Inflammatory Status in Moderate and Severe COPD Patients: What Are the Related Factors?

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Abstract

Background: Systemic inflammation is believed to have an important role in pathogenesis of Chronic Obstructive Pulmonary Disease (COPD) and its related factors should be considered in monitoring of the disease. In the current study, possible link between inflammatory status and various related factors in patients with COPD was assessed.

Method: Sixty-one COPD patients according to the inclusion criteria participated in this study. For assessing nutritional status, SGA (subjective global assessment) and 24-hour dietary recall method were used and Health-related quality of life (HRQoL) was assessed by St. George's respiratory questionnaire (SGRQ), instrumental activities of daily living scales (IADLs), and Katz Index. Moreover, Anthropometric and body composition measurements including weight, height, BMI, FFM, and FFMI were measured by standard methods and BIA. Additionally, muscle strength was assessed using a hydraulic hand dynamometer. Finally, blood samples were collected to assess biochemical factors including TNF-α, IL-6, MDA, vitamin C, magnesium, and Glutathione. Stepwise model was performed for evaluating the relationship between inflammatory markers (TNF-α and IL-6) and associated markers mentioned above. Characteristics of participants were expressed in percentage and mean ±SD and analyzed by SPSS software.

Results: The results of the current study showed that the intake of PUFA and vegetables, plasma vitamin C and serum MDA could possibly affect inflammation according to IL-6 and TNF- α concentrations. On the other hand, systemic inflammation (IL-6 and TNF-) aggravated mean right and left handgrip strength, Katz index and nutritional status (SGA score) significantly ($P < 0.05$).

Conclusion: To sum up, our results confirmed the inter-relationship between inflammatory markers and intake of some dietary components, oxidative stress biomarkers, muscle function, and nutritional status in COPD patients. These factors might affect over each other and further studies are needed to better elucidate this issue.

Keywords: Lung Disease, Inflammation, Muscle Strength, Oxidative Stress

1. Introduction

Chronic obstructive pulmonary disease (COPD) as a limited airflow disease, is a global epidemic concern,

prevalent in over 30 years old people by 6.3 percent (Li, Han, Zhang, Cao, & Su, 2020) and it's become more widespread in recent years as a fifth cause of death worldwide (Arora, Madan, Mohan, Kalaivani, & Guleria, 2019).

In COPD patients, some disturbances like hypercapnia, eating disorders, elevated metabolic rate and loss of ventilation along with oxidative stress leads to chronic airway complications and consequently systemic inflammation that initiates via neutrophils, macrophages, T-lymphocytes, and cytokines including IL-6, IL-8, and TNF-α overproduction (Hallin, Koivisto-Hursti, Lindberg, & Janson, 2006). Elevated inflammation as a principle feature of COPD is a key mechanism in pathogenesis of this illness which is related to extra pulmonary disease like cardiovascular diseases, osteoporosis, diabetes, and metabolic syndrome (Di Francia, Barbier, Mege, & Orehek, 1994; Eid et al., 2001; Itoh et al., 2004; Takabatake et al., 1999). In addition, muscle wasting as a factor affecting quality of life and physical activity, is closely associated with inflammation (Byun, Cho, Chang, Ahn, & Kim, 2017).

Tumor necrosis factor-alpha (TNF-α) and interleukin 6 (IL-6) are some crucial inflammatory mediators related to COPD (Ardestani & Zaerin, 2015). TNF-α as an inflammatory cytokine, is involved in increasing adhesion molecules, mucin secretion, and causes remodeling in respiratory tracts (Chiang, Chuang, & Liu, 2014). Furthermore, as a cytokine it may cause inflammation via tissue damaging and its relationship with body composition is a fact stated in many studies (Ren, 2017). IL-6 as another inflammatory marker involved in lung function decline, plays role in the muscle mass and muscle function decline and is related to immunity suppression (Bucchioni, Kharitonov, Allegra, & Barnes, 2003; Zhang, Dai, Zhai, Feng, & Lin, 2017; Park et al., 2013). On the other hand, inflammation and oxidative stress are tightly interconnected in pathophysiological conditions and chronic disease such as COPD due to involvement of inflammatory cells in releasing reactive oxygen species which can worsen the symptoms (Biswas, 2016).

