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Dietary intake of fatty acids and its relationship with FEV_1/FVC in patients with chronic obstructive pulmonary disease

Abril Jiménez-Cepeda [1], Giselle Dávila-Said [1], Arturo Orea-Tejeda [1], Dulce González-Islas [*, 1], Marcela Elizondo-Montes [1], Guillermo Pérez-Cortes [1], Candace Keirns-Davies [1], Luis Felipe Castillo-Aguilar [1], Leslie Verdeja-Vendrell [1], Viridiana Peláez-Hernández [1], Rocío Nayelí Sánchez-Santillán [1]

Heart Failure and Respiratory Distress Clinic at Instituto Nacional de Enfermedades Respiratorias "Ismael Cosío Villegas", Mexico City, Mexico

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SUMMARY

Background & aims: The deterioration of pulmonary function has been associated with increased levels of systemic inflammation that can be stimulated by consumption of saturated fatty acids and trans fats. We hypothesized that fatty acids intake impact on pulmonary function. However, evidence about the impact of different types of fatty acids on pulmonary function in patients with chronic obstructive pulmonary disease (COPD) is limited and heterogeneous. The aim of this study was to evaluate the association between intake of fatty acids and pulmonary function in patients with COPD.

Methods: Cross sectional study of patients diagnosed with COPD. The relationship between consumption of fatty acids and the FEV_1/FVC ratio obtained by spirometry was assessed. Patients with exacerbations during the prior 2 months, diagnosis of asthma or administration of a dietary supplement were excluded.

Results: A simple linear regression showed that for each gram of carbohydrates and total l fatty acids intake, the FEV_1/FVC ratio decreased −0.03 ml (β: −0.03, 95% CI −0.06 to −0.01, p = 0.008) and −0.009 ml (β: −0.00, 95% CI −0.02 to 0.00, p = 0.031) respectively. Pentadecanoic acid (C15:0) was associated with an increase of 0.47 ml in the FEV_1/FVC ratio for each milligram intake (β: 0.47, 95% CI 0.04 to 0.91, p = 0.031). Subsequently, when adjusted for calories intake, an increase of 0.53 ml was observed in the FEV_1/FVC for each milligram of C15:0 fatty acid intake (β:0.53, 95% CI 0.09 to 0.97, p = 0.018).

Conclusion: A positive association was observed between pentadecanoic acid and the FEV_1/FVC ratio with a beneficial effect on patients with COPD.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by a progressive and practically irreversible compromise of air flow associated with an abnormal inflammatory response in the alveoli and small airways. It is associated with a high risk of morbidity and mortality [1]; it is the third cause of death worldwide and fifth most common cause of disability [2,3]. The spirometry parameters used for diagnosis, evaluation of the severity of obstruction of air flow and prediction of morbidity and mortality are forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC) and the FEV_1/FVC ratio [1,4].

Tobacco has been identified as the principal risk factor for COPD, although the absolute risk among smokers is only 25%–30% [5]. Other environmental factors such as eating habits have been implicated and may play an important role in the development and

Abbreviations: BMI, Body mass index; COPD, Chronic obstructive pulmonary disease; DHA, Docosahexanoic acid; EPA, Eicosapentanoic acid; FEV_1, Forced expiratory volume in 1 s; FVC, Forced vital capacity; FEV_1/FVC ratio, Forced expiratory volume in 1 s/Forced vital capacity ratio; GOLD, Global Initiative for Obstructive Lung Diseases; OCFA, Odd chain fatty acid; PUFA, Polyunsaturated fatty acids; SFA, Saturated fatty acids; TI, Tobacco index.

* Corresponding author.
E-mail addresses: abriljimenezc7@gmail.com (A. Jiménez-Cepeda), giselledavilasaid@hotmail.com (G. Dávila-Said), oreatart@gmail.com (A. Orea-Tejeda), gzz.dulce@gmail.com (D. González-Islas), marceelizondo19@gmail.com (M. Elizondo-Montes), memo_karey@hotmail.com (G. Pérez-Cortes), mieshe@comcast.net (C. Keirns-Davies), drluisfc@gmail.com (L.F. Castillo-Aguilar), leslie_vendrell@hotmail.com (L. Verdeja-Vendrell), ana_judo@hotmail.com (V. Peláez-Hernández), rnsanchezs@gmail.com (R.N. Sánchez-Santillán).

