ORIGINAL ARTICLE

THE ROLE OF LIPOPROTEIN (A) AND PREGNANCY ASSOCIATED PLASMA PROTEIN A IN DIAGNOSTICS CORONARY HEART DISEASE IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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ABSTRACT

The aim: To identify the significance of biomarkers characterizing the role of lipid disorders and the processes of destruction atherosclerotic plaque for the early diagnosis of CHD in patients with COPD.

Materials and methods: There were examined 153 patients, men aged 40-70 years, including 53 patients with COPD, 56 with a combination of COPD and CHD and 44 patients with stable CHD. The level of LP (a) and PAPP-A in the serum was determined by ELISA.

Results: There was increased level of LP (a) and PAPP-A in patients with CHD and with a combination of COPD and CHD. This increased level of LP (a) and PAPP-A was associated with the level of C-reactive protein. The mid level of LP (a) and PAPP-A in patients with COPD did not significantly differ from the reference values.

Conclusions: The increase level of lipoprotein (a) more than 18 mg/dl in patients with COPD may be regarded as a predictor of the development of CHD. The level PAPP-A more than 5 mIU/L in plasma of patients with COPD makes it possible to isolate the groups for CHD risk. The definition of LP (a) and PAPP-A in patients with COPD may contribute to the early diagnostics of coronary heart disease in the absence of its pronounced clinical manifestations.

KEY WORDS: comorbidity of COPD and CHD, lipoprotein (a) (LP (a)), pregnancy-associated plasma protein A (PAPP-A), C-reactive protein

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INTRODUCTION

Coronary heart disease (CHD) and chronic obstructive pulmonary disease (COPD) are among the leading diseases in the world that contributing to their frequent combination. According to J.A. Falk et al. [1] comorbidity of CHD and COPD is from 18.7% to 88.3% in morbidity structure of patients over 40 years old. The combination of COPD and CHD increases the chances of a fatal outcome [2,3,4,5] and leads to the changes of the clinical picture and difficulty in diagnosing CHD [6,7]. Stress tests, ECG, daily monitoring of ECG, echocardiography, myocardial scintigraphy have not a sufficient level of specificity and sensitivity in the diagnosis of myocardial ischemia in patients with COPD, which determines the need further improvement of diagnostic methods taking into account the pathogenetic mechanisms of the disease.

Numerous studies have revealed essential significance in the development of CHD such indicators of blood lipid spectrum as cholesterol low-density lipoproteins (LDL cholesterol), high-density lipoprotein (LDL cholesterol), apolipoprotein Al [8,9]. It has been shown that the risk of developing CHD continuously increases over the whole range values of serum cholesterol [10]. However, at the same time in clinical practice, there are quite often patients with severe forms of CHD, which have a significant part of coronary events occur at normal levels of LDL- cholesterol and HDL- cholesterol in the blood [11]. The results of epidemiological studies indicate that even after reaching the target level of LDL cholesterol, there remains a significant residual risk for which can answer other, less studied, factors, for example, lipoprotein (a) (LP (a)) [8,12,13,14]. LP (a) is actively involved in the formation and growth of atherosclerotic plaque, stimulating the movement of monocytes, the oxidation of LDL and the capture of oxidized LDL by macrophages and promotes the growth of smooth muscle cells. However, in some studies, the relationship of LP (a) with the occurrence of CHD and its complications has not been established [15,16]. A sufficient amount of works has been devoted to the study of the lipid profile in patients with CHD and COPD. But, researches of the lipid profile in patients with a combination of COPD and CHD are rare and ambiguous. And we did not find researches of LP (a) and PAPP-A in patients with combination of CHD and COPD.

It is known that vascular inflammation is the main factor contributing to the progression of the atherosclerosis from the stage of atheroma's formation to the development of destructive changes and formation of a thrombus in the lumen of the coronary artery [17,18,19]. Analysis of inflammatory reactions in the vascular wall showed that the elements of

the vascular immune response could not only trigger atherogenesis, but also modulate and control it [20]. In this regard, in recent years, great interest is caused by the detection in the blood of biochemical substances, the concentration of which reflects the activity of vascular inflammation and endogenous destruction in atherosclerotic plaques. It has been established that the activation of inflammation increased the proteolytic activity of macrophages with the participation of metalloproteinases, that leads to the decrease in the thickness and strength of the fibrous plaque cap that separates blood from the high-thrombogenic substances of the lipid core [21]. There are separate studies in which it was shown that the most promising marker of endogenous destruction of an atheroma can be zinc-containing matrix metalloproteinase, pregnancy associated plasma protein A (PAPP-A) [22,23]. PAPP-A is secreted by activated macrophages that are involved in the local vascular inflammatory process and thus contribute to the development of atherosclerotic lesions and damage of atheroma [24].

