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Association between Ω3 and Ω6 fatty acid intakes and serum inflammatory markers in COPD☆

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Abstract

Dietary intake of polyunsaturated fatty acids, including omega-3 and omega-6, could modulate chronic obstructive pulmonary disease (COPD) persistent inflammation. We aimed to assess the relationship between dietary intake of omega-3 and omega-6 fatty acids and serum inflammatory markers in COPD. A total of 250 clinically stable COPD patients were included. Dietary data of the last 2 years were assessed using a validated food frequency questionnaire (122 items), which provided levels of three omega-3 fatty acids: docosahexaenoic acid, eicosapentaenoic acid and α-linolenic acid (ALA); and two omega-6 fatty acids: linoleic acid and arachidonic acid (AA). Inflammatory markers [C-reactive protein (CRP), interleukin (IL)-6, IL-8 and tumor necrosis factor alpha (TNFα)] were measured in serum. Fatty acids and inflammatory markers were dichotomised according to their median values, and their association was assessed using multivariate logistic regression. Higher intake of ALA (an anti-inflammatory omega-3 fatty acid) was associated with lower TNFα concentrations [adjusted odds ratio (OR)=0.46; *P*=.049]. Higher AA intake (a proinflammatory omega-6 fatty acid) was related to higher IL-6 (OR=1.96; *P*=.034) and CRP (OR=1.95; *P*=.039) concentrations. Therefore, this study provides the first evidence of an association between dietary intake of omega-3 and omega-6 fatty acids and serum inflammatory markers in COPD patients.

Keywords: Food intake; Inflammation; Public health; Pulmonary disease, chronic obstructive

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1. Introduction

Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality worldwide and is expected to become the fourth leading cause of mortality by 2030 [1]. It is characterized by a complex chronic inflammatory condition usually associated with smoking-induced inflammation and oxidative stress [2]. This persistent inflammatory condition is located not only in the lungs [3] but also in extrapulmonary organs and tissues [4]. Levels of systemic inflammatory markers increase during COPD exacerbations [5], suggesting that inflammatory processes play a key role in COPD evolution [6]. A longitudinal population-based study has reported lower lung function decline in subjects with decreasing levels of C-reactive protein (CRP), an inflammatory marker, when compared with subjects with stable or increasing levels, suggesting that reducing the levels of circulating inflammatory markers could be an effective way of reducing lung function decline [7]. Finally, CRP serum levels have been related to mortality in COPD patients [8,9].

It has been hypothesized that dietary intake of polyunsaturated fatty acids (PUFAs), including omega-3 and omega-6 fatty acids, could modulate persistent inflammation in COPD [10–12], although this hypothesis has never been tested so far. It is known that omega-3 fatty acids mostly promote anti-inflammatory activities [13]. In contrast, omega-6 fatty acids are the most relevant precursors of proinflammatory eicosanoids and, therefore, mostly mediate proinflammatory activities [14]. We hypothesized that COPD patients with higher omega-3 and lower omega-6 intakes would have lower levels of circulating inflammatory mediators.

Therefore, this study aims to assess the association between dietary intakes of omega-3 and omega-6 fatty acids and several serum inflammatory markers, specifically CRP, interleukin (IL)-6, IL-8 and tumor necrosis factor alpha (TNFα), in COPD patients in the framework of the 'Phenotype and Course of COPD Project' (PAC-COPD) [15].

2. Subjects and methods

2.1. Study population

This study is a cross-sectional analysis of the PAC-COPD. Briefly, the sample includes COPD patients recruited during their first hospital admission at 9 universitary hospitals in Spain between January 2004 and March 2006 with a confirmed diagnosis of COPD [postbronchodilator forced expiratory volume in the first second to forced vital capacity ratio (FEV_1/FVC)≤0.70] [16] and in a clinically stable condition at least 3 months after discharge. Detailed information on PAC-COPD recruitment, methods and results is available elsewhere [17]. The protocol was approved by the Ethics Committees of all the participating hospitals, and written informed consent was obtained from all the COPD patients.

Of the 342 patients included in the PAC-COPD cohort, a total of 250 had available information on dietary PUFAs and serum inflammatory markers. No differences regarding sociodemographic characteristics, comorbidities, dyspnea or lung function parameters were found between PAC-COPD patients who provided dietary information and those who did not, as previously published [18]. All epidemiological and clinical measures as well as blood samples were obtained during clinical stability at least 3 months after recruitment.

