UDC 616-004.6
DOI: 10.15587/2519-4798.2021.246598

THE RELATION OF ATHEROSCLEROTIC LESIONS OF BCA AGAINST THE BACKGROUND OF COPD IN PATIENTS AGED 40-60 YEARS. REVIEW OF THE LITERATURE AND RETROSPECTIVE ANALYSIS

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The aim: *to determine the possible relationship between chronic obstructive pulmonary disease and the presence of atherosclerosis of the brachiocephalic vessels in persons aged 40–60 years for the possibility of early prevention of cardiovascular events.*
Materials and methods: *to do this, we reviewed articles using open sources such as PubMED, Medscape and Cochrane library, highlighting the relationship between the development of atherosclerosis and the presence and severity of COPD. Also, based on the University Clinic of ONMedU and Military Clinical Center of the Southern Region, a retrospective analysis of patients with an inconclusively confirmed diagnosis of COPD and conducted biochemical blood tests was carried out in order to study changes in the lipid profile and the presence of BCS in these patients.*
Result: *In the course of a retrospective analysis of patients, a relationship was found between the presence of BCA atherosclerosis and the presence of COPD, and based on the literature data, a parallel was drawn between changes in the lipid profile in patients with COPD. But, in view of the insufficient number of patients, this topic requires additional research.*
Conclusions: *thus, based on the obtained data, it can be concluded that there is a connection between the presence of COPD, changes in the lipid profile, and the presence of BCA atherosclerosis. This connection can become one of the key mechanisms of early diagnosis of BCA atherosclerosis*
Keywords: *atherosclerosis, chronic obstructive pulmonary disease, chronic inflammation, matrix metalloproteinases, lipid profile, duplex scanning, sirutins*

How to cite:
Andrusyshyna, I., Batashova-Halinska, V., Horbenko, T., Kholopov, L. (2021). The relation of atherosclerotic lesions of BCA against the background of COPD in patients aged 40–60 years. Review of the literature and retrospective analysis. ScienceRise: Medical Science, 6 (45), 10–14. doi: http://doi.org/10.15587/2519-4798.2021.246598

1. Introduction

Atherosclerosis is a thickening and loss of elasticity of the arterial walls that occurs with the formation of atherosclerotic plaques inside the arterial intima [1].

In Ukraine, mortality from atherosclerosis is 3.2 % of all deaths [2].

Chronic obstructive pulmonary disease (COPD) is described as an incurable multisystem inflammatory disease defined by an airflow obstruction that is irreversible or partially reversible. Globally, COPD is the third leading cause of death with more than 3 million deaths per year, stroke – 2nd, killing more than 6 million per year [3]. During the disease, there are systemic consequences and some comorbidities (for example, cardiovascular disease, skeletal muscle dysfunction, bronchial malignancies, metabolic syndrome, diabetes), bronchoectasis, infections, impaired cognitive function, and depression. Clinical and epidemiological observations show that patients with COPD are more susceptible to acute cardiovascular events [4, 5] and about 30 % die from cardiovascular diseases [6, 7].

The relationship between COPD and atherosclerosis has been studied over the years. Many joint factors in the onset of these diseases have been identified.

The aim of this work is to determine the possible connection between chronic obstructive pulmonary disease and the presence of atherosclerosis of the brachiocephalic vessels in persons aged 40–60 years for the possibility of early prevention of cardiovascular events.

2. Materials and methods

Quite a lot of studies have been conducted and published on the relationship between the development of atherosclerosis and chronic inflammation, and we referred to such studies during the review of the literature. The articles were mostly taken from open sources like PubMED.

3. Result

Research was conducted of the association of sirutins with the progression of atherosclerosis in patients with COPD [8].

Sirtuins (Silent Information Regulator 2 proteins, SIR2) are a family of evolutionarily conserved NAD-dependent proteins with deacetylase or ADP-ribosyltransferase activity.

As you know, the chronic state of the inflammatory process is facilitated by the production of several pro-inflammatory cytokines, which increase in the serum and secretions of patients with cardiovascular diseases and COPD. Among them, C-reactive protein (CRP), fibrinogen, IL-1β, TNFα, MCP-1, IL-8, and IL-6 have been investigated as the most associated with disease progression and exacerbation. IL-β and TNFα appear to be the main stimuli that activate macrophages and transcription factors that play an important role in the synthesis of other pro-inflammatory cytokines and involved chemokines.

