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Paper Authors
Munira Khusainova Alisherovna

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XANTHINE METABOLISM IN THE PROGRESSION OF CHRONIC HEART FAILURE

Munira Khusainova Alisherovna

Samarkand State Medical Institute, Samarkand, Uzbekistan

Abstract. The article presents the data of a study on the study of xanthine metabolism disorders in patients with chronic heart failure (CHF), depending on the presence or absence of concomitant chronic kidney disease (CKD) at different stages of the disease. There was a significant increase in the activity of xanthine oxidase in patients with chronic heart failure with concomitant chronic kidney disease, which proves a change in the metabolism of this category of patients in the direction of the oxidase pathway of uric acid formation. The negative effect of xanthine metabolism disorders on the clinical course of CHF and the progression of the functional class of heart failure was demonstrated. At the same time, in patients with CHF with CKD, the progression of the functional class and a decrease in the left ventricular ejection fraction is associated with an increase in xanthine oxidase activity, while in patients with CHF without concomitant CKD – only with an increase in serum uric acid levels. The results also indicate an important role of the xanthine oxidase system in the deterioration of kidney function.

Keywords. xanthine oxidase, chronic heart failure, chronic kidney disease, hyperuricemia

I. Introduction.

The accumulated data suggest the existence of a direct pathophysiological role of increased xanthine oxidase activity in the progression of heart failure. Thus, in the course of experimental studies, it is hypothesized that in addition to increasing the level of uric acid in blood serum in conditions of tissue hypoxia in patients with chronic heart failure (CHF) there is a change in the metabolic pathways of formation of uric acid increased transformation xanthinoxidase in xanthine oxidase [1]. This in turn leads to the formation of reactive oxygen species simultaneously with uric acid, increased oxidative stress, endothelial dysfunction, and activation of systemic inflammation [2].

It is also believed that the association of serum uric acid concentration with cardiovascular morbidity and mortality is significantly stronger in patients with reduced glomerular filtration rate (GFR) [10]. However, it remains unclear how xanthine metabolism changes in patients with concomitant chronic kidney disease (CKD). It is assumed that hyperuricemia may be a predictor of adverse outcomes if it is a marker of increased xanthine oxidase activity, rather than a consequence of decreased renal uric acid excretion [3], but this hypothesis remains unexplored to date. 112 patients with chronic heart failure were examined, including 72 with concomitant chronic kidney disease and 40 with CHF without CKD. The etiological factors of CHF in the examined patients were ischemic heart disease and arterial hypertension. The age of the examined patients ranged from 49 to 94 years, and the average was (72.5+0.98) years.

The assessment of xanthine metabolism was carried out by determining the level of uric acid and the activity of serum xanthine oxidase. The uric acid level was determined using an enzymatic colorimetric test, a PAP method with an anti-lipid factor.

In the cohort of examined patients, we observed a negative effect of hyperuricemia on the clinical course of CHF and the progression of the functional class of heart failure, regardless of the indicators of xanthine oxidase activity. Thus, in patients with functional class (FC) III according to NYHA, the level of uric acid was significantly higher compared to the group of patients with FC II. Indicators of xanthine oxidase activity were also higher in patients with FC III, but did not reach reliability (Table 1).

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Table 1
Average levels of uric acid and indicators of xanthine oxidase activity, depending on the functional class of CHF

FC	Uric acid, mg/dl	Xanthine oxidase activity, IU / ml .
II	6,88±0,25*	5,96±0,61*
III	8,5±0,39*	7,22±1,2*

Note: the significance of the differences * - $p<0.01$.

There was also a significant positive correlation between the level of serum uric acid and the functional class of CHF ($r = 0.4$, $p<0.05$).

