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Main Features of Impaired Fibronolytic and Protolytic Activity of Blood Plasma in Patients with Osteoarthritis Depending on Comorbidity

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Abstract
The objective of the research was to study the features of impaired fibrinolytic and proteolytic activity of blood plasma in patients with osteoarthritis (OA), depending on the age levels of comorbidity.
Material and methods. The age features of comorbid processes prevalence in 120 patients with OA were clinically studied, fibrinolytic and proteolytic activity of blood, levels of fibrinogen and C-reactive protein were also studied using biochemical methods.
Results. Comorbidity in patients with OA at the age under 50 was established low. The level of comorbidity increases to at the age of 51-60, after 60 years the phenomenon of comorbidity is more significant by frequency and severity. The diseases of the cardiovascular system dominated, including metabolic syndrome, diseases of the digestive tract and kidneys were less frequent. Cardiovascular risk (CVR) levels were high after the age of 50, gastrointestinal risk was less frequent. Fibrinolysis minor disorders were observed in patients with low comorbidity, namely fibrinolytic and proteolytic activity of blood as a part of high CVR progressively deteriorated and the level of fibrinogen and C-reactive protein increased in the patients at the age after 50 (especially 60) on the background of high comorbidity levels.
Conclusions. The level of comorbidity and CVR increased in patients with OA with age, increase in disease severity and duration. These phenomena were accompanied by progressive disorders in fibrinolytic and proteolytic activity of the blood, increased levels of fibrinogen and C-reactive protein as one of the components of CVR.

Keywords
osteoarthritis; comorbidity; fibrinolytic, proteolytic activity levels

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Problem statement and analysis of the recent research

Osteoarthritis (OA) is one of the most common age-dependent diseases which affect joints, with an inflammatory component characterized by high level of poly- and comorbidity [6, 9]. Among them the most common diseases include the diseases of the cardiovascular system and digestive tract causing high levels of cardiovascular and gastrointestinal risks, especially in connection with the use of antirheumatics [9, 11, 12]. Comorbidity and high cardiovascular risk (CVR) are now recognized as the main issues in modern medicine [11, 13, 14]. The leading role of comorbidity requires more thorough research and development of new strategic approaches to diagnosis, treatment and prevention of internal diseases [6, 10]. Academician V.M. Kovalenko considers the definition of pathogenic platforms for associated diseases to be relevant in the problem of comorbidity in order to influence actively their mechanisms and minimum use of drugs as a way to avoid polypharmacy [6]. Most of scientific researches on CVR predictors are based on the study of atherosclerotic vascular endothelial dysfunction phenomena, etc. [11, 14]. However, blood rheology including fibrinolytic and proteolytic activity of plasma plays an important role in the development of CV-events [2]. The causes of these disorders may include numerous comorbid processes inherent in patients with OA. In particular, such disorders were detected in patients with diabetes mellitus, hypothyroidism [1, 7], patients with COPD and asthma [5], patients with OA and gastropathy [4]. However, the problem of comorbidity in patients with OA has been insufficiently studied including changes in proteolytic and fibrinolytic properties of blood depending on the stage of OA and levels of comorbidity. The study of these interrelated processes will help to understand better the pathogenic relation and to improve treatment and prevention programs.

The objective of the research was to study the features of in fibrinolytic and proteolytic activity of the blood in patients with OA according to age levels of comorbidity.

1. Material and methods

Comprehensive examination of 120 patients with OA of I-III clinical-radiological stages in the exacerbation at the age of

37-76 years was conducted. Women dominated among the patients (97 - 80.8%). The diagnosis of OA was made under the Recommendations of EULAR (2010) and the order of MOH of Ukraine of 12.10.2006 #676 "Clinical Protocol for Provision of Medical Care to Patients with Osteoarthritis". Associated comorbidities were verified according to examinations and the relevant protocols supported by the Ministry of Health of Ukraine and by specialized professionals. Exclusion criteria included patients with secondary OA, patients with primary OA, myocardial infarction or stroke, severe lesions and functional disorders of internal organs, patients with cancer, oncohematological processes, active ulcer of gastroduodenal localization.

