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ORIGINAL RESEARCH

Exploration of n-6 and n-3 Polyunsaturated Fatty Acids Metabolites Associated with Nutritional Levels in Patients with Severe Stable Chronic Obstructive Pulmonary Disease

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Background and Objective: Severe chronic obstructive pulmonary disease (COPD) is the terminal stage of the disease characterized by declined lung function, malnutrition, and poor prognosis. Such patients cannot tolerate long-time sports rehabilitation owing to dyspnea and fail to achieve the desired therapeutic effect; therefore, increasing nutritional support will be an important strategy for them. The present study applied metabolomics technology to evaluate the correlation between serum concentrations of polyunsaturated fatty acid (PUFA) metabolites, nutritional status, and lung function in patients with COPD to provide a theoretical basis for accurate nutritional support.

Materials and Methods: We enrolled 82 patients with stable severe COPD in our hospital. The general characteristics including height, weight, and lung function were recorded. Metabolomics was used to detect the concentrations of serum metabolites of n-3 and n-6 at baseline and at 24 and 52 weeks after enrollment. The correlations between nutrition level and pulmonary function and clinical indicators were evaluated.

Results: The concentrations of n-3 and n-6 increased over time along with the progression of COPD. Body mass index (BMI) and percent of ideal body weight (IBW%) decreased with disease development, and BMI was found to be significantly correlated with FEV1% predicted and FEV1/FVC. Serum levels of n-6 metabolites such as linoleic acid (LA), γ-linoleic acid (GLA), and arachidonic acid (ARA) (all $P < 0.01$) and the n-3 metabolites such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) (all $P < 0.05$) showed significant correlations with BMI and were closely correlated with FEV1% predicted and FEV1/FVC of lung function (all $P < 0.05$).

Conclusion: This study demonstrates that malnutrition in patients with severe COPD is progressive and is positively correlated with n-3 and n-6 polyunsaturated fatty acids and lung function.

Keywords: chronic obstructive pulmonary disease, metabolomics, nutritional level

Introduction

Chronic obstructive pulmonary disease (COPD) is a common chronic inflammatory disease of the lungs, characterized by incomplete and persistent limitation of airflow and progressive aggravation over time.[1–4] Accumulation of inflammatory cells and inflammatory cytokines in the respiratory tract can have adverse effects on the lungs including in the decline of lung function.[5,6] The persistent inflammation

and increased effort required for breathing increase patients' energy expenditure.[7] Furthermore, inappetence and anxiety can lead to reduced energy intake, leading to malnutrition.[8] Most patients with COPD exist in a state of protein malnutrition, and reductions in muscle mass and myofiber strength mean that the normal function of respiratory muscles are reduced. This leads to a decline in lung compliance, thus accelerating disease progression.[9]

Pulmonary rehabilitation has become an important strategy in the management of COPD, and can remarkably improve the quality of life and long-term prognosis of patients.[10] However, some patients with severe COPD and poor adherence to treatment may not tolerate this treatment.[10,11] Therefore, such patients are most suited to drug therapy in clinical practice.[11,12] The Global Initiative for Chronic Obstructive Lung Disease (GOLD) suggests that patients with grade 3–4 COPD would benefit from nutritional support during lung rehabilitation.[10,13-15] Purposeful adjustment of nutritional intake could improve prognosis and reduce acute episodes and the length of readmissions.[16]

Studies have shown that high-calorie diets or the maintenance of obesity can improve lung function of some patients with COPD, whereas excessive ingestion result in the obesity will exacerbate hypoxia.[8,17,18] Therefore, it is crucial to assess the nutritional level of patients before pulmonary rehabilitation ingestion intervention (the level and ratio of essential fatty acids), which is the basis of targeted nutrient schemes.[19–21]

As an important branch of systems biology, metabolomics can be used to elucidate the mechanisms underlying disease development, by providing solid biological evidence for personalized and precision medicine.[22,23] Metabolomics has obvious advantages for COPD, a disease with a complex phenotype for which the physiological mechanism is unknown. The approach also plays a key role in determining appropriate nutritional support for chronic diseases.[24,25] As a non-invasive test, metabolomics has great potential for investigations into the influence nutrient intake and the identification of biomarkers during disease progression.[26]