However, when dividing patients into subgroups depending on the presence or absence of concomitant CKD, it was found that in patients with CHF with CKD, FC progression was associated with both increased xanthine oxidase activity and hyperuricemia. While in patients with CHF without concomitant CKD – only with an increase in serum uric acid levels. Thus, when comparing the indicators of xanthine oxidase activity in patients with CHF II FC (n=44) and III-IV FC (n=28) with concomitant CKD, there was a tendency to increase the activity of xanthine oxidase with the functional class of CHF: (6.58+0.86) iU/ml and (9.19+1.39) iU/ml, respectively ($p=0.1$). Uric acid levels in this group of patients were also significantly higher in patients with NYHA FC III-IV compared to FC II: (8.53+0.48) mg / dl and (7.07+0.29) mg / dl, respectively ($p<0.05$).

In the group of patients with CHF without concomitant CKD, the xanthine oxidase activity index was higher in the subgroup of patients with FC II (n=21) compared to FC III-IV (n=19), but without a significant difference: (5.46+1.17) IU/ml and (3.76+0.93) iU/ml, respectively ($p>0.05$). The level of uric acid in the blood of patients with CHF with FC III-IV according to NYHA was significantly higher compared to the group of patients with CHF FC II: (8.51+0.56) mg/dl and (6.43+0.48), respectively ($p=0.008$) (Fig 1).

The analysis of xanthine metabolism in the subgroups of patients with CHF with FC II and III according to NYHA, depending on the presence or absence of concomitant CKD, revealed no significant differences in uric acid levels and xanthine oxidase activity between patients with CHF FC II according to NYHA with concomitant CKD and patients with CHF FC II without CKD ($p>0.05$). At the same time, in the subgroup of patients with CHF FC III according to NYHA, the indicators of xanthine oxidase activity were significantly higher in patients with CHF with concomitant CKD compared to patients without CKD ($p<0.01$). The level of uric acid was not significantly different.

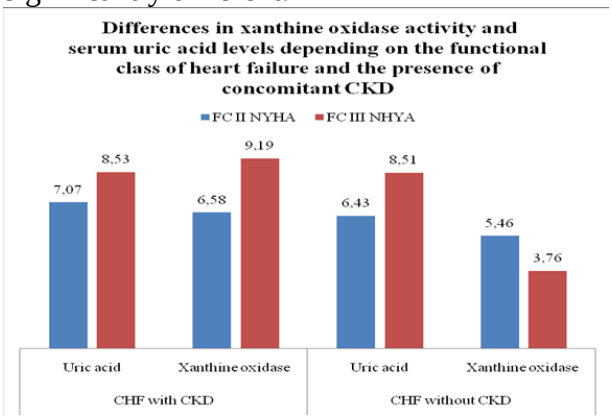

Figure 1. Differences in xanthine oxidase activity and serum uric acid levels depending on the functional class of heart failure and the presence of concomitant CKD.

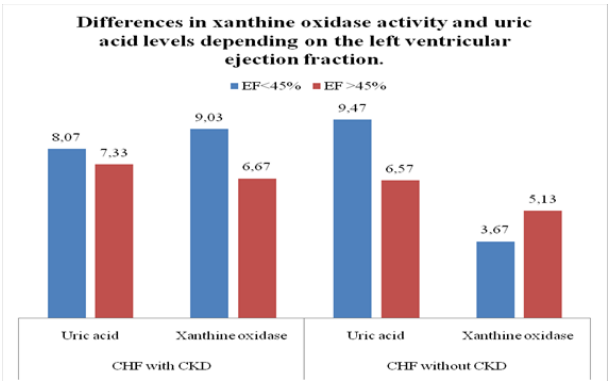

Figure 2. Differences in xanthine oxidase activity and uric acid levels depending on the left ventricular ejection fraction.

When studying the relationship of uric acid levels and xanthine oxidase activity with the left ventricular ejection fraction (EF),

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depending on the presence or absence of concomitant CKD, it was found that in patients with CKD, a decrease in EF is associated with an increase in xanthine oxidase activity, while in patients with CHF without concomitant CKD – with an increase in blood uric acid levels. Thus, in the group of patients with CHF without concomitant CKD, the activity of xanthine oxidase was higher in the subgroup with EF>45% (n=28) compared with the subgroup of patients with EF < 45% (n=12), but without a significant difference: (5.13+0.96) IU/ml and (3.67+1.29) IU/ml, respectively (p>0.05). At the same time, the level of uric acid in this group of patients was significantly higher in patients with FV < 45%: (9.47+0.78) mg/dl and (6.57+0.37) mg/dl, respectively (p=0.001) (Fig. 2).