Biomarkers associated with COPD include markers of systemic inflammation (CRP and fibrinogen) and indicators of disease activity (airway neutrophils and desmosin), which are also associated with increased vascular risk and atherogenesis. CRP was the first biomarker to be investigated in COPD.

An additional potential biomarker in COPD is fibrinogen, an acute phase plasma protein. Many studies have shown that blood fibrinogen levels are higher in people with COPD compared to healthy controls, regardless of current smoking status. An inverse relationship between fibrinogen levels and FEV1 has been reported in both healthy individuals and patients with COPD.

Since atherosclerosis is considered a disease of aging, age can be considered an independent risk factor for the development of atherosclerosis. Atherosclerosis is also associated with premature biological aging. A family of enzymes consisting of nicotinamide adenine dinucleotide (NAD) + -dependent histone protein deacetylases) called sirtuins have been identified as major regulators of life expectancy and health. Sirtuins also play an important role in vascular biology and may regulate aspects of age-related atherosclerosis [8].

Sibel Gunay, Muzaffer Sariaydin and Akif Achay in 2016 [9] investigated the relationship between plasma levels of lipid parameters and indicators of atherogenicity on the development of atherosclerosis in patients with COPD in the age group 64.0±8.7 years.

The study found that atherogenic lipid profiles and atherogenic indices (plasma atherogenicity index, atherogenic coefficient and cardiogenic risk ratio), which were calculated based on some ratios of serum cholesterol levels, were higher in patients with COPD than in healthy people.

Another finding is the correlation of these indicators of atherogenity with the level of airflow obstruction (e.g., FEV1) in high-risk COPD patients.

Serum C-reactive protein levels have been recorded as an inflammatory marker and indicator of disease activity in subjects with COPD. In addition, higher levels of C-reactive protein have been found to be associated with a higher risk of cardiovascular disease and atherogenesis. It was also found that serum triglycerides and all atherogenic indices were significantly higher, and serum high density lipoprotein levels were significantly lower in subjects with stable COPD than in control subjects. Also, these lipid levels and atherogenic indices did not differ in the groups with lower and higher risk of exacerbation [9].

M. Kraen, U. Neal and G. Engström in 2019 [10] studied the relationship of matrix metalloproteinases in patients with COPD in the age group 58–66 years, as a predictor of atherosclerosis, but with particular attention to smoking.

Matrix metalloproteinases (MMPs) are known biomarkers of atherosclerosis. MMPs are also involved in the pathophysiological processes underlying chronic obstructive pulmonary disease (COPD).

The last study group consisted of 417 participants who were subsequently divided into 4 groups based on the presence or absence of COPD or carotid plaque. Group I (n=157, no plaque and no COPD), Group II (n=136, plaque but no COPD), Group III (n=43, COPD but no plaque) and group IV (n=81, plaque and COPD). Of the 124 patients who could be diagnosed with COPD, the majority were in the mild stage of the disease.

It was found that all serum MMP levels except MMP-10 were significantly increased in the group; they found that all serum MMP levels except MMP-10 were significantly increased in group IV studied.

MMP-7 and -12 were also elevated in plaque subjects, while MMP-1 was elevated in groups II-IV. Correlation analysis showed a positive correlation with tobacco consumption and all MMPs, as well as with age for MMP-3, -7, and -12.

MMP-7 and -12 were also elevated in plaque subjects, while MMP-1 was elevated in groups II-IV. Correlation analysis showed a positive correlation with tobacco consumption and all MMPs, as well as with age for MMP-3, -7, and -12. As a result of this study, it was found that only MMP-1 and MMP-12 made a significant contribution to this model with odds ratios of 1.64 and 1.60, respectively.

As a conclusion from this study, it can be inferred that the levels of MMP-1, -7, -10 and -12 in serum depend on the current smoking, and the levels of MMP-1, -3, -7 and -12 are increased in subjects with COPD and carotid plaques in the early stages of the disease. These associations remain significant for MMP-1 and-12 after adjustment for traditional risk factors and smoking habits [10].

Based on the fact that atherosclerosis and COPD have some points of contact in the mechanisms of pathogenesis, clinical studies of groups of patients were carried out in order to confirm the assumptions of comorbidity.