For humans, n-3 and n-6 polyunsaturated fatty acids (PUFAs) are indispensable components of the daily diet, and are essential for maintaining normal physiological functions.[27,28] The metabolites of n-3 PUFAs possess anti-inflammatory activities, which could attenuate the partial pro-inflammatory effects of n-6; thus, consuming n-3-rich foods can reduce inflammation to some extent.[29–31] Furthermore,

n-6 PUFAs are involved in a variety of physiological and pathological processes, acting as the immediate precursor of thrombin, leukotriene, and prostacyclin, and are responsible for regulating the persistent inflammation of COPD.[27] Interestingly, because of homeostasis, increased intake of n-3 or n-6 does not significantly affect the amount of metabolites produced or the secretion of downstream inflammatory markers.[32–37]

Materials and Methods
Study Design and Patients
For the present retrospective case-control study, we recruited all consecutive patients with severe stable COPD (the diagnostic criteria met the latest 2020 Global Initiative for Chronic Obstructive Lung Disease reports) who were treated at our institute from October 2016 to June 2017 and met the following inclusion criteria: 1) aged 70–80, 2) forced expiratory volume in 1 second (FEV1) <50% and FEV1/forced vital capacity (FVC) ≤0.7, 3) no history of immune-related respiratory disease or extrapulmonary disease involving the lungs and 4) no history of diabetes or hypertension. Written signed informed consent was obtained from all patients before enrollment. Each patient underwent a 52-week follow-up, and serum samples were taken and clinical data collected from all participants at baseline, 24 weeks and 52 weeks. In addition, 29 healthy volunteers were recruited as healthy control subjects. This experiment was approved by the Ethics Committee of the First Affiliated Hospital of Guangzhou Medical University (NCT04042519). This study follows the ethical principles contained in the current version of the Helsinki declaration.

Lung Function Test
According to the requirements of the American Thoracic Society and the European Respiratory Society (ATS/ERS), pulmonary function tests were performed on participants using the Jaeger lung function instrument (MasterScreen, Leibnizstrasse, Hoechberg, Germany). Parameters included: FEV1, FVC, FEV1/FVC, total vital capacity, and total lung capacity (TLC). These indicators were used to diagnose and monitor COPD progression according to ATS/ERS criteria.[37]

Collection and Storage of Blood Samples
Participants underwent venous blood collection. Samples were centrifuged at 3000 r/min (1006.2 xg) for 10 min and

20 degrees Celsius. The resulting serum was sub-packed and stored at –80°C which for no longer than 2 years prior to use. Repeated freezing and thawing was avoided for metabolomics research.

Measurement of Metabolites by Ultra-Performance Liquid Chromatography/Time-of-Flight Mass Spectrometry

An Agilent 1290 Infinity LC system (Santa Clara, CA, USA) was used for targeted determination of metabolites in serum samples, and radiolabeled compound hydroxy-eicosatetraenoic acid-d8 and prostaglandin D_2-d4 (Ann Arbor, Michigan USA, Caymen) were used. The Metabolites were classified and matched according to the Kyoto Encyclopedia of Genes and Genomes (KEGG, Bioinformatics Center, Institute for Chemical Research, Kyoto University and Human Genome Center, Institute of Medical Science) and The Human Metabolome Database (HMDB4.0, University of Alberta, Edmonton, Canada). We used Agilent MassHunter Workstation Software Qualitative Analysis B.05.00 based on retention time, mass-charge ratio, and other molecular characteristics to analyze metabolite peak areas.

Statistical Analysis

Data were analyzed and graphed using SPSS (Statistics for Windows Version 22.0, IBM Corp, Chicago, IL, USA), GraphPadPrism 5.0 (GraphPad Software, San Diego, CA, USA), MedCalc, version 18.11 (MedCalc Software Inc., Acacialaan, Ostend, Belgium) and R-studio. The website Metaboanalyst (Xia Lab, McGill University) was used to create metabolite diagrams. Data are presented as the median ± standard deviation, evaluated using standardized indicators. Comparison of metabolites at each of the time points was analyzed using analysis of variance (ANOVA). We considered $P < 0.05$ to be statistically significant.

