Медицинская иммунология
2021, Т. 23, № 1,
стр. 157-162

Краткие сообщения
Short communications

Medical Immunology (Russia)/
Meditsinskaya Immunologiya
2021, Vol. 23, № 1, pp. 157-162

СОСТАВ ПОЛИНЕНАСЫЩЕННЫХ ЖИРНЫХ КИСЛОТ МЕМБРАН ЛЕЙКОЦИТОВ У ПАЦИЕНТОВ С ХРОНИЧЕСКОЙ ОБСТРУКТИВНОЙ БОЛЕЗНЬЮ ЛЕГКИХ

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Резюме. Цель исследования – анализ состава n-3 и n-6 полиненасыщенных жирных кислот (ПНЖК) цитомембран лейкоцитов крови при хронической обструктивной болезни легких (ХОБЛ) легкой и средней степени тяжести; установление роли нарушения состава ПНЖК в мембране клеток иммунной системы в прогрессировании ХОБЛ. В исследовании приняли участие 110 пациентов с легкой (60 человек) и средней степенью тяжести ХОБЛ (50 человек) (средний возраст 57,5±4,8 лет). Диагноз ХОБЛ выставлен в соответствии с Глобальной инициативой по хронической обструктивной болезни легких (GOLD-2017). Контрольную группу составили 32 практически здоровых некурящих добровольца с нормальной функцией легких (средний возраст 42,0±3,4 лет). Иммунологическое исследование включало проточно-цитометрическое определение субпопуляций иммунных клеток крови (Т-лимфоцитов ($CD3^+$), Т-хелперных клеток ($CD4^+$), цитотоксических Т-лимфоцитов ($CD8^+$) и В-клеток ($CD19^+$) (Becton Dickinson, США). Лейкоциты периферической крови выделялись на градиенте фиколл-верографина. Липиды из мембран лейкоцитов экстрагировались смесью хлороформ–метанол, 1:2 (по объему). Метиловые эфиры жирных кислот мембран лейкоцитов анализировали с помощью газожидкостной хроматографии “Shimadzu GC-2010” (Япония). При анализе профиля полиненасыщенных жирных кислот лейкоцитарных мембран у больных ХОБЛ выявлена низкая концентрация эссенциальной линолевой кислоты (18:2n-6) независимо от тяжести заболевания. Содержание длинноцепочечных n-6 ПНЖК, таких как дигомо-γ-линоленовой кислоты (20:3n-6), арахидоновой кислоты (20:4n-6) и докозатетраеновой кислоты (22:4n-6) были повышены у пациентов с ХОБЛ по сравнению с контрольной группой. Концентрация описанных выше n-6 ПНЖК в лейкоцитарных мембранах была увеличена у пациентов с ХОБЛ средней степени тяжести по сравнению с пациентами с легкой формой ХОБЛ. Выявлен значительный дефицит физиологически важной n-3 ПНЖК – эйкозапентаеновой кислоты (20:5n-3) в лейкоцитарной мембране у пациентов с ХОБЛ. В свою очередь низкий уровень докозагексаеновой кислоты (22:6n-3) является результатом дефицита его предшественника – 20:5n-3. Результаты исследования указывают на изменение состава n-3 и n-6 ПНЖК лейкоцитарных мембран крови у пациентов с ХОБЛ. Показано, что нарушение состава полиненасыщенных жирных кислот мембран лейкоцитов возникает уже на ранней стадии заболевания.

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Образец цитирования:

Ю.К. Денисенко, Т.П. Новгородцева, В.В. Кнышова, М.В. Антонюк «Состав полиненасыщенных жирных кислот мембран лейкоцитов у пациентов с хронической обструктивной болезнью легких» // Медицинская иммунология, 2021. Т. 23, № 1. С. 157-162.
doi: 10.15789/1563-0625-PFA-1980

For citation:

Yu.K. Denisenko, T.P. Novgorodtseva, V.V. Knyshova, M.V. Antonyuk “Polyunsaturated fatty acid status of leukocyte membranes in COPD patients”, Medical Immunology (Russia)/ Meditsinskaya Immunologiya, 2021, Vol. 23, no. 1, pp. 157-162.
doi: 10.15789/1563-0625-PFA-1980

DOI: 10.15789/1563-0625-PFA-1980

Следовательно, дисбаланс в составе жирных кислот лейкоцитов вносит значительный вклад в развитие и прогрессирование ХОБЛ.