Researches of changes the diagnostic and practical significance level of PAPP-A in patients with CHD are not numerous. Most studies have found an increase PAPP-A in patients with unstable atherosclerotic plaques and/or with recent heart attack [25,26]. At the same time, patients with stable CHD more often have normal or slightly elevated PAPP-A level. In this regard, it has been suggested that PAPP-A can be a perspective marker of atherosclerotic plaque damage, it's instability and serve as a predictor of an unfavorable prognosis of patients with CHD [23,27]. Nonetheless, some studies noted that PAPP-A levels can be increased in patients with stable CHD, and elevated concentrations of PAPP-A are associated with adverse heart events [28]. It was noted that PAPP-A levels in the blood with stable CHD were higher in patients with multi-vascular lesion and with complicated stenosis in the coronary arteries, according to coronary angiography, as well as with significant depression of the ST segment, according to the ECG. That is why we may assume that PAPP-A can play the role of an indicator of the presence of hemodynamically significant stenoses in the coronary arteries in patients with stable CHD [29].

A. Elesber et al. [30] found that in patients with stable CHD, the prognostic value of PAPP-A did not depend on the presence of traditional risk factors for coronary atherosclerosis or the magnitude of the ejection fraction, while the relationship between PAPP-A and the development of death or repeated acute coronary syndrome was significant even after correction existing atherosclerosis risk factors. This provided grounds for considering PAPP-A as an independent and informative marker of the risk of an atherosclerotic plaque damage [31]. Data about the study of the PAPP-A level in patients with a combination of CHD and COPD are absent.

Thus, the literature suggests that the combination of COPD and CHD has a high prevalence, but the main causes, mechanisms of occurrence and relationship of these pathologies, diagnostic and prognostic approaches require further study.

THE AIM

To identify the significance of biomarkers characterizing the role of lipid disorders and the processes of atherosclerotic plaque destruction for the early diagnosis of CHD in patients with COPD.

MATERIALS AND METHODS

There were examined 153 men aged 40–70 years, including 53 patients with COPD, 56 with a combination of COPD and CHD and 44 patients with stable CHD. The control group consisted of 30 practically healthy individuals. The verification of the COPD diagnosis and severity of patients was based on the recommendations of WHO experts – GOLD (2018) [32]. The diagnosis of stable CHD was established in accordance with European recommendations (2013) [33].

The level of LP (a) was determined using enzyme-linked immunosorbent assay (ELISA) – Cormay reagent kit, Diagnostic Automation, Inc., Poland. The content of PAPP-A in serum was determined by enzyme immunoassay using IBL-INTERNATIONAL PAPP-A US (ultra sensitive) Enzyme Immunoassay Kit (Germany).

Statistical processing of the results was performed using the "Statistica" v.10.0 and «Microsoft Office Excel 2010». The reliability of the results was assessed using Student's t-test; discrepancies at $p<0,05$ were considered significant. The relationship of signs was determined using Pearson and Spearman correlation coefficients (r). The Mann-Whitney test was used to compare averages means in two independent groups.

RESULTS

The level of LP (a) in the control group fluctuated in a significant range – from 6,78 to 20,4 mg/dL, averaging 14,37 ± 2,19 mg/dL. For the cut-off point from the standards, the LP (a) level was adopted – 15,50 mg/dL. The mean level of LP (a) was slightly elevated in 7 (13,20%) of 53 patients with COPD without CHD, averaged 18,53 ± 2,73 mg/dl ($p>0,05$). The increase in the level of LP (a) occurred in 23 (52,27%) of 44 patients with CHD, in the group with comorbid pathology in 34 of 56 patients – 60,71% ($p <0,05$). The average level of LP (a) was elevated both in the group of CHD patients (40,38 ± 1,84 mg/dl) and to a slightly greater extent in patients with cardiorespiratory pathology (46,55 ± 2,09 mg/dl) ($p <0,05$). Certain borderline LP (a) levels in the compared groups [34] were 15,91 mg/dl for the group of patients with isolated COPD, 27,96 mg/dl for patients with CHD and 30,56 mg/dl for patients with CHD and COPD.

The degree of change in the level of LP (a) did not depend on the severity of COPD, but was associated with the severity of CHD, both in monopathology CHD and in its combination with COPD. The level of LP (a) in patients with functional class III of angina pectoris was significantly higher than in patients with functional class II (respectively 43,56±1,88 versus 37,84±1,12 mg/dL in patients

with CHD and 48,65±2,14 versus 40,24±2,39 mg/dl in patients with a combination of COPD and CHD, p<0,05). An elevated level of LP (a) may increase the risk of cardiovascular disease due to the potentiation of atherogenesis as a result of the accumulation of LP (a) in the intima and prothrombotic effects of apoprotein Apo (A), which has a structural similarity to plasminogen molecule, but does not have fibrinolytic activity [35]. This circumstance allows us to consider the LP (a) as a marker of early and severe forms of CHD, independent of other risk factors, as indicated by other researchers [14,36]. The combination of elevated concentrations of LP (a) and other adverse risk factors (smoking, obesity, physical inactivity) or associated diseases, including COPD, further increases the risk of CHD [37]. It can be assumed that the presence of CHD in patients with COPD is decisive in the overproduction of LP (a) in comorbid pathology, and the combination of COPD + CHD is more unfavorable in relation to the development and severity of proatherogenic disorders of lipid metabolism, which may indicate the syndrome of mutual complication of diseases.