Results

Participants and Clinical Characteristics

Table 1 presents the background characteristics of the study population, which included 82 patients with COPD. There were no significant differences in gender, age, or body mass index (BMI) between the two groups. Percent of ideal body weight (IBW%) was significantly different in the COPD group are compared with the normal group ($P < 0.05$). The pulmonary function parameters, including FVC% predicted, FEV1% predicted, and the FEV1/FVC ratios were significantly lower in patients with COPD than in healthy controls. The COPD group was evaluated at three time points: baseline, 24 weeks, and 52 weeks after enrollment. The BMI and IBW% decreased over time, as did the percentage of FEV1 in the predicted value (FEV1 pred%) and FEV1/FVC. Neutrophil and white blood cell counts were significantly higher in the COPD group than the normal controls ($P < 0.05$).

Nutritional Status of Patients with Chronic Obstructive Pulmonary Disease

The body mass index (BMI) and ideal body weight percentage (IBW%) of patients with severe stable COPD declined over time (Figure 1), and BMI was significantly correlated with FEV1% predicted and FEV1/FVC (r=0.18 and r= 0.23 respectively, all $P < 0.01$).

Metabolites of n-3 and n-6 Polyunsaturated Fatty Acids

Table 2 presents the results of analysis of each metabolite at each of the time points. Figure 2 illustrates the general trends of n-3 and n-6 metabolites; the concentration of linoleic acid (LA), gamma-linoleic acid (GLA), and di-homo gamma-linoleic acid (DGLA) increased progressively over the three time points in patients with COPD. The concentration of the eicosanoic acid metabolites 5-hydroperoxyeicosatetraenoic acid (5-HPETE), 5-hydroxyeicosatetraenoic acid (5-HETE), and 12-HETE with arachidonic acid (ARA) as the immediate substrate were also increased over three follow-up time points in the study. The concentration of n-3 alpha-linoleic acid (ALA) and eicosapentaenoic aced (EPA) increased over time, while docosapentaenoic acid (DPA), docosahexaenoic acid (DHA), tetracosapentaenoic acid (TPA) and tetracosahexaenoic acid (THA) declined over time. Figure 3 shows the pathway diagram of the metabolites detected in this study. In addition, the levels of n-3 and n-6 in healthy control subjects were lower than COPD patients.

Correlation Between Metabolite Levels and Lung Function in Patients with Chronic Obstructive Pulmonary Disease

The n-6 metabolites LA, GLA, and ARA showed significant correlations with BMI (r = −0.23, −0.58, and −0.11, respectively, all $P < 0.01$), while EPA, DHA of n-3 metabolites were also significantly correlated with BMI (r = −0.54,

Table 1 Participant Characteristics

	Healthy Control	COPD Group			
		Baseline	24 Weeks	52 Weeks	P value
N	29	82	82	82	
Age	60±9.83	66±10.59	66±10.59	67±10.59	0.659
Male/Female	26/3	76/6	76/6	76/6	0.988
BMI	24.91±3.10	26.33±5.29	23.32±4.77	22.34±3.61	0.669
IBW%	100.7±16.38	108.9±19.28	99.78±17.44	96.33±15.81	0.001
WBC (10^9)	6.24±5.57	6.08±4.31	7.49±3.59	7.82±6.85	0.038
NEUT (10^9)	5.13±1.22	5.29±3.16	5.85±2.94	5.41±3.15	0.11
TLC (10^9)	1.37±1.61	1.35±0.60	1.27±0.67	1.36±0.73	0.644
Eos (10^9)	0.19±0.31	0.14±0.12	0.16±0.27	0.12±0.16	0.121
CRP (μg/L)	0.12±1.61	0.39±0.14	0.26±0.31	0.42±0.17	0.492
PCT (ng/mL)	0.20±1.46	0.21±0.75	0.31±1.10	0.27±1.07	0.342
CEA (ng/mL)	4.43±4.78	3.80±2.90	4.75±6.36	3.20±2.26	0.285
Glu (mmol/L)	6.12±5.56	6.15±2.29	6.35±3.26	6.21±1.82	0.561
TCH (mmol/L)	3.71±5.54	3.92±1.19	4.27±1.01	3.97±0.89	0.077
FEV1 (% predict)	91.68±4.50	58.10±12.86	34.10±9.07	23.85±7.84	0.001
FVC (% predict)	90.33±4.63	69.45±15.89	71.15±14.11	72.00±16.96	0.832
FEV1/FVC%	82.52±8.71	56.01±6.97	43.22±4.12	36.19±5.89	0.001