Also, a prospective cross-sectional study on the relationship of the presence of peripheral arterial disease in patients with COPD. The examined patients with COPD had a high prevalence of asymptomatic peripheral arterial disease. Abnormal results were associated with a higher prevalence of cardiovascular risk factors and more severe lung disease [11].

And a clinical study on the association of atherosclerosis with COPD in smokers. Studies have shown that the prevalence of carotid atherosclerosis in COPD is higher than in smokers from the control group or former smokers, but the differences appear to be related to

common risk factors. No evidence was found for an increased risk of atherosclerosis associated with exacerbations of COPD or exacerbation-like events [12].

Also, there was conducted a "reverse" study for the presence of COPD in patients with atherosclerosis in the age group 68.9–72.4 years. After diagnosis of brain and / or peripheral arterial disease by duplex sonography, 166 consecutive patients underwent body plethysmography with capillary blood gas analysis. As a result, it was revealed that COPD is widespread in patients with atherosclerotic arterial disease and a higher partial pressure of carbon dioxide (36.8±7.5 versus 34.4±4.4 mm Hg, P 0.05) according to compared to people without COPD. The presence of COPD has been associated with a predominance of diabetes mellitus, systemic neutrophilic inflammation associated with interleukin-8, and anemia [13].

Similar study on the relationship between the presence of a patients aged 63±7 with frequent exacerbations of COPD, and signs of atherosclerosis. The result of this study is to demonstrate that exacerbation phenotype versus non-exacerbation almost threefold increases the risk of subclinical carotid atherosclerosis after adjusting for the severity of COPD and cardiovascular disease. In addition, the severity of COPD was higher in the group with frequent exacerbations andalso in this group there was a trend towards higher values of cardiovascular risk.

It is known that patients with a large number and severity of exacerbations have a high mortality rate and global cardiovascular disease [14, 15]. Lee and others associated the severity of COPD with global cardiovascular risk (Framingham) [16] finding that adding global cardiovascular risk to FEV1 improves mortality prognosis in patients with COPD [17]. Several mechanisms could potentially explain the association between exacerbation and risk of cardiovascular disease; among others, an inflammatory systemic response caused by a viral or bacterial infection, hypoxemia during episodes, more β2-agonist prescription and discontinuation of β2-blockers. Oral corticosteroids are also associated with an increased risk of acute myocardial infarction.

Also, the researchers concluded that the presence of subclinical atherosclerosis, measured by the thickness of the intima – carotid artery media is independently associated with exacerbation phenotype after adjustment for COPD severity as measured by the BODE index [18] and global cardiovascular diseases. frequent risk, including COPDCoRi [19]. These differences are intensifying in younger patients [20].

Moreover, a massive clinical study was conducted to assess the risk of atherosclerosis in patients with COPD, predominantly over 60 years of age.

During the study, a higher level of C-reactive protein in the blood serum was found in patients with COPD compared with the control group. Serum low-density lipoprotein cholesterol, atherogenic indices such as cardiogenic risk coefficient and atherogenic coefficient were significantly higher, and serum high-density lipoprotein levels were significantly lower in subjects with COPD compared to controls. The results of this study also show that atherogenic lipid profiles and atherogenic indices (cardiogenic risk coefficient and atherogenic coefficient) were significantly increased in patients with COPD than in the control group. It was also found that the correlation of CRP with atherogenic indices was significantly positive for the ratio of cardiogenic risk and atherogenic coefficient only in patients with a low risk of COPD. No correlation was observed in high-risk COPD patients. A significant negative correlation was also observed with FVC and CRP in low-risk COPD cases.

It is also traditionally believed that dyslipidemia may be one of the most important risk factors for the development of cardiovascular disease. Elevated LDL cholesterol and lowered HDL cholesterol indicate an atherogenic lipid profile [21].

A similar study was conducted by Tomonori Sugiura, Yasuaki Dohi and Yasuyuki Takagi in 2020, which included a study of the relationship between subclinical atherosclerosis and lung function in men with an average age of 45 years. Multivariate regression analysis showed that the ankle-brachial index (ABI) was positively associated with the predicted % FVC and FEV1 % – after adjusting for factors including smoking intensity and cardio-ankle vascular index (CAVI) and carotid intimal medial thickness (CIMT). As a conclusion, participants with chronic obstructive pulmonary disease had a decrease in ankle-brachial index and an increase in cardio-ankle vascular index or carotid intima-media thickness compared to participants without COPD, and participants with carotid plaque had lower pulmonary function than participants without a plaque. Decreased FEV1 / FVC was an independent determinant of carotid plaque, and a decrease in ABI was an independent determinant of COPD [22].

