The role of activation of soluble tumor necrosis factor-α receptors in the development of comorbid pathology: chronic heart failure associated with type 2 diabetes and osteoporosis

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Abstract

Objective. To study the clinical and pathogenetic relationship between the risk of developing heart failure (CHF), type 2 diabetes mellitus (DM), and osteoporosis with the level of activation of soluble tumor necrosis factor-α 1 and type 2 receptors (TNF-α-SR1 and SR2) and osteoprotegerin, as well as to evaluate the effectiveness of bisphosphonate therapy in postmenopausal women.

Materials and methods. The study included 178 women aged 50 to 65: 48 women with CHF and type 2 diabetes (group 1), 93 patients with osteoporosis and CHF (group 2), 37 women with osteoporosis, CHF and type 2 diabetes type (group 3). The control group consisted of 35 postmenopausal women aged 50 to 65 years old, without clinical and instrumental signs of the pathology of the cardiovascular system and osteoporotic process. To determine the bone mineral density, an X-ray study was used by the method of dual-energy X-ray absorptiometry of the lumbar spine and the proximal femur. Determination of the concentration of TNF-α-SR1 and TNF-α-SR2 receptors, osteoprotegerin in the blood serum was carried out by the method of enzyme-linked immunosorbent analysis. Women with osteoporosis (n = 48) received bisphosphonates.

Results. Concentrations of TNF-α-SR1 and TNF-α-SR2 in groups 1-3 were higher ($p < 0.01$) than levels in the control group. It was also found that the levels of both receptors were significantly higher in group 3 compared to patients in groups 1 and 2. TNF-α-SR1 levels TNF-α-SR2 were divided into quartiles (Q1-Q4) according to the increase in the concentration of these markers. For TNF-α-SR2, there was an increasing gradient in risk, with the odds ratio (OR) of cardiovascular events increasing from 1.43 to 7.50, but the risk was statistically significant only for Q3-Q4. OR increased for TNF-α-SR1 levels significantly for Q2-Q4 compared to Q1. The cumulative incidence of the combined endpoint of adverse cardiovascular events decreased with bisphosphonate therapy by 24% ($p=0.01$), reflecting the beneficial effect of these on the regression of associated cardiovascular pathology.

Conclusion. Postmenopausal women with elevated levels of soluble TNF-α-SR1 and SR2 receptors are diagnosed with an increased risk of developing unfavorable cardiovascular pathology associated with impaired bone mineral density. The purpose of bisphosphonates prevents bone metabolic disturbances, reducing the risk of adverse cardiovascular events.

Keywords: tumor necrosis factor-α receptors; osteoprotegerin; comorbidity; heart failure; diabetes; osteoporosis; bisphosphonates.

Soluble tumor necrosis factor-α 1 and type 2 receptors (TNF-α-SR1 and SR2) have been identified in human serum, are produced together with TNF-α, and have greater stability of long-term biological effects compared to TNF-α [1, 2]. Soluble TNF-α-SR1 and SR2 receptors can function as TNF-α antagonists by binding to a cytokine, thereby reducing inflammation. At the same time, soluble receptors can retain the bioactive three-dimensional form of TNF-α and potentially serve as a reservoir (depot) for TNF-α, since their receptors can dissociate from the receptor-ligand complex. In clinically controlled studies, it was found that TNF-α-SR1 and SR2 receptors are associated with an increased risk of bone mineral density (BMD) disorders, an increased risk of osteoporotic fractures [3, 4, 5].

Hip fractures are a serious public health problem [6] with a projected annual increase of 50% to about 450,000 fractures by 2025 in the United States [7]. According to epidemiological studies, a high mortality rate persists not only during the first year but also increases more than 2 times within 10 years after a fracture in elderly women and men [8-9]. It has now been established that chronic systemic inflammation, characterized by an increase in the activation of the signaling system involving osteoprotegerin (OPG), RANKL/RANK/OPG, which regulates bone tissue and vascular wall remodeling, is associated with both the development of osteoporosis and cardiovascular events [10-13].

The proinflammatory cytokine TNF-α can stimulate osteoclastogenesis in vivo by increasing the sensitivity to the ligand of the receptor activator RANKL of nuclear factor Kappa-B [13-14].

In previous studies, Aderka D. et al. (1992) [14] and Cauley J.A. et al. (2007) [3] showed that the determination of serum TNF-α levels as a biomarker of the risk of osteoporotic clinical events and hip fractures is limited due to the short half-life of this cytokine and its large population variability compared to TNF-α receptors 1 and 2 type. The pathogenetic mechanisms by which the increased production of soluble TNF-α and osteoprotegerin receptors induces the development of comorbid pathology associated with chronic heart failure (CHF), type 2 diabetes mellitus (DM) and osteoporosis are not clear. Therefore, deciphering the mechanisms that determine the relationship of soluble TNF-α-SR1 and SR2 receptors with the development of these diseases is important for the development of new promising approaches to the study of poorly studied unconventional risk factors, the development of new methods of prevention and treatment using bisphosphonates (BP) of these socially significant diseases.