Abbreviations: COPD, chronic obstructive pulmonary disease; BMI, body mass index; IBW, ideal body weight; WBC, white blood cell count; TLC, total lymphocyte count; NEUT, neutrophile granulocyte; EOS, eosinophilic granulocyte; CRP, C-reactive protein; PCT, procalcitonin; CEA, carcinoembryonic antigen; GLU, glucose; TCH, total cholesterol; FEV1, forced expiratory volume in 1second; FVC, forced vital capacity.

−0.30, respectively, all $P < 0.05$). All those metabolites including LA, GLA, ARA, EPA and DHA were closely correlated with FEV1% predicted (r = −0.37, −0.35, −0.60, −0.47, −0.19, all $P< 0.05$) and FEV1/FVC (r = −0.26, −0.13, −0.44, −0.28, −0.72, respectively, all $P< 0.05$) (Figure 4). In addition, the total contents of n-3 and n-6 were found to be significantly correlated with FEV1/FVC (all $P < 0.05$).

Discussion

In this study, we observed at three time points that inflammation levels increased with the progression of COPD and lung ventilation function decreased. Meanwhile, patient nutritional levels declined over time. The total content of n-3 and n-6 PUFAs rose over time, and were significantly correlated with lung function, BMI, and IBW%. Therefore, n-3 and n-6 metabolites may represent novel evaluation indicators for nutritional support during pulmonary rehabilitation in patients with COPD.

The Relationship Between Nutrient Levels and Disease Progression in Patients with Chronic Obstructive Pulmonary Disease

Through the evaluation of BMI and IBW% at three follow-up time points, we found that the nutritional level of patients with severe stable COPD decreased gradually as the disease advanced, and was significantly correlated with the FEV1% predicted and FEV1/FVC. Malnutrition is one of the risk factors for persistent disease progression in patients with COPD.[4] Weight loss is a common extrapulmonary manifestation, and BMI and IBW% are simple, precise, and repeatable indicators of nutritional levels.[4,39,40] As COPD progresses, respiratory work generally increases, as does anxiety and anorexia, which lead to decreased nutrient intake and impaired lung ventilation.[41,42] Furthermore, malnutrition leads to decreased immune function and inflammatory damage to the normal structure of the bronchoalveoli, which result in decreased lung function and accelerated disease progression.[38,43,44] Therefore, we believe that nutritional support during pulmonary rehabilitation is crucial to end the negative cycle.

The sources of n-3 PUFAs mainly include deep-sea fish, shrimp, and beef, while n-6 PUFAs are mainly found in sunflower seeds, soybean oil, and meat.[45] Saini et al[46] reported that eating n-6-rich foods may increase the risk of chronic diseases, which may be antagonized by consumption of n-3 PUFAs. As essential fatty acids, the n-3 and n-6 are closely related to the level of inflammation, especially in the case of COPD. Roman et al[47] and Wood et al[48] reported that n-3 PUFAs can interfere with the process of chronic airway
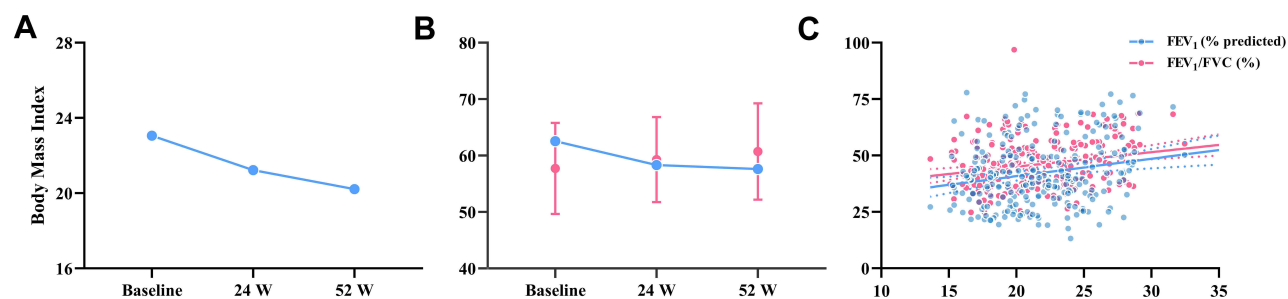
Figure I (**A**) and (**B**) Trends of BMI and IBW% in COPD patients at baseline, 24 W, and 52 W; (**C**) BMI was significantly correlated with FEV1% predicted and FEV1/FVC.