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progression of COPD. There is now a growing interest in identifying the eating patterns or specific nutrients associated with the development and evolution of COPD. Some studies have shown that consumption of abundant fruits, vegetables, whole grain cereals and polyunsaturated fatty acids (PUFA) is associated with a 33% lower incidence of COPD (hazard ratio 0.67, 95% CI 0.53 to 0.85) [6,7]. In addition, daily consumption of fish was associated with diminished deterioration of FEV_1 [8], and consumption of ≥25 g of total fiber had a positive association with FEV_1, FVC and FEV_1/FVC as well as a lower incidence of COPD (RR: 0.67, 95% CI 0.5 to 0.9, $p = 0.03$) [9,10]. Moreover, higher FEV_1 and FVC were observed in subjects who intake more vitamin D [11], and high consumption of vitamins C and E led to significant improvements in FEV_1 and FVC and lower prevalence of COPD [12]. At the same time, a 64% decrease in the prevalence of COPD was observed in patients with greater consumption of isoflavones (OR: 0.36, 95% CI 0.19 to 0.68, $p = 0.001$) [13]. Consumption of calcium and iron also lowered the prevalence of COPD and showed a low correlation with FEV_1 [14]. In contrast, a diet rich in cereals, refined sugars, red meat, French fries, salt and beer was associated with lower $FEV_1$and a 4.56 times greater risk for COPD (RR: 4.56, 95% CI 1.95 to 10.56, $p < 0.001$) [10,15]. Deterioration of pulmonary function has been associated with increased systemic inflammation [16], which can be stimulated by intake of saturated fatty acids (SFA) and trans fats. Thus, when total fatty acids represent 30–64% of the source of energy intake, they can lead to greater oxidative stress and inflammation [17–19]. However, information regarding the type of fatty acids ingested and their impact on pulmonary function is scanty and varied. In order to address this, the objective of this study is to evaluate the association between consumption of fatty acids and pulmonary function in COPD patients.

2. Methods and materials

2.1. Study population

A total of 189 out-patients ≥40 years of age diagnosed with COPD according to the criteria of the Global Initiative for Obstructive Lung Diseases (GOLD) with a FEV_1/FVC ratio <0.70 post-bronchodilator [20] were included in a cross sectional study. Patients with exacerbations that occurred during the prior 2 months, asthma or administration of any dietary supplement were excluded. Subjects were recruited from January, 2016 to May, 2017. The research protocol was approved by the Science and Research Bioethics Committee (C18-15) of the National Institute of Respiratory Diseases "Ismael Cosío Villegas". The confidentiality of patient information was guaranteed and informed consent was obtained from all patients.

2.2. Collection of data

The participants in the study were interviewed. The first part consisted of demographic and life style information including age, gender, exposure to wood smoke and tobacco smoke and respiratory symptoms. The second part of the interview involved a 24-hour food diary performed by a qualified nutritionist and standardized to obtain the dietary consumption of each patient. In order to achieve as much precision as possible in the 24-hour food diary, replicas of foods (NASCO *life form*) were used to aid the patient in identifying the size, weight and quantity of each food. A precise and complete nutritional analysis of the subjects' diets was obtained using the Food Processor® SQL Nutrition Analysis Software (version 7.9; ESHA Research). Respiratory function tests were performed using spirometry (Vmax encore B650 spirometer) [21]. Body mass index (BMI) was calculated based on weight (SECA 813 scale) and height (SECA 213 portable stadiometer) measured by conventional methods with the patient standing upright on a Frankfort horizontal plane without shoes [22].

2.3. Statistical analysis

Categorical variables were presented in frequencies and percentages. For continuous variables a normality analysis was first performed with Kolmogorov/Smirnov, then continuous variables with normal distribution were presented with mean and standard deviation. Variables without normal distribution were presented with median and 25–75 percentiles. Finally, in order to evaluate the association between diet and FEV_1/FVC ratio post-bronchodilator, simple and multiple linear regressions were performed with the multiple linear regression adjusted for energy intake. Statistical significance was considered to be p-value < 0.05. The analysis was performed with SPSS software, version 17 (SSPS for Windows, Rel 10.0 1999 Chicago, IL, USA, SPSS Inc).