2.2. Dietary assessment

A previously validated 122-item food frequency questionnaire [19] asking for dietary habits in the last 2 years was administered by trained interviewers. Reported information was converted into a daily intake frequency of each food, which was in turn converted into the daily intake in grams per day for each food. A food composition table from the US Department of Agriculture [20] was used to estimate intakes of three omega-3 fatty acids: docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA) and α-linolenic acid (ALA); and two omega-6 fatty acids: linoleic acid (LA) and arachidonic acid (AA). Additionally, the following ratios between omega-3 and omega-6 fatty acids were computed: ALA/LA, EPA/AA and DHA/AA. More details about the development and validation of the questionnaire have been previously published [19]. Additionally, our group tested the reproducibility of the questionnaire when telephonically administered in a subsample of 18 subjects. Briefly, moderate to high correlations were found between the first and second questionnaire administration, and no statistically significant differences in means of intakes of most food groups, macronutrient and micronutrients were found [18].

2.3. Systemic inflammation

Blood samples were obtained after fasting overnight and, after 30 min of blood withdrawing, centrifuged at 2000–3000 rpm for 10 min. Serum was separated and stored in cryotubes at −80°C. Serum levels of high-sensitivity CRP were determined by nephelometry, and those of IL-6, IL-8 and TNFα were determined by high-sensitivity enzyme-linked immunosorbent assay kit (Biosource, Camarillo, CA, USA). All analyses were performed in duplicate centrally at Hospital Universitari Son Dureta (Palma Mallorca, Spain). The lower limits of detection of these assays were 0.16 mg/L, 0.104 pg/ml, 0.10 pg/ml and 0.09 pg/ml for CRP, IL-6, IL-8 and TNFα, respectively. Intraassay variation was always <10%, and reported values correspond to the average of the two determinations.

2.4. Clinical and functional assessment

Information regarding sociodemographic characteristics, pharmacological treatment, respiratory symptoms and lifestyle was obtained using a standardized epidemiological questionnaire. Nutritional status was assessed through body mass index (BMI). Postbronchodilator spirometry (FEV_1, FVC and FEV_1/FVC ratio), and arterial oxygen (PaO_2) and carbon dioxide partial pressures were also measured. The Charlson index of comorbidity [21] was obtained by an expert pulmonologist from medical records and personal anamnesis and exploration. Detailed information on the methods is described elsewhere [15,17].

2.5. Statistical analysis

Sociodemographic and clinical characteristics, intakes of omega-3 and omega-6 fatty acids, and inflammatory markers were described by mean (S.D.), median (P25–P75) or number (%), as appropriate according to the distribution of each variable. Given their skewed distribution, inflammatory marker concentrations were dichotomised according to their median values (TNFα: 0.238 pg/ml, IL-6: 1.004 pg/ml, IL-8: 4.296 pg/ml and CRP: 0.37 mg/L). Levels of omega-3 and omega-6 fatty acid intakes according to inflammatory markers categories (above or below corresponding median values) were compared using Student's *t* test.

The association between PUFA intake and high levels (above the median) of inflammatory markers was estimated using logistic regression models. In order to improve the interpretability of the results, PUFA variables were also dichotomised at their median values (corresponding medians were as follows: DHA: 0.42 g/day, EPA: 0.21 g/day, ALA: 1.22 g/day, LA: 11.21 g/day, AA: 0.18 g/day, ALA/LA: 0.108, EPA/AA: 1.152, DHA/AA: 2.358). Lower intakes were always used as the reference category. The following confounders were considered and included in the final models if they were related to both the exposure and the outcome, or modified (>10% change in coefficient) the estimates for the variables of interest in each model: age, gender, BMI, FEV_1, smoking status, reported physical activity, total caloric intake, inhaled corticosteroid treatment, statin treatment and the Charlson index of comorbidity. Finally, a multivariate model for each inflammatory marker was built including all five fatty acids and confounders. Similarly, a multivariate model for each inflammatory marker was built including all three ratios and confounders. Effect modification by smoking status was assessed by means of both stratification of final models and inclusion of interaction terms. The goodness of fit of all the models was assessed using Hosmer–Lemeshow test [22]. As a sensitivity analysis, all analyses were repeated excluding women (7% of total subjects) and using exposure variables as continuous. Data analysis was conducted using Stata 8.2 (StataCorp, College Station, TX, USA).

3. Results

Table 1 shows the main characteristics of the patients. Ninety-three percent of participants were males with a mean age of 68 years. Most subjects had moderate to severe COPD (distribution in COPD severity stages: 4% mild, 54% moderate, 35% severe and 7% very severe).

In the bivariate analysis, higher intake of ALA (omega-3, anti-inflammatory) was related to lower TNFα levels (1.30 ALA g/day in the low-TNFα category vs. 1.21 g/day in the high-TNFα category, $P=.03$). Regarding omega-6 (proinflammatory), higher intakes of LA and AA were, respectively, associated with higher CRP and IL-6 levels (LA: 11.31 g/day in the low- vs. 12.35 g/day in the high-CRP group, $P=.03$; AA: 0.185 g/day in the low- vs. 0.202 g/day in the high-IL-6 group, $P=.05$). Remaining comparisons did not provide statistically significant differences.

Tables 2 and 3 show crude and adjusted associations between fatty acids intake and each of the inflammatory markers. Being in the