inflammation due to their anti-inflammatory properties. Many nutrition studies have also suggested the importance of the ratio of n-3 to n-6 in the formula of nutritional support for patients with COPD.[4,35,49-51] At present, this is the first longitudinal study to simultaneously evaluate the metabolites of n-3 and n-6 level in severe stable COPD patients.

The Relationship Between n-3 and n-6 Metabolites with Disease Progression

We identified an increase over time in the total content of n-3 and n-6 in serum samples. The anti-inflammatory activity of n-3 has been demonstrated in the context of various chronic inflammatory lung diseases, and can contribute to the reduction of neutrophil numbers in the lungs.[28,52,53] The n-6 PUFAs have pro-inflammatory effects and act as immediate precursors for a variety of potent pro-inflammatory mediators (leukotrienes and prostaglandins), which are responsible for airway remodeling and the destruction of alveolar structure.[6,54]

We identified a correlation between n-3 and n-6 PUFAs and lung function, indicating an imbalance between pro- and anti-inflammatory effects; thus, the total inflammation increases and lung function decreases. The overall concentrations of n-3 and n-6 PUFAs in serum samples reflect the data

Table 2 Peak Ratio of n-3 and n-6 Metabolites

| Metabolites	Total Peak Ratio	Peak Ratio at Different Times			F	P value
		Baseline	24 Weeks	56 Weeks		
ALA	8.94±5.51	5.02±3.62	7.86±4.26	13.15±5.61	5.02	0.032
EPA	32.93±51.43	12.15±19.74	39.55±34.16	59.44±63.51	32.77	0.001
DHA	272.1±163.7	246.6±128.7	266.7±187.6	323.3±157.2	26.05	0.001
Stearidonic	46.96±33.40	49.86±28.93	45.15±36.85	47.00±34.69	0.19	0.082
Nisinic	23.21±18.68	17.77±12.46	25.95±19.10	27.77±20.53	41.47	0.001
DPA	9.03±5.22	7.35±3.45	8.68±4.43	11.05±6.059	32.53	0.015
TPA	63.33±36.70	76.33±39.97	62.76±36.22	49.85±28.39	12.54	0.136
THA	6.69±5.96	7.08±5.57	7.79±7.21	5.89±2.79	16.34	0.078
LA	2459±2324	1952±859.1	2426±1082	3348±3614	36.59	0.001
GLA	463.2±309.7	272.1±189.4	434.4±172.9	600.7±399.1	38.87	0.001
DGLA	1.25±0.96	1.02±0.60	1.262±1.03	1.49±1.02	6.97	0.023
ARA	122.2±240.4	26.91±73.21	122.2±113.7	509.9±205.3	240.07	0.001
Adrenic acid	79.18±70.26	67.60±33.46	79.49±56.67	99.69±93.98	32.30	0.001
Osbond acid	45.97±41.22	44.80±44.78	48.98±40.50	45.7±38.58	0.15	0.804
5s-HPETE	1.02±1.25	0.40±0.69	1.22±0.99	1.42±1.52	2.69	0.022
12s-HPETE	0.45±1.09	0.04±0.23	0.69±0.74	1.883±1.208	4.81	0.364
15s-HPETE	0.05±0.32	0.03±0.07	0.09±0.51	0.04±0.13	5.26	0.631
12s-HETE	2.87±6.28	1.31±2.85	3.08±5.61	5.45±8.04	3.27	0.024
15s-HETE	2.73±8.76	0.244±2.34	3.10±6.33	4.91±12.68	17.27	0.130
5s-HETE	22.42±17.43	11.88±9.35	25.02±15.45	30.01±19.53	37.16	0.001