Analyzing the above, in most studies in patients with COPD, atherosclerosis of one or another localization was found. The relationship between atherosclerosis and COPD was revealed at the level of the pathogenesis mechanism. However, the severity of atherosclerosis did not depend on the severity of COPD and the presence of exacerbations. Also, the presence of these plaques was associated more with age than with the fact of the presence of COPD.

The review also demonstrates that the mechanism of systemic inflammation in COPD and the development of atherosclerosis can be the same. In this case, COPD can be considered a full-fledged risk factor for the development of atherosclerosis. But given the weak dependence of the severity of COPD and the presence and severity of progression of atherosclerosis, it is difficult to say how the development of atherosclerosis in patients with COPD can be corrected.

Alternatively, it is possible to suggest the introduction of a screening study for patients with COPD for the presence of markers of predictors of atherosclerosis or a duplex scan to directly identify the already existing atherosclerosis.

Considering that we did not find enough data on the relationship between COPD and BCA atherosclerosis in the 40–60 age group, we conducted a retrospective analysis of patients with COPD in the 40–60 age group. All patients underwent examination and treatment at the bases of the University Clinic of the Odessa National Medical University and the Military Medical Clinical Center of the Southern Region.

In these patients, the diagnosis of COPD was made on the basis of computer spirometry data, with the

post-dilation Tiffno index less than 0.7 and a decrease in FEV1 below 80 from the due value.

The presence of BCS atherosclerosis was determined by two methods: duplex scanning of BCS and transcranial dopplerography. The diagnosis of atherosclerosis was made in the presence of atherosclerotic plaques or IMF thickening of more than 0.8 mm. Thus, 8 patients aged 40-60 years were identified, in whom the diagnosis of COPD was instrumentally confirmed and at the same time various stages of BCA atherosclerosis were identified. Of these, 4 showed signs of IMC thickening and the presence of plaques.

3 had only the presence of atherosclerotic plaques.

And in 1 patient there were no changes in the BCA.

Of these, 1 patient had grade I COPD, 6 were diagnosed with grade III COPD, and 1 patient had grade IV COPD. Seven had changes in IMC and plaques of different sizes. One patient had no pathological changes in the

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brachiocephalic vessels, while this patient has an established diagnosis – Chronic obstructive pulmonary disease, degree of obstruction IV, clinical group D.

Given the small sample, which does not make it possible to reliably analyze the data, and also, based on the literature data regarding the relationship between changes in the lipid profile (an increase in the level of low-density lipoproteins and total cholesterol and fractions, B-lipoproteins and triglycerides, which are a risk factor for the development of atherosclerosis) a retrospective study was carried out for the presence of changes in the lipid profile in patients with COPD. We identified 23 patients in whom lipid profile changes were examined (Tab. 1).

Thus, an increase or approach to the upper limit of the norm for most of the lipid profile was revealed, especially in the group of patients with COPD GOLD IV, which is a direct risk factor for the development of atherosclerosis

Table 1

Indicators of lipid profile

COPD/lipid profile	Total cholesterol (up to 5.2)	HDL (0.9–1.9)	LDL (1.81–4.14)	Triglycerides (up to 1.7)	B-lipoproteins (35–55)
GOLD I	5.42±0.46	1.24±0.12	3.576±0.37	1.33±0.3	53.2±8.0
GOLD II	4.901±0.35	1.2±0.12	3.16±0.4	1.55±0.36	49.4±5.5
GOLD III	6.245±0.46	1.1±0.2	4.35±0.35	1.85±0.5	60.25±13.4
GOLD IV	–	–	–	–	–

4. Conclusion

Of the eight patients with COPD, only one had no atherosclerotic changes in the BCS, while when analyzing the lipid profile, we revealed changes in the direction of an increase in the lipid profile of patients with COPD. Given the large amount of literature data on the close relationship of atherosclerosis and COPD and the small number of studies in patients in the 40–60 age group, such studies are of great interest in younger patients. Early detection and prevention of COPD can help prevent the development of atherosclerotic changes. However, the data we have obtained require further research.

Conflict of interests

The authors declare that they have no conflict of interests.

Funding

The study was performed without financial support.

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Received date 05.08.2021
Accepted date 21.09.2021
Published date 30.11.2021

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