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# The State of the System of Matrix Metalloproteinases and of their Tissue Inhibitors in Patients with Metabolic Syndrome

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**Abstract:** ***Metabolic syndrome (MS) is a disease with a complex aetiology, the underlying cause of which may include genetic predisposition, excessive calorie intake, low physical activity, older age, some disorders (atherosclerosis, polycystic kidney disease, liver cirrhosis, chronic renal failure, sepsis, trauma) and medications. There is evidence of adverse effects of steroids on the course of symptoms in patients with MS. The prevalence of MS is about 10-20%, with the disease mainly affecting people older than 30 years; further, it is more common in men, whereas in women the incidence of MS increases during menopause [1-5]. A dramatic role in the development of the disorder belongs to external factors that adversely affect glucose utilization in body tissues. These include sedentary lifestyle and excessive consumption of fat. It was shown by G.Reaven, who demonstrated that insulin resistance (IR) affects 25% of people with sedentary lifestyle.***

**Keywords:** metabolic syndrome, system of matrix metalloproteinases, myocardial remodelling, arterial hypertension.

Metabolic syndrome (MS) is a disease with a complex aetiology, the underlying cause of which may include genetic predisposition, excessive calorie intake, low physical activity, older age, some disorders (atherosclerosis, polycystic kidney disease, liver cirrhosis, chronic renal failure, sepsis, trauma) and medications. There is evidence of adverse effects of steroids on the course of symptoms in patients with MS. The prevalence of MS is about 10-20%, with the disease mainly affecting people older than 30 years; further, it is more common in men, whereas in women the incidence of MS increases during menopause [1-5]. A dramatic role in the development of the disorder belongs to external factors that adversely affect glucose utilization in body tissues. These include sedentary lifestyle and excessive consumption of fat. It was shown by G.Reaven, who demonstrated that insulin resistance (IR) affects 25% of people with sedentary lifestyle [4].

In the recent years, much attention has been paid to the role of extracellular matrix (EM) in the processes of geometric reorganization of cardiac muscle in people with cardiovascular system disorders. According to the literature, investigations of various substances that regulate the exchange of extracellular space components are of great interest. General insights into the system of matrix metalloproteinases (MMP) are mainly based on the results obtained in experimental studies in animals or human tissue culture; however, the mechanisms that provide the effect of these endopeptidases on human heart, still remain unclear [6−10].

Materials and Methods: We studied 76 patients with MS and 24 patients with arterial hypertension (AH) associated with obesity (OB) and insulin resistance (IR). The control group consisted of 20 apparently healthy volunteers. All examined patients underwent heart ultrasound with calculation of hemodynamic parameters, investigation of MMP-1 and tissue inhibitor of metalloproteinases (TIMP-1) system.

Results and discussion: we conducted a comparative analysis of the levels of proMMP-1 and TIMP-1 in the patients with MS and in the control. Thus, we found that in the total group of patients with MS, average levels of proMMP-1 and TIMP-1 exceeded those in the control group (3.49 ± 0.16 ng/ml, 397.0 ± 3.02 ng/ml and 1.49 ± 0.63 ng/ml, 364.6 ± 4.1 ng/ml, respectively, $p < 0.05$ for both).

To study the relationships between BP, pulse and mean BP and average levels of proMMP-1 and TIMP-1, we compared the abovementioned parameters in the groups of patients with four- and three-component MS (Table 1).

**Table 1:** Comparative analysis of proMMP−1 and TIMP− 1 activity in patients with MS vs. control (Mean±SD)

| Groups / Parameters | Control group | Patients with metabolic syndrome | |
|---|---|---|---|
| | | four-component MS | three-component MS |
| Number | 20 | 36 | 40 |
| CP (mm Hg) | 117.5±2.9 | 173.7±3.6^ | 166.7±3.2^ |
| DP (mm Hg) | 76.5±1.3 | 102.1±2.6^ | 100.8±1.9^ |
| PP (mm Hg.) | 48.2±3.2 | 72.3±3.3^ | 65.9±2.1* |
| meanBP (mm Hg.) | 75.5±1.5 | 137.5±7.6^ | 134.5±6.8^ |
| proMMP−1 (ng/ml) | 1.49±0.63 | 4.15±0.26*** | 3.13±0.19* |
| TIMP−1 (ng/ml) | 364.6±4.1 | 406.2±5.5* | 392.7±3.47* |

**Note**: * - statistically significant differences vs. the control group ($p < 0.05$),
** - statistically significant differences between the groups of patients ($p < 0.05$),
^ - statistically significant differences vs. the control group ($p < 0.001$).