Abbreviations: ALA, α-linolenic acid; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; DPA, docosapentaenoic acid; TPA, tetracosapentaenoic acid; THA, tetracosahexaenoic acid; LA, α-linolenic acid; GLA, γ-linolenic acid; DGLA, dihomo-γ-linolenic acid; ARA, arachidonic acid; HETE, hydroxy-eicosatetraenoic acid; HPETE, hydroperoxy-eicotetraenoic acid.
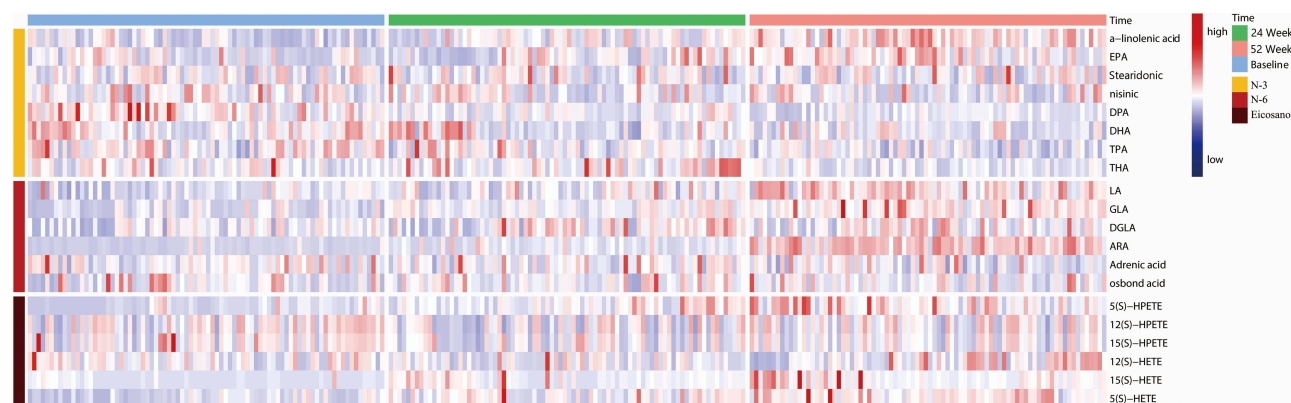
**Figure 2** Levels of n-3 and n-6 at different stages of COPD progression. The heatmap shows different metabolite levels at baseline, 24 W, and 52 W in patients with severely stable COPD.

Abbreviations: EPA, eicosapentaenoic acid; DPA, docosapentaenoic acid; DHA, docosahexenoic acid; TPA, tetracosapentaenoic aicd; THA, tetracosahexaenoic acid; LA, linoleic acid; GLA, γ-linolenic acid; DGLA, dihomo-γ-linolenic acid; ARA, arachidonic acid; HETE, hydroxy-eicosatetraenoic acid; HPETE, hydrogen peroxide eicarboxylic acid.
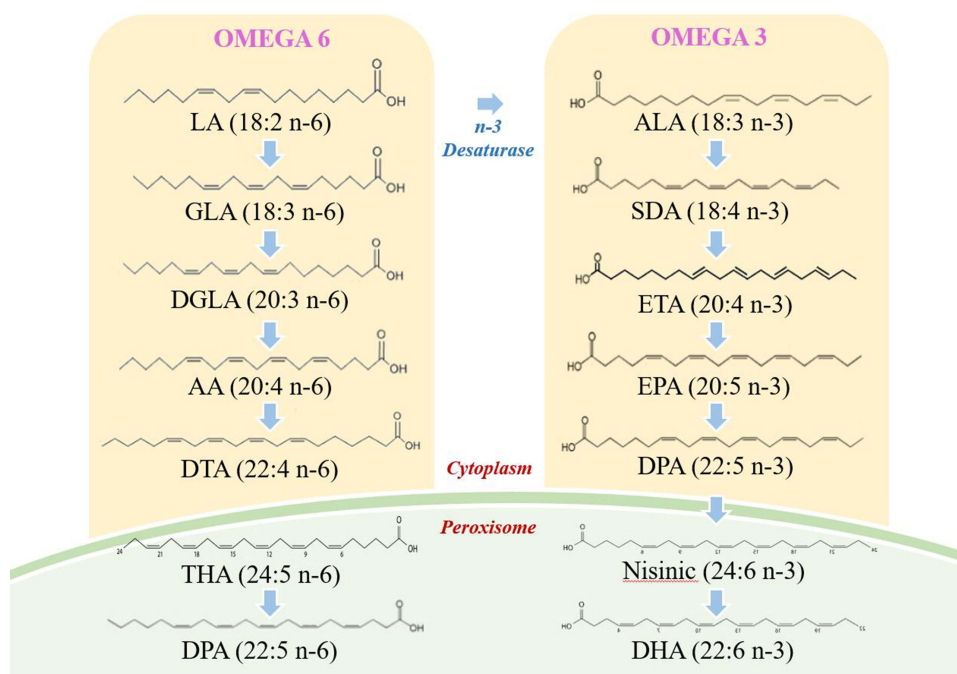
Figure 3 Pathway maps of n-3 and n-6 metabolism.