OA duration constituted 3-19 (12.1 $\pm$ 3.3) years, the duration of comorbidities constituted 2-7 (3.1 $\pm$ 0.62) years. All comorbid processes were in a state of unstable or stable remission (diabetes mellitus type II - a state of compensation). CVR level was determined by means of a calculator based on SCORE scale [4]. The level of comorbidity was defined by Charlson M.E et al. [15]. 30 apparently healthy individuals (AHI) of representative age (the control group) were also examined.

The fibrinolytic activity of blood plasma was studied according to azofibrin lysis (reagents from Danish Ltd, Lviv), followed by the further determination of the total fibrinolytic activity (TFA), non-enzymatic fibrinolytic activity (NFA) and enzymatic fibrinolytic activity (EFA) by calculation method (EFA = TFA-NFA). The research of blood proteolytic activity was conducted with the help of azoalbumin lysis (breakdown of low molecular weight proteins), azocasein (catalysis of high molecular weight proteins) and azocol (decrease in collagen) (reagents from Danish Ltd, Lviv) [2, 8].

Statistical data processing was conducted using the application software package: Microsoft Excel, Statistica 6.0. The arithmetic mean (M), mean error (m), the probability of differences between comparative groups was determined using Mann-Whitney test, Student's t-test. Correlation analysis was performed according to Pearson correlation coefficient. The differences were considered statistically significant at $p<0.05$.

2. Results and Discussion

Determination of the prevalence and a range of comorbidities in terms of age was the basis of the analysis. In this context, OA patients were divided into three groups: under the age of 50, at the age of 51-60 and over 60 (Table 1).

According to Table 1, comorbidities were detected in 4.75% of the patients at the age of 50. Other patients had 2-3 comorbid processes at the early stages. Usually, one of them was cardiovascular system (CVS) disease (hypertension stage 1), other disease occurred before OA or NSAID-induced gastropathy. OA was detected at I-II clinicoradiological stage.

All patients at the age of 51-60 had 4-6 comorbid diseases. Moreover, they were clinically more significant. The patients repeatedly consulted relevant specialists about their exacerbations and took medicines prescribed by them. A wider range of cardiovascular system diseases was observed as well as frequent cases of diabetes mellitus type 2, obesity, cholecystopancreato-hepatopathy and bowel diseases in the digestive system. Genitourinary system disorders, OA mainly stage II and less frequently of III radiologic stages became more frequent.

OA manifested in polyosteoarthrosis of stage I and mainly of stage II in patients older than 60. CVS comorbidities were not only more significant, but they had symptoms of chronic heart disease, metabolic syndrome and the range of digestive system diseases became broader. In general, the patients were diagnosed with 7-9 and more comorbidities. Combination of hypertension and ischemic heart disease, and gastropathy, cholecysto-pancreatopathy, steatohepatosis were more frequent leading to high levels of CVR and gastrointestinal risks (GIR), but CVR dominated. In this aspect, studying features of fibrinolytic and proteolytic activity of blood seemed to be important (Table 2).

No significant differences in proteolytic properties of blood were detected in patients with OA at the age under 50 (with low comorbid processes) in comparison with healthy individuals. However, the TFA was significantly reduced ($p<0.05$) due to EFA. The changes constituted 9.3% and 28.8% respectively. Reliable increase in albumin lysis was also noticed.

Reliable increase in the content of fibrinogen in the blood (35.03%) was noticed in patients with OA at the age of 51-60 (high comorbidity) while decrease in total fibrinolytic activity (by 22.7%), non-enzymatic (by 21.2%) and enzymatic fibrinolytic activity (by 25.43%) was observed. At the same time reliable increase in proteolysis of low-molecular (by azoalbumin lysis) and high-molecular (by asacasein lysis) weight proteins by 58.22% and 59.16% respectively, and also collagen activity of blood (by azocol lysis) by 64.06% was detected.

