Risk of fractures in patients with osteoporosis associated with chronic heart failure and type 2 diabetes mellitus

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ABSTRACT

Introduction and Aim: Although the pathophysiological processes underlying the association between congestive heart failure (CHF) and osteoporosis (OP) are unknown, there is evidence that several changes observed in CHF may play a role in bone loss. The objective of the study is to examine the impact of soluble TNF-alpha receptor 1 (sR1-TNF-alpha) and soluble TNF-alpha receptor 2 (sR2-TNF-alpha) on the risk of fractures in patients with OP associated with CHF and type 2 diabetes mellitus (T2DM).

Methods: This study included 178 women aged 50–65 years, divided into four groups. Group 1 consisted of 48 women diagnosed with HF and T2DM. Group 2 included 93 patients with OP and HF. Group 3 consisted of 37 women with OP, HF, and T2DM.

Results: The levels of sR1-TNF-alpha and sR2-TNF-alpha in patient groups 1 through 3 were significantly higher than in the control group (p<0.01). Furthermore, it was demonstrated that patients in group 3 had much greater levels of both receptors than those in groups 1 and 2.

Conclusion: High levels of sR1-TNF-alpha and sR2-TNF-alpha in postmenopausal women with CHF are associated with an increased risk of a poor outcome during OP.

Keywords: Chronic heart failure; tumor necrosis factor-alpha; type 2 diabetes mellitus; postmenopausal women; loop diuretics.

INTRODUCTION

Congestive heart failure (CHF) induces a degree of hypoxia in tissues (1, 2). This may be one cause of osteoporosis in patients with CHF (3, 4). One of the mechanisms of bone injury in patients with CHF is increased activity of the renin-angiotensin-aldosterone system, which causes a resulting increase in parathyroid hormone. Aldosterone directly affects bone tissue, as shown by the finding of mineralocorticoid receptors in bone cells (4, 5). OP may also be caused by other secondary hyperparathyroidism reasons that are frequently observed in patients with CHF, such as chronic kidney disease and hypovitaminosis D (6). A significant decrease in bone and muscle mass can result from the reduction in motor activity that follows the loss of functioning (7, 8). In Kyrgyzstan, OP conditions worsen with aging and are relatively prevalent, affecting not only elderly people but also individuals of every age (9, 10).

A decrease in osteoprotegerin (OPG) levels in women has been associated with the onset of postmenopausal OP. This is as a result of the expression of this protein being reduced in the absence of estrogen (11). OPG has an effect on the endothelium, which prevents the artery wall from being calcified. Early OP and arterial calcification in OPG-deficient mice have a strong correlation with the severity of bone loss (12). An increased risk of cardiovascular disease and the severity of coronary heart disease have been linked to high OPG levels. In patients with HF, higher levels of OPG were associated with more severe symptoms, a decline in bone mineral density (BMD), and greater mortality from all causes (13).

Tumor necrosis factor-alpha (TNF-alpha) and interleukin-6 (IL-6) levels are increased in patients with HF, which causes macrophage activation, microvascular dysfunction, alterations in the way muscles contract, and fibrogenesis (14). These cytokines increase the risk of fractures by stimulating the resorption of bone in the bones. TNF-alpha has been shown to have a catabolic effect (15, 16). This is because it encourages osteoclastogenesis, stops the addition of osteoblast progenitor cells, lowers the expression of genes for bone matrix proteins, and may cause some resistance to calcitriol. Serum levels of soluble TNF-alpha receptor 1 (sR1-TNF-alpha) and soluble TNF-alpha receptor 2 (sR2-TNF-alpha), which were found to be the most accurate indicators of prolonged TNF-alpha exposure, have been linked to an increased risk of hip fracture, even in the
absence of other risk factors (15). Furthermore, taking drugs to treat HF may be dangerous to bone health. The role that loops diuretics play in improving the kidney’s ability to excrete calcium is notable.

Although the pathophysiological processes underlying the association between CHF and OP are unknown, there is testimony that several changes observed in CHF may play a role in bone loss (1). The objective of the study is to evaluate the impact of sR1-TNF-α and sR2-TNF-α on the risk of fractures in patients with OP associated with CHF and type 2 diabetes mellitus (T2DM).