The study aimed to determine the clinical and pathogenetic relationship of the risk of developing heart failure, type 2 diabetes mellitus, and osteoporosis with the level of activation of soluble TNF-α receptors and osteoprotegerin, as well as to evaluate the effectiveness of bisphosphonate therapy in postmenopausal women.

Materials and methods

Study participants. The study included 178 women aged 50 to 65: 48 women with CHF and type 2 diabetes (group 1), 93 patients with osteoporosis and CHF (group 2), 37 women with osteoporosis, CHF and type 2 diabetes type (group 3) (Table 1). The control group consisted of 35 postmenopausal women aged 50 to 65 years old, without clinical and instrumental signs of the pathology of the cardiovascular system and osteoporotic process.

Table 1. Clinical characteristics of women in the studied groups

Index	Group 1 CHF + D (n=48)	Group 2 CHF+OP (n=93)	Группа 3 CHF+D+OP (n=37)
Age, years	61.2±4.3	63.2±5.7	60.3±4.9
Duration of postmenopause, years	14.2±4.6	16.6±4.1	13.4±3.9
Duration of D, years	7.28±4.3	-	7.3±4.9
Glycated hemoglobin, %	6.2±0.3	-	6.4±0.3
BMI, kg/m2	32.9±2.2	30.8±2.4	32.3±1.8
FC CHS, n (%): FC 2 FC 3 FC 4	 22 (45.8%) 18 (37.5%) 8 (16.7%)	 48 (51.6%) 31 (33.3%) 14 (15.1%)	 17 (46.0%) 13 (35.1%) 7 (18.9%)
CAS (points)	7.3±0.7	7.1±0.5	7.8±0.9
LVEF, %	48.1±2.2	50.4±4.4	47.2±2.9
Total cholesterol, mmol/l	4.4±0.5	4.7±0.5	4.2±0.7
T-criteria	-	-2.6±0.11	-2.8±0.17
Myocardial infarction, n (%)	9 (18.6%)	14 (15.1%)	11 (29.7%)*
ACVA, n (%)	5 (10.4%)	8 (8.6%)	8 (21.6%)*
AH, n (%)	44 (91.7%)	81 (87.1%)	35 (94.6%)

Note. *- $p<0.05$ with groups 1 и 2.

CHF – chronic heart failure, D – diabetes, OP – osteoporosis, FC - functional class, BMI – body mass index, CAS - clinical assessment scale, LVEF - left ventricular ejection fraction, – acute cerebrovascular accident, AH – arterial hypertension

Study exclusion criteria included prior bisphosphonate therapy and the use of corticosteroids and estrogen medications at the beginning of the study.

Women with osteoporosis were divided into groups: group 1 (n = 82) included patients who received basic therapy for CHF, group 2 (n = 48) included patients who, in addition to basic CHF therapy, were prescribed alendronic acid preparations and ibandronic acid belonging to the BP group for the treatment of osteoporosis.

Study methods. To determine the bone mineral density, an X-ray study was used by the method of dual-energy X-ray absorptiometry of the lumbar spine and the proximal femur. The T-test was used to characterize the decrease in bone mineral density; the diagnosis of osteoporosis was determined when the T criterion was <-2.5. Determination of the concentration of TNF-α-SR1 and TNF-α-SR2-receptors, osteoprotegerin in the blood serum was carried out by the method of enzyme-linked immunosorbent assay.

Statistical analysis. Statistical processing of the results was carried out using the STATISTICA statistical software package. The mean value and standard error of the mean value of the studied quantitative variables (M ± m) were determined. To select possible predictors of an unfavorable course of CHF and osteoporosis, or to check the influence of various indicators, the OR (odds ratio) estimate was used with the limits of the confidence intervals (-95% CL; + 95% CL).

Results

When analyzing the main clinical characteristics in women, it was found that the average age, duration of menopause, the level of glycated hemoglobin, LVEF, total cholesterol, and body mass index in the studied groups were comparable (Table 1). It was also found that the levels of

both receptors were significantly higher in group 3 compared to patients in groups 1 and 2 (Table 2).