3. Results

Of the 189 participants, 57.5% were men, mean age was 70.85 ± 9.89 years and body mass index (BMI) was 26.28 ± 5.75. As respects etiology, 49.72% were tobacco, 42.7% were biomass and the rest mixed etiology. The tobacco index (TI) was 39 [12–59] pack years; the wood smoke index was 160 [36–360] hours/year without current exposure. The most common symptoms were shortness of breath 67.2%, fatigue 56.9%, cough 45.6% and phlegm 51.7%. As far as pulmonary function was concerned, $FEV_1$was found to be 56.51 ± 13.76, FVC 80.14 ± 23.11 and FEV_1/FVC ratio 56.51 ± 13.76.

As respects nutritional consumption of the subjects, the kilocalorie mean was 1573 ± 619.14 with 196.52 [150.06–272.15] grams of carbohydrates, 62.71 ± 26.83 g of protein and 42.83 [29.55–62.15] grams of total fatty acids (Table 1).

The simple linear regression showed that for each gram of carbohydrates and total fat intake, the FEV_1/FVC ratio decreased −0/03 (β: −0.03, 95% CI −0.06 to −0.01, $p = 0.008$) and −0.009 ml (β: −0.009, 95% CI −0.02 to 0.00, $p = 0.031$) respectively. However, when each fatty acid was evaluated, a positive association was

Table 1
Population characteristics.

	Total
	n = 189
Men, %	57.5
Age (years)	70.8 ± 9.89
BMI (kg/m^2)	26.28 ± 5.75
Type of COPD	
Smoking, %	49.72
Biomass, %	42.7
Mixed, %	7.56
Prior Smoking pack-years	39 [12–59]
Prior Wood smoke index (Hours-year)	160 [36–360]
Shortness of breath, %	67.2
Fatigue, %	56.9
Cough, %	45.6
Phlegm, %	51.7
FEV_1 (% post-bronchodilator)	52.16 ± 23.31
FVC (% post-bronchodilator)	80.14 ± 23.11
FEV_1/FVC ratio (% post-bronchodilator)	56.51 ± 13.76
Energy (Kcal)	1573.98 ± 619.14
Carbohydrates (g)	196.52 [150.06–272.15]
Proteins (g)	62.71 ± 26.83
Total fats (g)	42.83 [29.55–62.15]

BMI: Body mass index; FEV_1: Forced expiratory volumen in 1 s; FVC: Forced vital capacity; Forced expiratory volumen in 1 s and Forced vital capacity ratio; Kcal: Kilocalories.

found between the intake of fatty acids with odd numbered chains and the FEV_1/FVC ratio. Pentadecanoic acid (C15:0) was associated with an increase of 0.47 in the FEV_1/FVC ratio for each milligram intake (β: 0.47, 95% CI 0.04 to 0.91, p = 0.031), and when adjusted for calories intake, an increase of 0.53 in the FEV_1/FVC ratio for each milligram of pentadecanoic acid intake (β: 0.53, 95% CI 0.09 to 0.97, p = 0.018) was observed. No other association between the remaining nutrients and the FEV_1/FVC ratio was found (Table 2).

4. Discussion

The principal finding of this study was the positive association between the FEV_1/FVC ratio and consumption of pentadecanoic acid (C15:0). Prior studies have shown similar results to ours, *i.e.*, a positive association between the FEV_1/FVC ratio and diet. For example, Siedlinski et al., found a relationship between white wine and diminished risk of airway obstruction [23]. Consumption of vitamin D also had a positive effect on pulmonary function [24]. Pentadecanoic acid is an odd chain fatty acid (OCFA). The principal OCFA are C15:0, C17:0, C17:1 and C23:0 [25]. Pentadecanoic acid, which is produced in large part by the fermentation of the microbiota of ruminants [26], is the most studied. It is considered to be a biomarker of consumption of fats from dairy products, especially milk, which contains about 1.2% pentadecanoic acid [27–31]. It is also found in lower concentrations in beef, lamb, and fish [32]. In spite of the evidence that a diet high in SFA increases serum cholesterol and the incidence of coronary artery disease [33], the complexity of the structure of SFA and the diversity of their biological functions is little known, so a blanket generalization about their effects is not warranted [34]. Short chain SFA, that is fewer than 10 carbons, act as a rapid source of energy and are the preferred fuel for the heart. They do not increase total serum cholesterol and have a low tendency to form adipose tissue [35,36]. In fact, butyric acid (C4:0) has antitumor properties and modulates the immune and inflammatory response. Capryllic (C8:0) and capric (C10:0) acids are recognized for their antiviral and antibacterial functions as is lauric acid, a middle length chain fatty acid (12:0) [37–39]. Stearic acid (C18:0) has been shown to diminish total serum cholesterol [40]. On the other hand, myristic (C14:0) and palmitic (C16:0) fatty acids are known to atherogenic [35].