MATERIALS AND METHODS

This study included 178 women aged 50–65 years, divided into four groups. Group 1 consisted of 48 women diagnosed with HF and T2DM. Group 2 included 93 patients with OP and HF. Group 3 consisted of 37 women with OP, HF, and T2DM. As a control group, 35 postmenopausal women aged 50–65 years were considered, without clinical and instrumental signs of cardiovascular diseases or OP. To assess BMD, an x-ray examination of the lumbar spine and proximal femur was performed using dual-energy x-ray absorptiometry. A T-test was used to characterize the decrease in BMD; OP was diagnosed with a T-score less than -2.5. The determination of the concentration of sR1-TNF-α and sR2-TNF-α receptors in blood serum was carried out using the enzyme-linked immunosorbent assay.

Patients who had undergone prior bisphosphonate therapy were not included in the sample, nor were those who were receiving corticosteroids or estrogen drugs at the time of the study.

All patients were divided into two groups after a 36-month follow-up: a group with an unfavorable course of OP and a group with a favorable course. Based on the results of dual-energy x-ray absorptiometry, the course of OP was evaluated by looking at records of low-traumatic fractures of large skeletal bones (like hips, vertebral bodies, and radii) and/or a decrease in BMD.

Statistica v8.0 (StatSoft Inc., Tulsa, USA) was used for the statistical analysis. The collected data are shown as mean ± standard deviation (M±m). The odds ratio and corresponding 95% confidence intervals (-95% CI, +95% CI) were used as a statistical tool to find probable markers of an unfavorable course of CHF and OP as well as to evaluate the effect of different indicators. At p<0.05, differences were considered statistically significant. The acquired data was kept confidential, and the study was given approval by the Bioethics Committee of the International Higher School of Medicine (Protocol No. 5 dated September 05, 2021).

RESULTS

When the main clinical characteristics of women were looked at, the study groups had similar average values for age, length of menopause, glycated hemoglobin, left ventricle ejection fraction, total cholesterol, and body mass index (Table 1).

However, a significantly larger number of patients in the group with CHF, OP, and T2DM had a history of myocardial infarction and acute stroke compared with women from the groups 1 and 2.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Group 1 CHF+DM (n=48)</th>
<th>Group 2 CHF+OP (n=93)</th>
<th>Group 3 CHF+DM+OP (n=37)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>61.2±4.3</td>
<td>63.2±5.7</td>
<td>60.3±4.9</td>
</tr>
<tr>
<td>Duration of menopause, years</td>
<td>14.2±4.6</td>
<td>16.6±4.1</td>
<td>13.4±3.9</td>
</tr>
<tr>
<td>Duration of DM, years</td>
<td>7.2±4.3</td>
<td>-</td>
<td>7.3±4.9</td>
</tr>
<tr>
<td>Glycated hemoglobin, %</td>
<td>6.2±0.3</td>
<td>-</td>
<td>6.4±0.3</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>32.9±2.2</td>
<td>30.8±2.4</td>
<td>32.3±1.8</td>
</tr>
<tr>
<td>Functional classification of CHF, n (%):</td>
<td>22 (45.8%)</td>
<td>48 (51.6%)</td>
<td>17 (46.0%)</td>
</tr>
<tr>
<td>Class II</td>
<td>18 (37.5%)</td>
<td>31 (33.3%)</td>
<td>13 (35.1%)</td>
</tr>
<tr>
<td>Class IV</td>
<td>8 (16.7%)</td>
<td>14 (15.1%)</td>
<td>7 (18.9%)</td>
</tr>
<tr>
<td>Left ventricle ejection fraction, %</td>
<td>48.1±2.2</td>
<td>50.4±4.4</td>
<td>47.2±2.9</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>4.4±0.5</td>
<td>4.7±0.5</td>
<td>4.2±0.7</td>
</tr>
<tr>
<td>T-criterion</td>
<td>-</td>
<td>-2.6±0.11</td>
<td>-2.8±0.17</td>
</tr>
<tr>
<td>Myocardial infarction, n (%)</td>
<td>9 (18.6%)</td>
<td>14 (15.1%)</td>
<td>11 (29.7%)*</td>
</tr>
<tr>
<td>Acute stroke, n (%)</td>
<td>5 (10.4%)</td>
<td>8 (8.6%)</td>
<td>8 (21.6%)*</td>
</tr>
<tr>
<td>Arterial hypertension, n (%)</td>
<td>44 (91.7%)</td>
<td>81 (87.1%)</td>
<td>35 (94.6%)</td>
</tr>
</tbody>
</table>