Table 2. Results of a comparative analysis of the levels of TNF-α-SR1, TNF-α-SR2, and osteoprotegerin in the studied groups (M±m)

Index	Group 1 CHF+D (n=48)	Group 2 CHF+OP (n=93)	Group 3 CHF+D+OP (n=37)	Control (n=37)
TNF-α-SR1 (pg/ml)	1512.8±87.6*	1643±85.4*	1943.1±132.3*#	1198.2±95.4
TNF-α-SR2 (pg/ml)	2876.3±131.2*	1911.4±111.6*	3265.8±154.3*#	2454.5±165.3
Osteoprotegerin (pmol / l)	8.6±0.9*	7.3±1.1*	7.5±0.4*	4.2±0.5

Note.*- p<0.01 with control; #- p<0.01 with groups 1 и 2.
CHF – chronic heart failure, D – diabetes, OP – osteoporosis, TNF-α-SR1 – soluble tumor necrosis factor-α 1 receptor, TNF-α-SR2 - soluble tumor necrosis factor-α 2 receptor.

For further analysis, TNF-α-SR1 levels TNF-α-SR2 were divided into quartiles (Q1-Q4) by increasing the concentration of these markers. For TNF-α-SR2, an increasing risk gradient was observed, with the odds ratio (OR) of cardiovascular events increasing from 1.43 to 7.50, but the risk was statistically significant only for Q3-Q4 (Table 3). OR increased for TNF-α-SR1 levels significantly for Q2-Q4 compared to Q1.

Table 3

Prognostic significance of TNF-α-SR1, TNF-α-SR2 levels in assessing the risk of adverse cardiovascular events

Index	Quartile	Odds Ratio	95% CI	p-value
TNF-α-SR1	Quartile 1 (Q1)	2.40	0.52-11.00	0.2414
	Quartile 2 (Q2)	3.44	1.09-10.85	0.0311
	Quartile 3 (Q3)	3.51	1.14-10.78	0.0251
	Quartile 4 (Q4)	5.40	1.70-17.21	0.0036
TNF-α-SR2	Quartile 1 (Q1)	1.43	0.47-4.33	0.5198
	Quartile 2 (Q2)	2.43	0.50-11.79	0.2527
	Quartile 3 (Q3)	5.25	1.03-26.82	0.0384
	Quartile 4 (Q4)	7.50	2.19-25.72	0.0011

Note. TNF-α-SR1 – soluble tumor necrosis factor-α 1 receptor, TNF-α-SR2 - soluble tumor necrosis factor-α 2 receptor, odds ratio, 95% CI - 95% confidence interval.

Evaluation of the effectiveness of oral BP alendronate and ibandronate, aimed at preventing comorbid cardiovascular pathology of CHF, type 2 diabetes, and osteoporosis, showed an inverse proportional relationship with the level of TNF-α receptors (p=0.001). We concluded convincing evidence of the effectiveness of using BP for the secondary prevention of cardiovascular pathology and osteoporosis in postmenopausal women. Long-term (12 months) therapy with oral BP alendronate and ibandronate was also accompanied by a 23% decrease (p=0.05-0.01) in low-density lipoproteins (LDL) and an increase in antiatherogenic high-density lipoproteins (HDL) in the blood by 17%. The cumulative frequency of the combined endpoint decreased during BP therapy by 24% (p=0.01), reflecting the beneficial effect of these on the regression of associated cardiovascular pathology.

Discussion

Data from a randomized, clinically controlled, long-term prospective study showed that in postmenopausal women, higher blood levels of soluble TNF-α-SR1 and SR2 receptors were associated with an increased risk of developing comorbid cardiovascular pathology: CHF, type 2 diabetes, and osteoporosis - with a fairly high OR unfavorable course of cardiovascular pathology. The number of patients with a history of myocardial infarction and acute cerebrovascular accidents in the group with CHF, osteoporosis and type 2 diabetes was significantly higher compared to women in groups 1 and 2. Concentrations of TNF-α-SR1 in groups 1-3 were higher ($p < 0.01$) than the level in the control group, as well as the concentration of the TNF-α-SR2 receptor ($p < 0.01$). When studying the level of osteoprotegerin in the blood serum, it was found that in all groups of women with comorbid pathology, the concentration of the marker was significantly higher than in the control group. This study added additional diagnostic information to predict the adverse course of osteoporosis - the development of fractures).

The linear trend test showed an increase in OR for abnormalities in bone mineral density (BMD) with higher quartiles TNF-α-SR1 and SR2 ($p=0.01$), associated with an increased risk of osteoporotic bone disorders. The levels of soluble TNF-α receptors, like OPG, were significant predictors of high cardiovascular risk of adverse events and mortality based on the cumulative frequency of the combined endpoint.

It is generally accepted that inflammation is one of the key pathogenetic factors that play an important role in the development of cardiovascular disease and osteoporosis. Excessive activation of proinflammatory cytokines in the development of CHF plays a special role [15], which in turn are inducers of bone tissue resorption [16]. Common inflammatory mediators for atherosclerosis, coronary artery disease, heart failure, type 2 diabetes, and osteoporosis are the PANKL/PANK/OPG regulatory system, C-reactive protein, interleukins (interleukin-1, interleukin-6), macrophage colony-stimulating factor, TNF-α [11, 16-19]. It has been established that in atherosclerosis and ischemic heart disease, the process of inflammation is accompanied by damage to the endothelium, the formation of an atherosclerotic plaque, and its calcification at later stages. In bone tissue, these same mediators induce the resorptive capacity of osteoclasts.