As regards pentadecanoic acid, its beneficial effects on health, including reduction of body weight, waist and hip circumference, BMI, LDL-HDL index, plasma triglycerides, systolic blood pressure and plasma glucose as well as lower risk of cardiovascular disease, coronary artery disease, cerebrovascular disease and type 2 diabetes (DM2) [41–43], have been observed. However, the way that OCFA lead to these physiological benefits is not known. OCFA are present in the phospholipid layer of membranes at a concentration below 1% [43]. A study of patients with anorexia nervosa showed that when essential fatty acids diminished in the phospholipid membrane, the OCFA increased and improved the fluidity of the cellular membrane [44]. Thus, one of the mechanisms proposed is the regulation of homeostasis in phospholipid membrane function, and small changes in the circulating levels of OCFA can be biologically relevant [43]. Studies in mice with mitochondrial dysfunction receiving supplemental triheptanoin (3 seven carbon fatty acids that provided anaplerotic—intermediate–substrates) have shown that these fatty acids maintained mitochondrial function and renovated architecture and metabolic variables like oxidation of metabolites and glucose tolerance [45,46]. Pfeuffer et al., have suggested that in patients with diabetes mellitus, a condition associated with mitochondrial dysfunction [47] pentadecanoic acid could provide the same benefits as triheptanoin. Since its final product is propionyl CoA, and it could be converted into anaplerotic substrates for the citric acid cycle, they propose this mechanism to restore glucose homeostasis [48].

In patients with COPD, exposure to tobacco smoke, increased energy demands, and inflammatory processes affect the structure and function of mitochondria, leading to mitochondrial dysfunction as a response to oxidative stress, inflammatory response, proliferation, apoptosis, fibrosis and metabolic alterations [49,50]. As a result, the expression of oxidative phosphorylation and enzymatic activity of the citric acid cycle diminish, contributing to a cycle that accentuates the severity of the disease [49]. This may be the way that OCFA participate in improvement of respiratory function in patients with COPD.

As far as the beneficial effects of milk are concerned, they have been attributed mainly to calcium. Other nutrients found in milk,

Table 2
Relationship between nutrients and pulmonary function based on FEV_1/FVC.

	FEV_1/FVC			FEV_1/FVC		
	Crude Model			Energy-adjusted model		
	β	CI (95%)	p	β	CI (95%)	p
Energy (Kcal)	−0.00	(−0.00 to 0.00)	0.259			
Protein (g)	−0.00	(−0.00 to 0.00)	0.417	0.01	(−0.00 to 0.02)	0.235
Carbohydrates (g)	−0.03	(−0.06 to −0.01)	0.008	0.00	(−0.06 to −0.07)	0.013
Total fatty acids (g)	−00.0	(−0.02 to 0.00)	0.031	0.00	(−0.04 to 0.04)	0.985
Saturated fatty acids (g)	−0.02	(−0.09 to 0.03)	0.385	−0.00	(−0.09 to 0.09)	0.934
Butyric (g)	6.00	(−1.49 to 13.49)	0.116	6.31	(−1.18 to 13.81)	0.098
Pentadecanoic acid (mg)	0.47	(0.04 to 0.91)	0.031	0.53	(0.09 to 0.97)	0.018
Monosaturated fatty acids (g)	−0.04	(−0.12 to 0.03)	0.274	−0.01	(−0.21 to 0.17)	0.869
Oleic (g)	−0.08	(−0.20 to 0.41)	0.189	−0.08	(−0.33 to 0.16)	0.502
Polyunsaturated fatty acids (g)	−0.02	(−0.08 to 0.03)	0.474	0.07	(−0.09 to 0.24)	0.36
Omega 3 (g)	−0.02	(−0.11 to 0.05)	0.476	0.10	(−0.12 to 0.33)	0.357
DHA (g)	−0.04	(−0.19 to 0.96)	0.503	0.20	(−0.19 to 0.61)	0.304
EPA (g)	−0.07	(−0.27 to 0.13)	0.500	0.29	(−0.26 to 0.85)	0.306
Omega 6 (g)	−0.10	(−0.47 to 0.26)	0.564	0.04	(−0.43 to 0.52)	0.849
Vitamin A (IU)	2.70	(−0.00 to 0.00)	0.991	0.00	(−0.00 to 0.00)	0.418
Vitamin C (mg)	0.00	(−0.01 to 0.02)	0.421	0.00	(−0.01 to 0.02)	0.382
Vitamin D (mg)	0.01	(−0.00 to 0.02)	0.091	0.01	(−0.00 to 0.02)	0.082
Vitamin E (IU)	−0.02	(−0.07 to 0.03)	0.461	0.10	(−0.12 to 0.34)	0.365
Calcium (mg)	−0.00	(−0.00 to 0.00)	0.405	0.00	(−0.00 to 0.00)	0.895
Magnesium (mg)	−0.00	(−0.00 to 0.00)	0.451	0.00	(−0.00 to 0.01)	0.395
Selenium (mg)	−0.00	(−0.00 to 0.00)	0.552	0.00	(−0.00 to 0.00)	0.232