It was more significant in patients with OA with high comorbidity and at the age over 60 that in patients at the age of 51-60 years in terms of TFA and FFA, and lysis of low molecular weight proteins was reliably worse than in patients under the age of 60. It should be noted that patients with dominant CVS and MS lesions suffered from more severe disorders of fibrinolytic and proteolytic activity than in case of comorbid gastroenterological processes prevalence or those of kidneys. Moderate feedback between TFA and fibrinogen ($r = - 0.47$; $p<0.05$) and direct correlation between the values of albumin lysis and fibrinogen ($r = 0.41$; $p<0.05$), azocasein lysis of and fibrinogen ($r = 0.39$; $p<0.05$), azocol and fibrinogen ($r = 0.44$; $p<0.05$) was detected in the patients at the age of 51-60. These correlation principles increased but within moderate intensity, TFA and fibrinogen $r = -0.64$ ($p<0.01$); values of fibrinogen lysis and azoalbumin $r = 0.58$ ($p<0.01$); azocasein and fibrinogen lysis $r = 0.54$ ($p<0.01$); azocol and fibrinogen lysis $r = 0.61$ ($p<0.01$) in patients at the age over 60.

Therefore, patients with OA experienced decrease in the fibrinolytic properties of blood and increase in the proteolytic

Table 1. Age features of poly- and comorbid diseases in patients with osteoarthritis (n, %)

Nosology	Patients under 50 (n=15)	Patients at the age of 51-60 (n=49)	Patients over 60 (n=56)	Total (n=120)
Without comorbidity	6 (5.0%)	-	-	6 (5.0%)
Arterial hypertension stage 1	4 (26.67%)	14 (28.57%) 40.81%	12 (21.43%) 66.07%	30 (25.0%) 50.83%
Arterial hypertension stage 2	-	6 (12.24%)	25 (44.64%)	31 (25.83%)
IHD, moderate forms	2 (13.33%)	7 (14.28%)	21 (37.5%)	30 (25.0%)
IHD, severe forms (with heart failure, arrhythmia)	-	1 (2.04%)	4 (7.14%)	5 (4.17%)
Obesity stage 1	3 (20%)	15 (30.61%) 44.89%	15 (26.78%) 76.78%	33 (27.5%) 56.67%
Obesity stage 2-3	-	7 (14.28%)	28 (50.0%)	35 (29.17%)
Diabetes mellitus type 2	-	5 (10.20%)	13 (23.21%)	18 (15.0%)
Steatohepatosis	2 (13.33%)	17 (34.69%)	37 (66.07%)	56 (46.67%) 53.34%
Steatohepatitis	-	2 (4.08%)	6 (10.71%)	8 (6.67%)
Cerebral forms of atherosclerosis with dyscirculatory encephalopathy stages I-II	-	3 (6.12%)	11 (19.64%)	14 (11.67%)
Chronic cholecystitis	7 (46.67%)	24 (48.97%)	34 (60.71%)	65 (54.17%)
including calculous cholecystitis	-	5 (10.20%)	7 (12.5%)	12 (10.0%)
Gastritis, duodenitis	8 (53.33%)	26 (53.06%)	32 (57.14%)	64 (53.33%)
Peptic ulcer	-	3 (6.12%)	6 (10.71%)	9 (7.5%)
Chronic pancreatitis	-	6 (12.24%)	15 (26.78%)	21 (17.5%)
Enterocolonopathy	-	15 (30.61%)	29 (51.78%)	44 (36.67%)
COPD, bronchitis	1 (6.67%)	5 (10.20%)	7 (12.50%)	13 (10.83%)
Chronic renal disease stages I-II	-	6 (12.24%)	6 (10.71%)	12 (10.0%)
Chronic adnexitis	1 (6.67%)	7 (14.28%)	6 (10.71%)	14 (11.74%)
Chronic prostatitis or BPH	-	2 (4.08%)	3 (5.35%)	5 (4.17%)
ENT diseases	2 (13.33%)	4 (8.16%)	5 (8.93%)	11 (9.17%)
Eye diseases(cataract, glaucoma)	1 (6.67%)	3 (6.12%)	5 (8.93%)	9 (7.5%)
Skin diseases (dermatoses, mycoses)	1 (6.67%)	4 (8.16%)	6 (10.71%)	11 (9.17%)

processes along with the age growth of comorbidity. Osteoarthritis and almost all diagnosed comorbid processes are known to be characterized by non-specific effects of oxidative stress. Under these conditions partial breakdown of proteins in the form of their fragmentation or even denaturation in the tissues and blood occurs. These proteins are a substrate for intracellular proteases [2]. Increase in the proteolysis enzyme activity in the blood causes activation of the kinin-kallikrein, the renin-angiotensin-aldosterone system and complement, the development of inflammatory and destructive processes in the body.