All data are mean ± standard deviation. *p<0.05. CHF = Chronic heart failure, DM = Diabetes mellitus, OP = Osteoporosis (OP).
When evaluating the features of the course of OP during 36 months of observation in group 2, osteoporotic fractures of large bones of the skeleton and/or a progressive decrease in BMD were observed in 32 patients (34.4%) and 22 women (59.5%) in group 3. In group 1 women with CHF and T2DM without previous OP at the time of inclusion during the observation period, only five women showed a decrease in BMD corresponding to the criterion of OP.

Compared to the control, the levels of sR1-TNF-α and sR2-TNF-α in patient groups 1 to 3 were considerably greater (p<0.01). Additionally, it was shown that group 3 patients had much higher levels of both receptors than patients in groups 1 and 2 (Table 2). Subsequently, levels of sR1-TNF-α and sR2-TNF-α were divided into four groups (Q1–Q4) in ascending order of their concentration. The level of sR2-TNF-α showed an increasing gradation of risk, where the odds ratio of osteoporotic events increased from 1.4–12.83. However, a statistically significant risk was found only for Q3–Q4. For the Q4 level of sR1-TNF-α, an increase in the risk of osteoporotic fractures of large bones of the skeleton and/or a progressive decrease in BMD over 36 months was also revealed (OR=5.25, p=0.038).

The use of loop diuretics was found to be a predictor of a high risk of osteoporotic fractures in patients with CHF (OR=6.29, 95% CI=1.45–17.26, p=0.015). This was found when other possible predictors of an unfavorable course of OP were looked at.

**DISCUSSION**

In a prospective, randomized, controlled clinical trial, higher blood levels of sR1-TNF-α and sR2-TNF-α in postmenopausal women were related to a higher risk of osteoporotic fractures in the presence of comorbidities including CHF, T2DM, and OP.

In a study by Cauley *et al.*, the predictive value of sR1-TNF-α and sR2-TNF-α was low (17). In a study by Ing *et al.*, women with the highest levels of soluble TNF-α receptors had a risk of hip fracture that was more than twice as high as women with the lowest levels of soluble TNF-α receptors, even when other risk factors were considered (15). This study is like ours because both looked at how the concentrations of sR1-TNF-α and sR2-TNF-α affected the risk of fractures (15). On this basis, it can be assumed that the use of TNF-α blockers for the prevention and treatment of OP may be promising.

TNF-α is a vital immune system component that controls innate and adaptive immunity and helps to start and maintain inflammation. Macrophages and immune cells, which are activated in response to infections or tissue injury, are the main cellular producers of TNF-α (14). To promote tissue homeostasis and prevent infections, this cytokine must be expressed in an organized way. On the other hand, dysregulated TNF-α expression and signaling can contribute to diseases that cause chronic inflammation and tissue damage. Therapies that block TNF-α signaling have been developed to prevent its pro-inflammatory and tissue-degenerative effects. Rheumatoid arthritis, psoriasis, and ankylosing spondylitis have all been effectively treated with these anti-TNF therapies. Although anti-TNF drugs have demonstrated clinical efficacy, they are associated with notable adverse effects, such as invasive fungal infections, opportunistic infections, tuberculosis reactivation, the development of other autoimmune illnesses, and lymphomas (18). Additionally, it has no

**Table 2:** Results of a comparative analysis of the sR1-TNF-α and sR2-TNF-α levels in the studied groups

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group 1 (n=48)</th>
<th>Group 2 (n=93)</th>
<th>Group 3 (n=37)</th>
</tr>
</thead>
<tbody>
<tr>
<td>sR1-TNF-α (pg/ml)</td>
<td>1512.8±87.6*</td>
<td>1643±85.4*</td>
<td>1943.1±132.3*#</td>
</tr>
<tr>
<td>sR2-TNF-α (pg/ml)</td>
<td>2876.3±131.2*</td>
<td>1911.4±111.6*</td>
<td>3265.8±154.3*#</td>
</tr>
</tbody>
</table>