The level of PAPP-A in the control group was 3,12±0,42 mIU/L. In patients with stable CHD, the level of PAPP-A was moderate, but well above the control group (5,61±0,23 mIU/L, p<0,05). The degree of change in the level of PAPP-A in patients with COPD was not significant (4,03±0,32 mIU/L, p>0,05). The combination of CHD and COPD showed a slightly higher degree of increase in PAPP-A compared with the group of CHD patients without COPD (6,34±0,26 mIU/L, p<0,05). Boundary values of PAPP-A for the group of patients with COPD is 3,67 mIU/L, for patients with CHD – 4,56 mIU/L, for patients with a combination of COPD and CHD – 4,89 mIU/L. The sensitivity of PAPP-A determination for the diagnosis of CHD in patients with COPD is 79%, specificity – 72%.

There was a tendency to increase the level of PAPP-A with increasing functional class (FC) of stenocardia in patients with CHD without COPD: in patients with FC II, the content of PAPP-A was 4,98±0,28 mIU/L, and with FC III – 6,28±0,21 mIU/L (p<0,05). When combined CHD and COPD, the association of PAPP-A with severity of CHD was more pronounced: in patients with FC II, PAPP-A was 5,38±0,19 mIU/l; with FC III – 6,91±0,21 mIU/l (p<0,01).

DISCUSSION

It can be assumed that the enhancement of local inflammation in the bronchi and pulmonary parenchyma has a systemic effect and contributes not only to the progression of COPD, but also to the activation of vascular inflammation, the development and progression of atherosclerosis, followed by destabilization of the atherosclerotic plaque [38,39]. This may be indicated by the presence of a correlation between the PAPP-A content and the level of C-reactive protein in the blood, determined by a highly sensitive method in patients with a combination of COPD and CHD (r=0,41; p<0,05). No convincing correlation was found between the level of PAPP-A with age (r=0,18), body mass index (r=0,17), LDL cholesterol level (r=0,20; p>0,05), blood pressure value (r=0,22; p>0,05). A moderate feedback was observed between the levels of PAPP-A and HDL cholesterol, which can be explained by the presence of the anti-inflammatory effect of HDL (r=-0,32; p<0,05). There is evidence that healthy people with HDL are characterized by the ability to inhibit the chemotaxis of monocytes, and their anti-inflammatory effect is 0.38, while people with CHD have a pro-inflammatory effect with an index equal to 1.38 [40]. An association has been established between the levels of LP (a) and C-reactive protein, which may indicate the potentiating effect of LP (a) on the process of nonspecific inflammation in the vascular wall in patients with CHD. Since the content of LP (a) in the blood is a genetically determined individual trait of the patient and, having reached stable values by 2 years, remains constant throughout life [41], its high level associated with the induction of inflammation can be considered a criterion of severe forms of CHD or it's exacerbations, including when combined with COPD.

CONCLUSIONS

The study confirmed the importance of introducing into practice methods for determining new independent risk factors for the occurrence and progression of CHD in patients with COPD – levels of LP (a) and PAPP-A. An increase in LP (a) level more than 18 mg/dL can be considered in patients with COPD as a possible predictor of CHD, and its increase in excess of 30 mg/dL is a reliable criterion for CHD, indicating a hereditary predisposition to early development of coronary atherosclerosis. An elevated level of LP (a) is associated with more severe forms of CHD in patients with a stable course of CHD, both in the monopathology group and in combination with COPD.

Detection of elevated level of PAPP-A (more than 5 mIU/l) in the blood plasma of patients with COPD makes it possible to isolate risk groups for CHD even in the absence of its pronounced clinical manifestations. Increased PAPP-A levels in the blood plasma of CHD patients and with a combination of COPD and CHD are not associated with the generally accepted risk factors of CHD in patients, but correlate reliably with plasma concentration of CRP and LP(a) level, which may indicate an association of inflammation and destruction in the atherosclerotic process, its progression and the possible development of complications.

Determining the concentration of PAPP-A in the blood of patients with COPD may be an important laboratory marker of CHD. Increased plasma PAPP-A levels of more than 5 mIU/L in patients CHD and CHD in combination with COPD should be regarded as an indicator of damage an atherosclerotic plaque, a potential biomarker of its instability, and therefore, as a predictor of cardiovascular complications. The combination of COPD and CHD is characterized by more pronounced changes in the level of PAPPA-A and LP (a), which characterizes the mutual influence of these diseases.

There is a need for epidemiological studies to clarify the diagnostic and prognostic significance of PAPP-A and LP (a) in asymptomatic subjects and in subjects with documented CHD with cardiorespiratory comorbidity.

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