Ключевые слова: жирные кислоты, полиненасыщенные жирные кислоты, лейкоциты, клеточная мембрана, хроническое воспаление, ХОБЛ

POLYUNSATURATED FATTY ACID STATUS OF LEUKOCYTE MEMBRANES IN COPD PATIENTS

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Abstract. The aim of the study was to analyze n-3 and n-6 polyunsaturated fatty acid (PUFA) profile of blood leukocyte cytomembranes in mild and moderate COPD, and to establish possible role of these fatty acids in COPD progression. The study involved 110 patients with mild disease (n = 60) and moderate COPD (50 patients), at average age of 57.5±4.8 years old. The control group consisted of 32 practically healthy non-smoking people with normal pulmonary function (average age 42.0±3.4 years). The immunological study included flow cytometric determination of blood immune cell subpopulations, i.e., T lymphocytes ($CD3^+$), T helper cells ($CD4^+$), cytotoxic T lymphocytes ($CD8^+$), and B cells ($CD19^+$) using Becton Dickinson machine (USA). Fatty acid methyl esters redissolved in hexane were analyzed using "Shimadzu GC-2010" gas-liquid chromatographic system (Japan). Analysis of the polyunsaturated fatty acid profile of leukocyte membranes in COPD patients revealed a reduced concentration of essential linoleic acid (18:2n-6) regardless of the disease severity. The leukocyte membrane levels of the long-chain n-6 PUFAs, such as dihomo-γ-linolenic acid (20:3n-6), arachidonic acid (20:4n-6), and docosatetraenoic acid (22:4n-6), were elevated in patients with COPD compared with the control group. However, the concentration of the described above n-6 PUFAs in leukocyte membranes was increased in patients with moderate COPD compared to the patients with mild COPD. The significant deficiency of a physiologically important n-3 PUFA, eicosapentaenoic acid (20:5n-3), in leukocyte membranes in the COPD patients was revealed. In turn, the low level of 20:5n-3 could result from the deficiency of its precursor, docosahexaenoic acid (22:6n-3). The results of the study indicate the modification in the PUFA composition of blood leukocyte membranes in the patients with COPD. It was shown that altered composition of long-chain fatty acid of leukocyte membranes emerges already at the early stage of the disease. Therefore, the imbalance in fatty acids composition of leukocytes makes a significant contribution to the development and the progression of COPD.

Keywords: fatty acids, polyunsaturated fatty acids, leukocytes, cell membrane, chronic inflammation, COPD

Chronic obstructive pulmonary disease (COPD) is a steadily progressive disease characterized by inflammation of the lower respiratory tract and bronchial obstruction (edema). COPD refers to a common respiratory pathology that causes a disability [7]. The chronic airway inflammatory process maintained by systemic inflammation underlies COPD pathogenesis [3]. The cellular and molecular mechanisms of chronic systemic inflammation in COPD involve all aspects of structural and functional state of immune cells [3, 4].