All data are mean ± standard deviation. *p<0.01 with control, #p<0.01 with groups 1 and 2.

sR1-TNF-α = soluble TNF-α receptor 1, sR2-TNF-α = soluble TNF-α receptor 2, CHF = Chronic heart failure, DM = Diabetes mellitus, OP = Osteoporosis (OP)

**Table 3:** Prognostic significance of sR1-TNF-α and sR2-TNF-α levels in assessing the risk of an unfavorable course of OP

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Quartile</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>sR1-TNF-α</td>
<td>Q1 1.2</td>
<td>0.41-3.50</td>
<td>0.729</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Q2 1.79</td>
<td>0.61-5.26</td>
<td>0.278</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Q3 2.4</td>
<td>0.52-11.00</td>
<td>0.241</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Q4 5.36</td>
<td>1.05-27.42</td>
<td>0.041</td>
<td></td>
</tr>
<tr>
<td>sR2-TNF-α</td>
<td>Q1 1.4</td>
<td>0.32-6.12</td>
<td>0.642</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Q2 2.29</td>
<td>0.68-7.70</td>
<td>0.173</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Q3 6.7</td>
<td>2.03-22.07</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Q4 12.83</td>
<td>3.40-48.38</td>
<td>0.001</td>
<td></td>
</tr>
</tbody>
</table>

sR1-TNF-α = soluble TNF-α receptor 1, sR2-TNF-α = soluble TNF-α receptor 2, 95% CI = 95% confidence interval, Q = Quartile

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effect on treating some diseases based on autoimmune damage to tissue structures, such as multiple sclerosis. Undergoing therapy with anti-TNF medications is restricted and contraindicated for several reasons.

Anti-TNF therapy may have problems because TNF-α can have different effects on different parts of the body through two different TNF receptors, sR1-TNF-α and sR2-TNF-α (19). In various animal models of disease, genetic deletion of sR1-TNF-α is usually associated with the absence or reduction of disease, while ablation of sR2-TNF-α exacerbates the disease. Based on these and other data, TNF-α signaling through sR1-TNF-α is responsible for pro-apoptotic and inflammatory responses, while sR2-TNF-α helps regulate the immune system and heal damaged tissues.

Elevated levels of TNF are found among different chronic diseases, including HF and OP, along with inflammatory diseases for which anti-TNF treatment is authorized (14). Neutralization of TNF-α in HF may improve the course of the disease, according to preclinical studies on models of HF. Clinical trials with TNF-α antagonists, however, had a negative impact on the development of HF and increased mortality. Studies on mice that used TNF-α receptor activation showed that sR1-TNF-α and sR2-TNF-α have opposite effects on tissue remodeling, hypertrophy, inflammation, and cell death in HF. sR1-TNF-α activation, on the other hand, has positive effects on these processes, whereas activation of sR1-TNF-α exacerbates these events (20). Another study showed that following myocardial infarction, sR1-TNF-α activation worsens left ventricular remodeling while sR2-TNF-α signaling improves myocardial status (21). These findings suggest that while TNF-α has a preventive function in HF, full TNF-α blockade is not recommended. Therefore, using anti-TNF treatment to prevent and treat OP in patients with CHF doesn’t seem promising.

According to the results of the present study, patients with CHF who underwent therapy with loop diuretics had an increased risk of osteoporotic fractures. Calcium and magnesium are prevented from being reabsorbed when loop diuretics increase the quantity of these elements in the urine. This may result in a loss of calcium in the urine, which could promote bone loss and affect the formation of new bones. There is a significant association between the use of loop diuretics and a decrease in BMD (22). Studies on the impact of loop diuretics on the incidence of hip fracture, however, have not consistently shown a link (23–27), which may be because when evaluating individuals, various risk factors for OP and their risk of falling due to hypovolemia and/or poor cardiac output varied.

CONCLUSION

High levels of sR1-TNF-α and sR2-TNF-α in postmenopausal women with CHF are associated with an increased risk of a poor outcome during OP. In patients with CHF, using loop diuretics has been linked to a higher incidence of osteoporotic fractures.

CONFLICT OF INTEREST

None to declare.

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