As can be seen from Table 1, in patients with MS, all blood pressure (BP) parameters differed significantly from the respective values in the control group. In patients with 4-component MS significantly higher proMMP-1 levels (4.15 ± 0.26 ng/ml) were found, not only in comparison with the control group (1.49 ± 0.63 ng/ml, $p < 0.05$), but also in comparison with patients with 3-component MS, etc. (3.13 ± 0.19 ng/ml, $p < 0.05$). TIMP-1 in this group (406.2 ± 5.5 ng/ml) differed significantly only from the respective value in the control group (364.6 ± 4.1 ng/ml, $p < 0.05$). In patients with 3-component MS, average levels of proMMP-1 (3.13 ± 0.19 ng/ml) and TIMP-1 (392.7 ± 3.47 ng/ml) also exceeded the respective values in the control group ($p < 0.05$).

Table 2 shows similar results obtained for patients with AH associated with metabolic disorders. Thus, proMMP-1 in these patients was significantly higher than in the control group. In patients with AH+IR it was 2.95 ± 0.78 ng/ml, and in patients with AH+OB 3.43 ± 0.34 ng/ml. There was no statistically significant difference between these two subgroups, but there were significant differences between the average values of proMMP-1 level in patients with AH+IR and with 4-component MS (2.95 ± 0.78 ng/ml and 4.15 ± 0.2 ng/ml, respectively, p <0.05). TIMP-1 levels in patients with AH+IR and AH+OB were significantly higher than in the control, 389.3 ± 2.8 ng/ml and 391.7 ± 4.6 ng/ml, respectively, p <0.05.

**Table 2:** Comparative analysis of proMMP−1 and TIMP− 1 activity in patients with AH associated with IR and OB vs. Control group (Mean±SD)

| Groups / Parameters | Control group (n=20) | Groups of patients with AH+IR (n=12) | Groups of patients with AH+OB (n=12) |
|---|---|---|---|
| CP(mm Hg) | 117.5±2.9 | 162.8±9.07 | 159.2±8.07 |
| DP(mm Hg) | 76.5±1.3 | 92.14±6.8 | 97.9±3.4 |
| PP(mm Hg.) | 48.2±3.2 | 70.7±5.23 | 61.2±7.06 |
| meanBP(mm Hg.) | 75.5±1.5 | 119.1±7.6 | 115.8±6.8 |
| proMMP−1(ng/ml) | 1.49±0.63 | 2.95±0.78* | 3.43±0.34* |
| TIMP−1(ng/ml) | 364.6±4.1 | 389.3±2.8* | 391.7±4.6* |

**Note**: *− statistically significant differences vs. the control group (p<0.05).

The results of experimental studies conducted indicate that decreasing MMP-1 activity and increasing activity of TIMP-1 in plasma contribute to the development of pathological processes in the myocardium in form of its remodelling with subsequent left ventricle (LV) dysfunction. In this regard, we analysed proMMP-1 and TIMP-1 levels according to the type of LV remodelling (Table 3).

**Table 3:** Levels of proMMP−1 and TIMP−1, hemodynamic parameters and echocardiographic parameters of LV in patients with metabolic disorders according to the type of myocardial remodelling (Mean±SD)

| Groups / Parameters | NLVG (n=27) | CLVR (n=25) | CLVH (n=13) | ELVH (n=11) | CONTROL (n=20) |
|---|---|---|---|---|---|
| CP (mm Hg) | 169.1±4.4^ | 166.1±3.3^ | 181.2±5.15^ | 167.5±4.15^ | 117.5±2.9 |
| DP (mm Hg) | 102.1±2.5^ | 100.9±2.8^ | 101.2±2.21^ | 105.7±5.7^ | 76.5±1.3 |
| AH duration (years) | 11.02±1.07 | 12.02±1.5 | 13.5±2.37 | 13.1±2.88 | ———— |
| PP (mm Hg) | 67.2±2.9 | 65.2±2.7 | 80.6±4.01^ | 62.5±4.92 | 48.2±3.2 |
| TPVR | 2.91±0.18 | 3.07±0.17 | 3.6±0.32* | 2.27±0.1 | 2.71±0.2 |
| STPVR | 5.51±0.34 | 5.71±0.36 | 7.59±1.12* | 4.43±0.06 | 4.91±0.3 |
| EF (%) | 62.8±1.15 | 65.1±1.03 | 62.9±2.05 | 56.1±2.2* | 64.5±0.98 |
| LVMM (r) | 161.6±3.56* | 164.3±3.25* | 199.8±6.56^ | 224.8±10.6^ | 122.6±4.6 |
| LVMMi ($g/m^2$) | 85.0±1.8* | 87.8±1.9* | 106.9±4.46^ | 114.6±2.42^ | 77.02±2.7 |
| rLVPWT | 0.41±0.003 | 0.48±0.006* | 0.49±0.17* | 0.38±0.01 | 0.38±0.006 |
| rIVST | 0.41±0.003 | 0.49±0.005* | 0.51±0.02* | 0.39±0.01 | 0.39±0.006 |
| rLVWT | 0.4±0.003 | 0.49±0.006* | 0.5±0.02* | 0.38±0.02 | 0.39±0.011 |
| proMMP−1(ng/ml) | 2.43±0.15 | 3.31±0.1** | 5.33±0.29^ | 8.14±0.14^ | 1.49±0.63 |
| TIMP−1 (ng/ml) | 373.03±3.35 | 405.4±2.67** | 427.0±5.41^ | 453.02±9.4^ | 364.4±4.1 |