According to modern studies, n-3 and n-6 polyunsaturated fatty acids (n-3 PUFAs and n-6 PUFAs) play an important role in the functioning of immune cells [5, 13]. It has been shown that PUFAs impact on each type of immune cells in various ways, modulate all known macrophage-mediated defense mechanisms, such as phagocytosis, respiratory burst, and cytokine production [1, 12, 13]. Moreover, PUFAs has been established to influence on the immune response by several independent mechanisms. Firstly, fatty acids are essential components of membrane phospholipids [11]. As a result, changes in the PUFA composition of cell membranes modulate the physicochemical properties of them membranes (fluidity) and individual membrane domains (lipid rafts), which leads to the modification of cell signal pathways and gene expression [12, 14]. Secondly, fatty acids serve as ligands for receptors of immune cells, including peroxisome proliferator-activated receptor gamma (PPARγ) and G-protein coupled receptor 120 (GPR120), thereby directly affecting the activation and protein synthe-

sis of the cells [8]. Thirdly, the oxidized derivatives of n-3 and n-6 PUFAs (prostaglandins, prostacyclins, thromboxanes, leukotrienes, lipoxins, resolvins, protectins, and marensins) are powerful immunoregulators that have diverse effects on immune cells [9].

Despite the importance of PUFAs in the development of many pathological conditions, the role of modifying lipid composition of immune cell membranes in COPD pathogenesis still remains to be investigated. We suggest that one of the mechanisms of chronic inflammation in COPD is a violation of PUFA composition of immune cell membranes.

The aim of the study was to analyze n-3 and n-6 PUFA composition of blood leukocyte cytomembranes in mild and moderate COPD and to establish the role of these fatty acids in COPD progression.

Materials and methods

The study involved 110 patients with mild (60 people) and moderate COPD (50 people) (average age 57.5±4.8 years). The disease was diagnosed in accordance with the Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD-2017) [7]. The patients with acute infectious diseases, exacerbations of chronic diseases, decompensated heart failure were excluded from the examination. The control group consisted of 32 practically healthy non-smoking people with normal pulmonary function (average age 42.0±3.4 years). The study was approved by the local Ethics Committee, all participants gave written informed consent.

Spirometry, assessing dyspnea using Modified British Medical Research Council (mMRC) scale, assessing quality of life using COPD Assessment Test (CAT), blood sampling for the isolation of leukocytes and the determination of immunological status were performed in patients with COPD in one visit.

The maximum expiratory volume was measured three times by spirography (FUK.UDA, Japan) with recording the highest value of forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC). The examination was repeated 20 minutes after inhaling 200 μg of salbutamol through a spacer device.

Blood samples were collected in EDTA tubes (BD Biosciences, USA) to the analysis of immune cell subpopulations by flow cytometery (BD FACS Canto II, BD Biosciences, USA) and the isolation of leukocytes to the subsequent assessment of fatty acid composition. The immunological study included the flow cytometric determination of subpopulations of the blood immune cells (T lymphocytes ($CD3^+$), T helper cells ($CD4^+$), cytotoxic T lymphocytes ($CD8^+$), and B cells ($CD19^+$) (Becton Dickinson, USA). Data processing was carried out using the FCAP Array 3.0 software (BD Biosciences, USA). The immunoregulatory index ($CD4^+/CD8^+$) was calculated.

Peripheral blood leukocytes were isolated by the ficoll-verographin double density-gradient centrifugation method. Lipids were extracted from leukocyte membranes with chloroform/methanol (1:2 by volume) solution. Methyl ethers were extracted with hexane and purified by thin-layer chromatography in benzene. Fatty acid methyl esters redissolved in hexane were analyzed using gas-liquid chromatograph "Shimadzu GC-2010" (Japan) equipped with a flame ionization detector, a capillary column "Supelcowax 10" (0.25 mm 30 m) with a bonded phase. The column temperature was 210 °C; the detector temperature was 250 °C; the carrier gas was helium. Fatty acids were identified by relative retention times and calculated equivalent chain lengths. The data were expressed as a percentage of total fatty acids.

Statistical analysis was performed by Statistica 6.1 software (1203C series for Windows). Differences in the studied parameters were evaluated using Mann–Whitney and Kolmogorov–Smirnov tests and considered significant when $p < 0.05$.