Oxidized LDL can induce a decrease in bone mineral density with the development of osteoporosis and its complications in patients with increased cardiovascular risk [3-5, 20-21].

Of interest is the work of Cauley J.A., et al. (2007) to study the prognostic significance of a series of inflammatory markers: IL-6, TNF-α, C-reactive protein, soluble IL-6 and IL-2 receptors versus soluble TNF-α-SR1 and SR2 receptors for stratification of bone fracture risk in healthy elderly volunteers 70-79 years old [3]. A prospective cohort study included > 3000 people, multivariate-adjusted OR (95% CI) values in Q4 compared to Q1-Q3 for TNF-α-SR1 and SR2 were not high at 1.72 (1.14-2.51) and 1.48 (1.0-2.2), respectively. Due to the small number of femoral fractures, the predictive value of these markers was low.

In another solid study, WHI-OS (Women's Health Initiative) Barbour K.E. et al. (2012) [4] investigated TNF-α-SR1 and SR2 as pro-inflammatory predictors of the hip fracture using a case-control design. The highest quartiles of these soluble receptors were compared to the lowest three quartiles. The study showed that the inclusion of inflammatory markers (TNF-α-SR1 and TNF-α-SR2) in the prognosis analysis predicted hip fracture in the highest quartile (OR 2.05; 95% CI=1.35-3.12).

In a recent study by Ing S.W. et al. (2015) [22] among participants in the Women's Health (WHI) program aged 50-79 years, which included 400 pairs of patients with cases of hip fracture and the use of hormone replacement therapy with estrogen drugs after menopause. The odds ratio of the risk of hip fracture was considered following the quartiles of the expression levels of soluble TNF-α-SR1 and SR2 receptors. Women with the highest level of soluble TNF-α receptors had a more than twofold increase in the risk of hip fracture, regardless of other risk factors for hip fracture OR for TNF-α-SR1 was 2.24; CI=1.05-4.79; for TNF-α-SR2 2.83; CI=1.34-5.99. The prophylactic administration of polyunsaturated fatty acids (PUFA, with high or low intakes) did not affect inflammation factors and reduce the risk of hip fracture. The effect of PUFA consumption on the

risk of adverse cardiovascular events and mortality has not been evaluated. The effectiveness of the administration of bisphosphonates, which can affect the associated cardiovascular pathology and bone metabolism at the same time, were not analyzed in the studies presented.

Knowledge of the additional effect of BP on bone metabolism prescribed to patients with increased cardiovascular risk factors allows doctors to select the most optimal pathogenetic therapy, in particular for CHF of ischemic origin, type 2 diabetes, lipid metabolism disorders, considering the initial clinical manifestations of bone loss (according to densitometry data) or osteoporosis.

The strengths of our study include a new research project within a prospective (12-month) randomized, clinically controlled study of soluble TNF-α-SR1 and SR2 receptors with the inflammatory mediator system RANKL/RANK/osteoprotegerin, evidence-based prediction of bone metabolic disorders and osteoporotic fractures, new data on covariances associated with inflammation receptors: indicators of associated high-risk cardiovascular pathology (CHF, type 2 diabetes and osteoporosis), assessment of the quality of life and physical tolerance.

The potential limitations of the study lie in determining only the baseline level of TNF-α receptors. The study was limited to including only postmenopausal women.

Conclusion

Postmenopausal women with increased levels of soluble receptors TNF-α-SR1 and SR2 are diagnosed with an increased risk of developing unfavorable cardiovascular pathology associated with an increased level of OPG, abnormalities in bone mineral density.

The appointment of oral BP alendronate or ibandronate prevents bone metabolism disorders, allowing doctors to choose the optimal pathogenetic therapy for the treatment of CHF, type 2 diabetes, and osteoporosis in persons with increased cardiovascular risk factors. Bisphosphonates, which have a positive effect on the pathogenesis of these diseases at the same time, help to improve the compliance of patients with an increased risk of long-term preventive therapy with these drugs.

Chronic immune inflammation is the leading modulator of the signaling system with the participation of osteoprotegerin (OPG), RANKL-RANK-OPG, convincingly demonstrated the involvement in the pathogenesis of CHF, type 2 diabetes, and osteoporosis, which are independent risk factors for the development of cardiovascular events and mortality. At the same time, the commonality of their etiology and pathogenesis is associated with an increased risk of impaired bone mineral density and fractures, and bisphosphonates can reduce the risk of cardiovascular events and osteoporotic fractures by inhibiting cytokines and through other mechanisms.

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