**Note**: *− statistically significant differences vs. the control group (p<0.05),
**− statistically significant differences vs. the control group (p<0.01),
^ − statistically significant differences vs. the control group (p<0.001)

As can be seen from Table 3, in all groups of patients systolic blood pressure (CP) and diastolic blood pressure (DP) were significantly increased as a result of AH which was found in all patients with MS.

When analysing each type of myocardial remodelling separately, we found that although in patients with normal geometry of LV (NLVG), average LV myocardial mass (LVMM) and LVMM index (LVMMi) (comprising 161.6 ± 3.56 g and 85.0 ± 1.8 $g/m^2$ p <0.05), were within the normal range (according to A.Ganau, 1992), but were statistically higher than the respective values observed in the control group. The group of patients with concentric LV remodelling (CLVR), along with increased average LVMM and LVMMi (164.3 ± 3.25 g and 87.8 ± 1.9 $g/m^2$, p <0.05), also had increased average values of the relative LV posterior wall thickness (rLVPWT), relative interventricular septum thickness (rIVST) and relative LV wall thickness (rLVWT) (0.48 ± 0.006, 0.49 ± 0.005, 0.49 ± 0.006, p <0.05). The most striking results were observed in patients with hypertrophic types of LV myocardial remodelling. Thus, in the group with concentric LV hypertrophy (CLVH) in comparison with the control group, a significant increase in pulse pressure (PP), total peripheral vascular resistance (TPVR) and specific total peripheral vascular resistance (STPVR) were observed (80.6 ± 4.01 mm Hg, (p <0.001);

3.05 ± 0.32, 7.05 ± 1.12 (p <0.05) and 48.2 ± 3.2 mm Hg., 2, 71 ± 0.2, 4.91 ± 0.3, respectively), as well as increased LVMM, LVMMi (199.8 ± 6.56 g, 106.9 ± 4.46 g/m$^2$ (p <0.001 for both) and rLVPWT, rIVST and rLVWT (0.49 ± 0.17, 0.51 ± 0.02, 0.5 ± 0.02, (p <0.05 for all). The group of patients with eccentric LV hypertrophy (ELVH) had maximum values of LVMM and LVMMi (224.8 ± 10.6 g and 114.6 ± 2.42 g/m2 (p <0.001) together with normal values of relative LV wall thickness and decreased ejection fraction (EF) (56.1 ± 2.1%).

Plasma levels of proMMP-1 and TIMP-1 in all groups exceeded the respective values in the control group and tended to increase in parallel with increasing LVMM. Thus, although no statistically significant differences were observed for the patients with NLVG (2.43 ± 0.15 ng/ml and 373.03 ± 3.35ng/ml) compared with the control (1.49 ± 0.63 ng/ml and 364.4 ± 4.1 ng/ml) (p> 0.05), the average values in this group of patients were slightly higher. In the group with CLVR, the differences in proMMP-1 and TIMP-1 (3.31 ± 0.1 ng/ml and 405.4 ± 2.67 ng/ml) reached statistical significance when compared with the control group (p <0.01). However, more exemplary results were obtained for patients with hypertrophic types of myocardial remodelling. Thus, average levels of proMMP-1 and TIMP-1 in the groups with CLVH and ELVH were maximal: 5.33 ± 0.29 ng/ml, 427.0 ± 5.41 ng/ml and 8.14 ± 0 14 ng/ml, 453.02 ± 9.4 ng/ml, respectively (p <0.001).

To further investigate the role of MMP-1/TIMP-1 system in the myocardium, we additionally analysed the following structural and functional characteristics of LV: end-systolic and diastolic dimensions and volumes and stroke volume (SV), stroke index (SI), cardiac output (CO), cardiac index (CI), depending on the particular type of heart muscle remodelling (Table. 4).