Fibrinolytic system plays an important role in maintaining hemostasis providing normal blood flow in the vessels [2]. The weakening process of fibrinolysis and increase in fibrinogen level in the blood were found in the study group of patients, indicating increased ability of blood to possible microthrombosis, impaired microcirculation and tissue metabolism in all structures of the human body. The mech-

Table 2. Indicators of fibrinolytic and proteolytic activity of plasma levels of fibrinogen and C-reactive protein in the blood of patients with OA according to age comorbidity (M ± m, p)

Rates, units of measurement	Apparently healthy individuals, n=30	Patients with OA at the age under 50 (low comorbidity rate), n=15	Patients with OA at the age of 51-60 (high comorbidity rate), n=49	Patients with OA at the age over 60 (high comorbidity rate), n=56
Fibrinogen, g/l	3.54±0.32	3.78±0.36	4.78±0.33***	5.1±0.42***
Blood TFA, E440/ml/h	1.63±0.05	1.48±0.07*	1.26±0.06***	1.1±0.07***#
Blood NFA, E440/ml/h	1.04±0.04	1.06±0.05	0.82±0.06***	0.73±0.04***
Blood EFA, E440/ml/h	0.59±0.03	0.42±0.04*	0.44±0.03*	0.38±0.02*#
Lysis of low molecular weight proteins mmol/ azoalbumin/1 ml/h	2.92±0.12	3.06±0.17	4.62±0.16***	4.96±0.18***#
Lysis of high molecular weight proteins mmol /azocasein/1 ml/h	2.62±0.16	2.94±0.24	4.17±0.28***	4.56±0.22***
Lysis of collagen mmol/azocol/1ml/h	0.64±0.06	0.98±0.09*	1.05±0.07***	1.39±0.11***
C-reactive protein, mg	2.8±0.18	5.2±0.46*	6.6±0.43***	7.8±0.56*** #

Note.

* - the difference in the rates is reliable ($p<0.05$-0.001) compared to those in apparently healthy individuals;

** - the difference in the rates is reliable ($p<0.5$-0.01) compared to those in patients at the age under 50;

\# - the difference in the rates is reliable ($p<0.05$) compared to those in patients at the age of 51-60.

anism of disorders in fibrinolytic and proteolytic activity of blood in case of high level of comorbidity is probably very complex, universal and non-specific, especially in case of the cardiovascular system diseases prevalence. However, it is important that they are integral components of high cardiovascular risk in these patients. In a complex regimen of their treatment in the context of CVR prevention they should be kept in mind as the metabolic basis of a number of disorders and the means of metabolic and rheological correction should be used.

3. Conclusions

1. The comorbidity occurs in patients with osteoarthritis with age, increase in disease severity and duration mainly due to the cardiovascular system disorders, metabolic syndrome, digestive system diseases and increased levels of cardiovascular and gastrointestinal risks.

2. Age-increasing levels of comorbidity in patients with osteoarthritis are accompanied by significant progressive decrease in fibrinolytic properties of blood, increased levels of fibrinogen and increased blood proteolytic activity.

3. Disorders of proteolysis and fibrinolysis in the blood of this group of patients are one of the pathophysiological components of high cardiovascular risk and vascular-metabolic disorders in different tissues and organs. They should be taken into account in the implementation of preventive measures and as an addition to the used rheological means of metabolic action.

4. Prospects for further research

Different medication with vascular-metabolic-rheological properties is advisable to be tested to determine criteria and duration of its use in the treatment of patients with OA and high comorbidity.

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