL-C 37(23-81) mg/dl, p=0.01) and in the NYHA 3 groups (HDL-C 32(8-53) mg/dl, p=0.01) – as compared to the control group (vs. HDL-C 48(42-58) mg/dl). Regarding the concentration of apoAI: in all patients (apoAI 103(47-164) mg/dl, p=0.01), in patients with NYHA 2 (apoAI 115(76-150 mg/dl), p=0.01) and in patients with NYHA 3 (apoAI 94(47-117 mg/dl, p=0.01) – as compared to the control group (apoAI 158(142-167 mg/dl). However, statistical analysis showed no significant differences in the concentrations of other lipid parameters. The concentrations of NTproBNP, creatinine, hs-CRP and LPO are presented in Table 2. Here, the statistical analysis showed that in both groups of patients (NYHA 2 and NYHA 3), concentrations of NT-pro-BNP, hsCRP and LPO were significantly increased, in comparison to the control group. However, NYHA 3 patients had higher NT-proBNP, creatinine, hsCRP and LPO levels than did NYHA 2 patients (Table 2.)
Table 2. Concentration of NT-proBNP, creatinine, hsCRP and lipid hydroperoxide in patients with chronic heart failure (Media±SD and Median (min-max))

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Controls n=15</th>
<th>Patients with NYHA 2 n=25</th>
<th>Patients with NYHA 3 n=12</th>
</tr>
</thead>
<tbody>
<tr>
<td>NT-proBNP (pg/ml)</td>
<td>Media±SD 163±155</td>
<td>2200±1503</td>
<td>11419±10 303</td>
</tr>
<tr>
<td></td>
<td>Median 101</td>
<td>1703</td>
<td>1714***- 6177</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>Media±SD 0.99±0.34</td>
<td>1.51±1.07</td>
<td>1.66±0.74</td>
</tr>
<tr>
<td></td>
<td>Median 0.92</td>
<td>1.52</td>
<td>1.67**</td>
</tr>
<tr>
<td>hs-CRP (mg/l)</td>
<td>Media±SD 0.06±0.10</td>
<td>0.47±0.39</td>
<td>0.58±0.41</td>
</tr>
<tr>
<td></td>
<td>Median 0.06</td>
<td>0.31***</td>
<td>0.52***</td>
</tr>
<tr>
<td>LPO (µm/ml)</td>
<td>Media±SD 0.54±0.23</td>
<td>0.83±0.17***</td>
<td>1.37±2.24***</td>
</tr>
<tr>
<td></td>
<td>Median 0.44</td>
<td>0.81**</td>
<td>1.54***</td>
</tr>
</tbody>
</table>

*p < 0.05; **p < 0.01; ***p < 0.001 vs. reference group
+ p < 0.05; +++ p < 0.001 vs. NYHA 2 patients
hs-CRP – high sensitivity-C-reactive Protein, LPO – lipid hydroperoxide

The results revealed a significant positive correlation between LPO concentration and hs-CRP levels (R = 0.792, p = 0.001), and between LPO concentration and creatinine levels (R = 0.628, p = 0.05) in the NYHA 3 patients. Moreover, in all patients, a significant positive correlation can be seen between NTproBNP concentration and creatinine levels (Figure 5), and a significant negative correlation is noticeable between NTproBNP concentration and apoAI levels (Figure 6). Moreover, a significant negative correlation is demonstrated between the creatinine concentration and apoAI levels (Figure 7). This suggests worsening renal function in patients with CHF.
CONCLUSION

The study results suggest that disorders in serum concentrations of NTproBNP, LPO, hsCRP, apoAI and creatinine levels, and progressive heart failure gradually accompany progressive chronic renal failure. Such disorders may lead to cardiovascular events and to renal failure, consequently, to patient death.
REFERENCES