of their antagonistic actions in metabolism reported by Calder et al and Leuti et al.[30,55] The concentration of ALA and EPA increased over time, and we speculated that this upregulation may lead to antagonization of the pro-inflammatory activities of n-6 metabolites, as has been mentioned in a previous study by Duvall et al.[52] Notably, because of the mechanisms of homeostasis and the intestinal flora, in spite of the concentration of n-3 is on the rise, it does not mean that all category of lipid metabolites on n-3 pathways are all on the rise.[56,57] Although the present study provides some insight, the trends

in metabolites of PUFAs in patients with COPD have not been fully elucidated and require further exploration.

Evaluation of n-3 and n-6 Lipid Metabolites and Nutritional Status in Patients with Chronic Obstructive Pulmonary Disease

The key metabolite of n-6 PUFAs (ARA) and the core metabolites of n-3 PUFAs (EPA and DHA) and the total
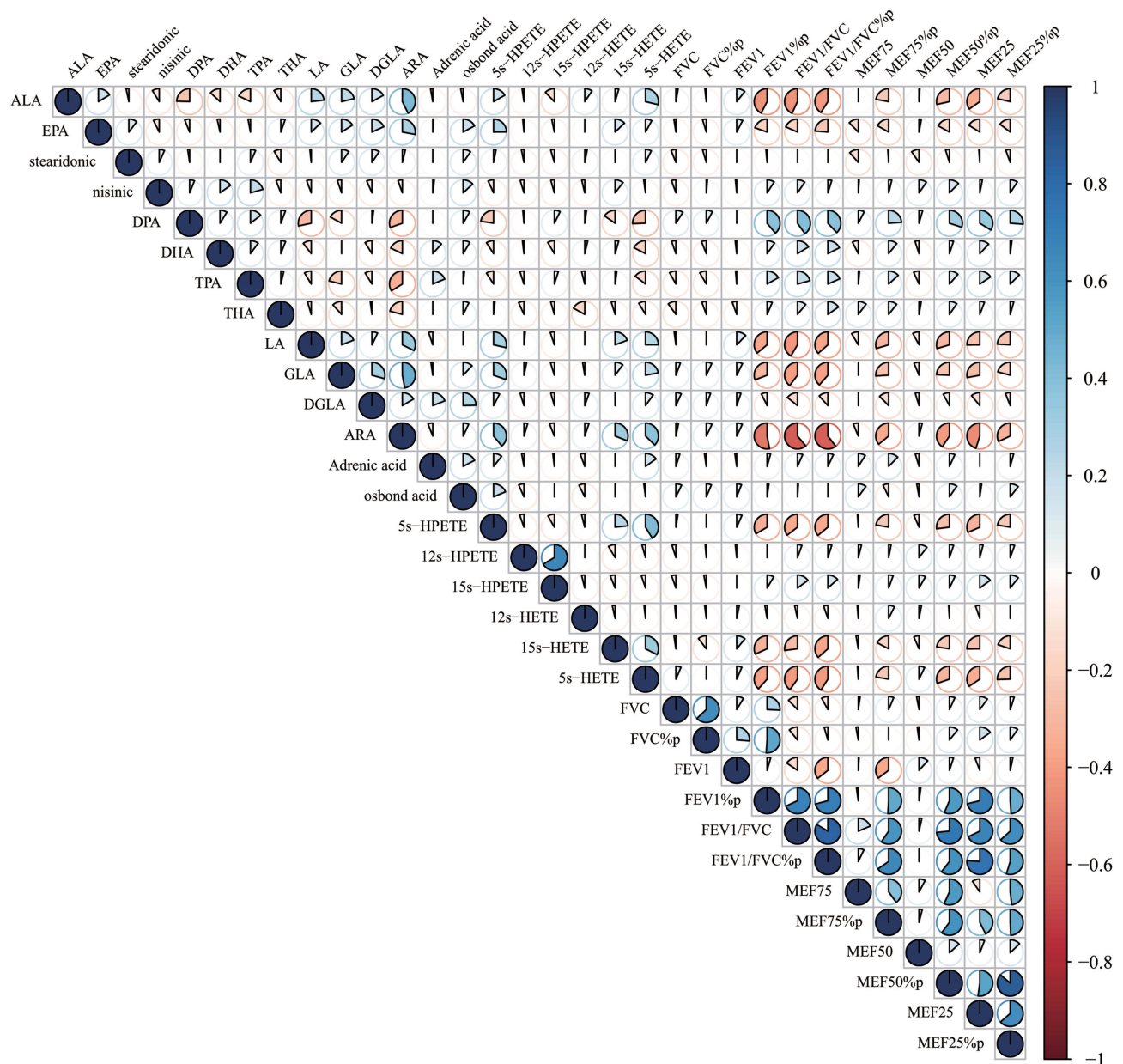
Figure 4 Correlation between n-3 and n-6 metabolites and lung function. The n-6 metabolites LA, GLA, and ARA showed significant correlations with BMI (r = −0.23, −0.58, and −0.11, respectively, all $P < 0.01$), while EPA, DHA of n-3 metabolites were also significantly correlated with BMI (r = −0.54, −0.30, respectively, all $P < 0.05$). All those metabolites including LA, GLA, ARA, EPA and DHA were closely correlated with FEV1% predicted (r = −0.37, −0.35, −0.60, −0.47, −0.19, all $P< 0.05$) and FEV1/FVC (r = −0.26, −0.13, −0.44, −0.28, −0.72, respectively, all $P<0.05$).