To study the activity of xanthine oxidase in patients depending on the severity of concomitant CKD,we divided patients of the main group (CHF with CKD) into subgroups: group I – patients with GFR ≥ 60 ml/min/1, 73m2 (n=15), group II (n=49) with GFR=30-59 ml/min/1, 73m2,group III (n=8) with GFR<30 ml/min/1, 73m2. Xanthine oxidase activity and uric acid levels increased with the progression of renal dysfunction. Thus, they increased, respectively, from (3.96+0.74) iU / ml and (5.87+0.39) mg / dl (group I) to (10.41+3.58) iU/ml and (8.32+0.67) mg/dl (group III) (p<0.05 and p<0.001, respectively) (Table 2).

Table 2

Mean levels of uric acid and xanthine oxidase activity in CHF patients with CKD, depending on GFR

GFR, ml/min/1,73m^2	Uric acid mg/dl	Xanthine oxidase IU/ml
Group I GFR ≥ 60	5,87±0,39	3,96±0,74
Group II GFR = 59-30	8,12±0,32*	8,41±0,84**
Group III GFR < 30	8,32±0,67*^	10,41±3,58°^

Note. Reliability of the difference:

with group I - *p<0.001; * * p<0.01; °p<0.05;

between groups II and III - ^p>0.05.

The relationship between increased xanthine oxidase activity and impaired renal function is confirmed by the revealed significant negative correlation between xanthine oxidase activity and GFR (r = -0.5, p<0.05).

Different biological and pathophysiological significance of hyperuricemia is assumed in patients with and without renal dysfunction [12]. It is hypothesized that hyperuricemia without CKD is due to hyperproduction of uric acid in heart failure, while hyperuricemia in patients with CKD is largely associated with a decrease in renal urate excretion [3]. Therefore, hyperuricemia is associated with the development of adverse outcomes in patients with CHF without concomitant CKD.

In our study, it was found that in patients with CHF with concomitant CKD, as the functional class of CHF progresses, the left ventricular ejection fraction decreases, there is a significant increase in xanthine oxidase activity and uricemia. At the same time, the index of xanthine oxidase activity in patients with severe CHF (FC III according to NYHA, EF < 45%) and concomitant CKD was significantly higher than in patients with CHF without CKD.

In patients with CHF without concomitant CKD, the progression of heart failure was associated with an increase in serum uric acid levels, which has a negative impact on the clinical course and prognosis of the disease. This is confirmed by the data of studies that show a close relationship between uric acid and the severity of CHF, the risk of mortality and adverse outcomes [5; 7].

Some studies have found a relationship between uric acid levels and decreased glomerular filtration rate, but interpretation of these data is difficult due to the fact that CKD can lead to increased uricemia, just as hyperuricemia can cause and exacerbate CKD. Most studies show the role of hyperuricemia as an independent risk factor for the development and progression of CKD [6; 9]. However, when analyzing the progression of CKD in stages 3-4, most researchers do not find an independent relationship with uric acid levels [8; 11]. Therefore, it is assumed that uric acid is a marker of oxidative stress under the influence of xanthine oxidase, and not a mediator of the disease. This is confirmed by the data on the possibility of allopurinol to slow the progression of CKD [4].

In our study, in patients with CHF with concomitant CKD, as renal function decreased, there was a significant increase in xanthine oxidase activity, which proves a change in metabolism in patients with CHF with CKD towards the oxidase pathway of uric acid formation.

CONCLUSION.

Disorders of xanthine metabolism play a significant role in the progression of heart failure in patients with CHF with concomitant CKD. Thus, an increase in xanthine oxidase activity is associated with a deterioration in the clinical course of CHF (progression of the functional class), a decrease in the left ventricular ejection fraction and glomerular filtration rate.

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