**Table 4:** Echocardiographic parameters of LV in patients with MS according to the type of myocardial remodelling (Mean±SD)

| Groups / Parameters | NLVG (n=27) | CLVR (n=25) | CLVH (n=13) | ELVH (n=11) | CONTROL (n=20) |
|---|---|---|---|---|---|
| SV (ml) | 81.1±2.7 | 71.2±2.49 | 72.1±4.97 | 102.0±8.9^ | 69.7±2.13 |
| SI (ml/m$^2$) | 42.9±1.57 | 39.3±1.5 | 39.1±3.07 | 51.4±2.27** | 37.9±1.6 |
| CO (l/min) | 6.52±0.28 | 5.8±0.22 | 6.34±0.5 | 7.41±0.27 | 6.43±0.54 |
| CI (l/m$^2$) | 3.45±0.15 | 3.19±0.15 | 3.44±0.31 | 3.78±0.09 | 3.14±0.19 |
| EDD (cm) | 5.19±0.05 | 4.75±0.06* | 4.86±0.13 | 6.01±0.32* | 5.15±0.08 |
| EDV (ml) | 130.1±3.01 | 105.9±3.15 | 112.7±6.95 | 186.1±24.7* | 127.7±4.54 |
| ESD (cm) | 3.36±0.06 | 2.97±0.05 | 3.13±0.11 | 4.21±0.37 | 3.32±0.06 |
| ESV (ml) | 46.6±2.1 | 34.6±1.66^ | 40.3±3.59 | 82.2±16.1 | 45.4±2.29 |
| EDDi (cm/m$^2$) | 2.76±0.03 | 2.56±0.04* | 2.58±0.1* | 2.98±0.08* | 2.73±0.04 |
| EDVi (ml/l$^2$) | 70.3±2.25 | 57.06±1.57 | 59.5±3.85 | 92.08±7.9^ | 70.3±4.05 |
| ESDi (cm/m$^2$) | 1.78±0.03 | 1.6±0.03* | 1.66±0.09 | 2.13±0.06^ | 1.76±0.03 |
| ESVi (ml/m$^2$) | 26.4±1.32 | 20.3±1.55 | 21.5±2.24 | 40.1±5.04^ | 26.3±1.8 |
| IMSi (kPa/mm) | 52.3±2.17 | 44.4±1.2 | 47.5±1.54 | 58.24±3.18^ | 47.8±3.3 |

**Note**: *− statistically significant differences vs. the control group (p<0.05), **− statistically significant differences vs. the control group (p<0.01), ^ − statistically significant differences vs. the control group (p<0.001).

No statistically significant differences were found between the control group and the group with NLVG. In regard to CLVR, there was a downward trend in all LV diameters and volumes (EDD – 4.75±0.06 cm, EDV − 105.9±3.15 ml, ESD − 2.97±0.05 cm, ESV − 34.6±1.66 ml) compared to the control group (EDD – 5.15±0.08, EDV – 127.7±4.54, ESD – 3.32±0.06 cm, ESV – 45.4±2.29 ml). As to ELVH, there was a contrasting pattern with mostly increased diameters and volumes (EDD − 6.01±0.32 cm, EDV – 186.1±24.7 ml, ESD – 4.21±0.37 ml, ESV – 82.2±16.1 ml), as well as the corresponding indexes (EDDi – 2.98±0.08 cm/m$^2$, EDVi – 92.08±7.9 ml/m$^2$, ESDi – 2.13±0.06 cm/m$^2$, ESVi – 40.1±5.04 ml/m$^2$), and statistically significantly elevated SV and SI (102.0±8.9 ml and 51.4±2.27 ml/m$^2$) compared to the control group (SV – 69.7±2.13 ml, SI – 37.9±1.6 ml/m$^2$). The group with CLVH had intermediate values between the highest and the lowest average values found in the groups with CLVR and ELVH, and differed significantly from the control group only in EDDi 2.58±0.1cm/m$^2$ (control – 2.73±0.04 cm/m$^2$).

## Conclusions

The obtained general characteristics of each type of LV myocardial remodelling are consistent with most experimental data from previous studies, which favour the preference of the cell transformation theory in the structural and geometric reorganization of LV. In patients with MS and AH associated with metabolic disorders, such as IR and OB, decreased plasma MMP-1 and increased TIMP-1 are accompanied by myocardial extracellular matrix remodelling with subsequent formation of left ventricular geometry of a certain type. In turn, the orientation of changes of distant fibrosis markers depends on the number and combination of MS features. In subjects with 4-component MS hypertrophic types of LV myocardial remodelling were seen more often (CLVH - 25% and ELVH - 25%) compared with the patients with 3-component MS (CLVH - 10% and ELVH - 5%). A distinct positive correlation between the levels of proMMP-1, TIMP-1 and LVMM and LVMMi indicators was demonstrated.