concentrations of n-3 and n-6 PUFAs were found to be significantly correlated with BMI and IBW, respectively. In addition, these concentrations were significantly correlated with FEV1/FVC and FEV1. Therefore, the nutrient levels of patients with moderate-to-severe COPD decreased with disease progression, and we confirmed that n-3 and n-6 concentration reflected the decline in pulmonary function and could be used to evaluate the nutritional status of patients. Personalized medicine plays

a key role in improving the symptoms of COPD; nutritional support and the establishment of a rational diet are of particular importance and require accurate assessment of the nutritional status of patients before a regimen is initiated.[39] The emergence of metabolomics has led to rapid developments in dietary therapy, which is gradually moving closer to clinical application.[58] Initial results and views have been presented in studies on multiple chronic diseases (diabetes, fatty liver, obesity, and cardiovascular

disease);[59] therefore, metabolite-trend analysis also has immense potential in the evaluation of the nutriture of patients with severe stable COPD. We believe that the n-3 and n-6 lipid metabolites may represent novel indicators for such evaluation; in particular, EPA, DHA, and ARA, which not only reflect the nutriture of patients but also present a significantly negative correlation with lung function.

Conclusion

The EPA (n-3), DHA (n-3) and ARA (n-6), and the total concentration of lipid metabolites of n-3 and n-6 can reflect the nutriture of patients with severe stable COPD, which is closely related to the degree of disease progression. In the future, these may be used as novel indicators for the evaluation of nutrient levels of patients with COPD to inform nutritional support for pulmonary rehabilitation. Future research should focus on establishing a theoretical basis for the development of individualized nutrition programs. Moreover, we found that although there was antagonistic effect between n-3 and n-6, the content of the two does not present a tendency of increasing and decreasing, but that n-3 was also up-regulated to resist the pro-inflammatory effect of n-6. Therefore, the specific trend of metabolites in n-3 and n-6 needs to be further explored.

Acknowledgments

Disclosure

The authors report no conflicts of interest in this work.

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