Kcal: Kilocalories; DHA: Docosahexanoic acid; EPA: Eicosapentenoic acid.

including vitamins C, D and E, also provide multiple benefits leading to improved $FEV_1$and FVC [11,12]. Magnesium, selenium and vitamin A may also limit pulmonary damage by preventing oxidative stress and inflammation [51]. However, when we analyzed these nutrients we found no association with the FEV_1/FVC ratio. On the other hand, Jiang et al., observed consumption of dairy products was associated with a positive effect on FVC. They found that subjects in the highest quintile of dairy products ingested had FVC 72 ml greater than those in the lowest quintile [52]. Wood et al., evaluated the relationship between lipid intake and respiratory function in older people; their results were similar to ours in that they found no association between $FEV_1$and total energy intake, SFA, monounsaturated fatty acids and omega 3 and 6 PUFA. In their study total lipid intake reduced the FEV_1 by 1.1% and the FVC by 0.5%. However, they did not examine the effect of OCFA. Moreover, Broekhuizen et al., found that consumption of omega 3 fatty acids had no effect on the FEV_1 [53].

Omega 3 fatty acids (eicosapentanoic acid (EPA) and docosahexanoic acid (DHA)) may attenuate the deterioration of respiratory function since they are associated with lower levels of systemic inflammation [16]. It could be that omega 3 fatty acids replace arachidonic acid in the cell membrane and inhibit the production of pro-inflammatory eicosanoids and activation of nuclear factor kB (a regulator of the codification of inflammatory mediator genes) [54]. A meta-analysis by Li et al., showed that omega 3 PUFA reduced C reactive protein, interleukin 6 and tumor necrosis factor α in chronic diseases. However, this meta-analysis did not include respiratory diseases [55]. Omega 3 PUFA have been found to benefit patients with COPD by improving quality of life and reducing systemic inflammation [56,57]. Nevertheless, some studies show no association between omega 3 fatty acids and inflammation and respiratory function [58,59]. The fatty acids EPA and DHA are precursors of "resolvins", entities with anti-inflammatory properties. In COPD they attenuate inflammation induced by cigarette smoke, reducing cell death, stimulating efferocytosis and promoting the production of interleukin 10 (IL-10) [60,61]. Csanky*et al*., showed a positive association between EPA and FEV_1 [62]. Various studies that evaluated the relationship between fatty acids in serum phospholipids and respiratory function found a positive association between DHA and EPA and FEV_1, FVC and the FEV_1/FVC ratio [60,63,64]. However, in a Dutch study a negative association between DHA intake and FEV_1 and greater risk of respiratory symptoms with EPA intake were observed [58]. We found no relationship between intake of DHA or EPA and respiratory function, perhaps because of the low consumption of these fatty acids in our population.

As regards this report, we recognize the inherent limitations of a transverse study and the small sample size. However, it does explore new and relevant information about the relationship between pentadecanoic fatty acid and the FEV_1/FVC ratio and indicates the need to pursue new longitudinal studies to clarify the effect of odd chain fatty acids on respiratory function and the physiological mechanisms involved. This could lead to inclusion of OCFA in the diet as a novel therapeutic strategy in patients with COPD. Other possible limitations of our study could be the 24-hour diet record, since it relies on memory and the reluctance of the subject to provide the information during an interview [65]. However, Wolk et al., demonstrated that a 24-hour diet record is a valid tool to estimate dietary OCFA, which supports its use in our research protocol [66].

5. Conclusion

Pentadecanoic fatty acid was observed to have a beneficial impact on the FEV_1/FVC ratio in patients with COPD.

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Appendix A. Supplementary data

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