Results

The obtained results are presented in the table 1. The immune system status in the patients with COPD was characterized by a decrease in the absolute number of lymphocytes, $CD3^+$ cells, $CD4^+$ cells, as well as $CD8^+$ cells (only in patients with mild COPD). Impaired differentiation of immune cells appears to reduce an adequate response to the pathogen and lead to the development of chronic inflammation.

The analysis of the polyunsaturated fatty acid profile of leukocyte membranes in COPD patients was found the low concentration of essential linoleic acid (18:2n-6) regardless of the disease severity. The leukocyte membrane levels of the long-chain n-6 PUFAs, such as dihomo-γ-linolenic acid (20:3n-6), arachidonic acid (20:4n-6), and docosatetraenoic acid (22:4n-6), were elevated in patients with COPD compared with the control group. However, the concentration of the described above n-6 PUFAs in leukocyte membranes were increased in patients with moderate COPD compared with patients with mild COPD. The significant deficiency of a physiologically important n-3 PUFA, eicosapentaenoic acid (20:5n-3), in leukocyte membrane in the COPD patients was revealed. In turn, the low level of 20:5n-3 was resulted from the deficiency of its precursor, docosahexaenoic acid (22:6n-3).

The detected disorders of the composition of long-chain n-3 and n-6 PUFAs in the COPD patients seem to be associated with changed synthesis of eicosanoids, main PUFA metabolites involving in the regulation of inflammation and smooth muscle contraction.

The alteration in the composition of physiologically important FA causes the enhancement in the ratio of 20:4n6/20:5n3 in all studied groups of COPD

TABLE 1. CLINICAL, IMMUNOLOGICAL AND BIOCHEMICAL CHARACTERISTICS OF PATIENTS WITH COPD

Parameters	Control group	Mild COPD	Moderate COPD
FEV1, % predicted	101.88±3.23	90.13±1.99	73.9±2.56
mMRC apnea scale, scores	0	1	2
CAT, scores	0	4-6	7-9
Parameters of the immune system			
Leukocytes, × 10^9 cells/l	5.51±0.91	5.69±0.21	5.91±0.11
Lymphocytes, %	34.9±0.9	27.34±0.81	29.24±1.02
Lymphocytes, cells/μl	1804.8±75.9	1532.70±52.25	*1696.53±47.21
$CD3^+$, %	72.55±2.04	67.70±1.34*	70.41±0.82
$CD3^+$, cells/μl	1252.87±86.12	1033.27±45.87***	**1185.17±27.91
$CD4^+$, %	47.14±1.91	44.80±1.07	45.21±1.00
$CD4^+$, cells/μl	818.22±67.97	684.77±29.50**	*750.95±16.19*
$CD8^+$, %	22.91±1.95	20.19±0.78*	***23.81±0.49
$CD8^+$, cells/μl	391.19±38.6	304.59±16.78***	***411.66±19.46
$CD4^+/CD8^+$	2.24±0.23	2.38±0.10	***1.97±0.07
$CD19^+$, %	11.74±1.04	11.14±0,88	10.54±0.44
$CD19^+$, cells/μl	201.02±20.86	163.48±11.69	178.62±8.14
Blood leukocyte membrane PUFAs (% of total FAs)			
18:2n-6	12.96±2.44	8.97±0.96***	9.59±1.19***
20:3n-6	0.41±0.39	1.34±0.21***	1.37±0.27***
20:4n-6	5.52±3.29	13.87±1.57***	*14.03±1.4***
20:5n-3	0.86±0.3	0.47±0.05***	0.49±0.12***
22:4n-6	0.41±0.25	1.46±0.15***	**1.59±0.17***
22:5n-3	0.53±0.2	1.14±0.08***	1.07±0.27***
22:6n-3	1.24±0.44	0.35±0.12**	0.51±0.15**
20:4n6/20:5n3	6.41±0.21	29.5±1.09***	28.6±1.5***

Note. Statistical significance in comparison with the control group (right) and the group of patients with mild COPD (left): *, $p < 0.05$; **, $p < 0.005$; ***, $p < 0.001$.

patients. The identification of levels of 20:4n6 and 20:5n3 is indicative of eicosanoid cycle impairment and, respectively, the risk for the development of inflammatory process. It is known that n-6 FAs are the key substrate for the biosynthesis of pro-inflammatory eicosanoids (leukotrienes, tromboxanes, prostaglandines) that initiate cascade of reactions resulting in the activation of immune and smooth muscles cells [11]. The marked increase in n-6 PUFA level in membranes of leukocytes indicates the ability of the cells to product of lipid pro-inflammatory mediators. While, anti-inflammatory (prostaglandines) and pro-resolving (maresins, resolvins, protectins) oxylipins are formed from eicosapentaenoic acid (20:5n-3) [9]. The imbalance between n-6 and n-3 PUFAs can be a prognostically unfavorable sign of chronic inflammation and impaired resolution of inflammatory process.

Discussion

The results of the study indicate the modification in the PUFA composition of blood leukocyte membranes in patients with COPD. It was shown that the violation of long-chain fatty acid composition of leukocyte membranes emerges already at the early stage

of the disease. The disorders of FA metabolism and plasma membrane architectonics detected in patients with mild COPD are aggravated as the disease progresses. The pathogenetic importance of the identified modification is due to the functional and structural role of lipids in immune cell function. The ratio between n-6 and n-3 fatty acids esterified into phospholipids determines the basic physical properties of the cytomembrane, including fluidity, permeability, viscosity, and elasticity [12, 13]. These properties are essential to the ability of immune cells to phagocytose and express receptors. *In vivo* and *in vitro* studies relating to the effect of fatty acids on macrophage phagocytosis have shown that an elevated unsaturated fatty acid content in cytomembrane correlates with an increased phagocytosis rate [1]. It is reasonable to assume that the enhancement of membrane fluidity, which is caused by fatty acid-mediated cytoskeleton remodeling, improves the phagocytic function of the cell. Another important aspect combining the immune properties of the cell and the composition of its cytomembrane is the formation of specialized membrane microdomains called lipid rafts [10]. Various membrane receptors of immune cells can be expressed only in lipid rafts [12]. Thus, lipid rafts are primarily considered as platforms for the accumulation of activated receptors.

Finally, the role of fatty acids is associated with the fact that PUFAs are precursors for the synthesis of biologically active substances, such as eicosanoids and pro-resolving lipid mediators [2]. Metabolites of FAs locally regulate the functions of the endothelium and smooth muscle cells, vasodilation reaction, platelet aggregation, microcirculation, and inflammation. The increased content of PUFAs from the n-6 family contributes to the inflammation process, affects the aggregation properties of platelets, and the functioning of the immune system. The high content of 20:4n-6 and its metabolite (22:4n-6) in leukocyte membranes in patients with COPD indicates a rise in the concentration of substrate for the synthesis of inflammatory and bronchospasm mediators. In addition, the enhanced synthesis of arachidonic acid is observed against the background of a significant deficiency of eicosapentaenoic acid (20:5n3), its main inhibitor and competitor for cyclooxygenase and lipoxygenase metabolic pathways. The lack of eicosapentaenoic acid, the main substrate for the production of pro-resolving lipid mediators, in the membrane of immune cells determines the eicosanoid imbalance that is one of the causes of chronic inflammation. Balode L. et al. have revealed impaired synthesis of pro-resolving lipid mediators, in particular lipoxin A4, in COPD [2]. The inhibition of mechanisms for inflammation resolution in COPD may be a fundamental pathogenetic mechanism of chronic inflammation.

Therefore, the imbalance in fatty acids composition of leukocytes makes significant contribution to the development and the progression of COPD. Further comprehensive and in-depth studies are needed to establish the pathophysiological role of PUFAs and their oxygenase metabolites in chronic respiratory diseases.

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Поступила 23.03.2020
Принята к печати 11.05.2020

Received 23.03.2020
Accepted 11.05.2020