Due to high prevalence of malnutrition by approximately 20–40% and interaction between the function of respiratory system and nutritional status in COPD patients, diet can act as a modifying factor (Aniwidyaningsih, Varraso, Cano, & Pison, 2008). Moreover, despite the fact that interrelationship between inflammation and nutritional status in COPD patients is not clear, complex changes in metabolism, nutritional deprivation, and hyper-metabolism can be a consequence of systemic inflammation and here the question arises that which dietary component is more associated with this context (Hallin et al., 2011; Ezzell & Jensen, 2000).

Because no study is available about assessing the relationship between COPD as an inflammatory disease and its related factors, the aim of our study was to assess the possible link between inflammatory markers and body composition, oxidative stress, nutritional status and some food ingredients in patients with moderate to severe COPD.

2. Method

2.1 Study Design

A present cross-sectional study in COPD patient was done in September to December 2018. Participants were recruited from four medical centers affiliated to Shiraz University of Medical Sciences, Shiraz, Iran (Rajai, Nemazee, Shahid Faghihi and Ali-asghar hospitals) and specialized respiratory clinics with medical history from March 2011 to June 2018. A total of 1957 patients were screened in study, 120 patients were recruited, but only 61 of them were satisfied and included. All were male outpatients aged 40-70 years, COPD patients diagnosed for at least 3 months, moderate to severe disease condition, COPD patients according to medical history since 7 years. Patients with infections, malignancies and any other organ failure did not take part in the current study. The study protocol was approved by the Ethics Committee of Shiraz University Medical Sciences and all enrolled patients signed the informed written contest.

2.2 Participants' Characteristics

A retrospective review of the medical record covering age, educational degree, job circumstances, smoking habits, type of tobacco used, and age of onset, duration of smoking, and medical history were recorded.

2.3 Disease Severity

Classification of COPD patients by severity was determined by spirometry test and was done for all patients. This assessment was implemented by a standard method (Vitalograph Pneumotrac 77000PC based spirometry, England) based on FEV (forced expiratory volume) in a second and the highest FEV in three times measurement was considered as the main value (Cazzola et al., 2008).

2.4 Nutritional Assessment

An experienced investigator used PG-SGA (patient generated subjective global assessment) as a nutrition assessed tool, to evaluate the nutrition-associated complications correlated to medical history (BMI, %weight loss, food intake, gastrointestinal symptoms, quality of life, and respiratory stress) and physical examination (muscle wasting, subcutaneous fat loss, and edema) (Bauer, Egan, & Clavarino, 2011). Severe malnutrition assigned to patients that received score >17 (Sohrabi, Eftekhari, Eskandari, Rezaianzadeh, & Sagheb, 2016). Moreover, Participants were asked to recall all foods consumed in 3 days (two weekdays and one weekend day) based on 24-hour dietary recall method (Rodrigues et al., 2016). For calculation of nutrient intakes, Diet Analysis Nutritionists IV software (N Squared Computing, San Bruno, SA, USA) was used (Schröder et al., 2001).

2.5 Health-Related Quality of Life (HRQoL) Assessment

Quality of life was measured according to lung function by questionnaire tools including St. George's respiratory questionnaire (SGRQ), instrumental activities of daily living scales (IADLs) and Katz Index.

SGRQ questionnaire is a quality of life tool assessment, which includes 14 items in 3 categories of symptoms (frequency and severity of respiratory), activity (role limitations due to breathlessness), and impact (psychological and social functioning disturbances due to respiratory disorder). The total score was obtained from 3 categories in a range of 0 to 100 and a higher score indicates a worse situation (Jones, 2008).

IADL scale was used for assessing the ability to perform daily tasks independently and it score was 0 to 8. Another scale, dependency status in activities of daily living (ADL), was determined by using Katz-ADL index and scored 0 (severely dependent) to 6 (independent). The content of ADL questionnaire was dependency from activities such as bathing, dressing, toileting, transporting, continence, and feeding (Graf, 2008).

2.6 Anthropometric Measurements and Body Composition

Anthropometric measurements including weight, height, BMI, calf circumference (CC), segmental lean body mass, FFM, and FFMI were assessed by an experienced nutritionist by standard methods.

Participants were weighed using calibrated scale (Omron, Korea) while wearing light clothing and no shoes to the nearest 0.1 kg and height was measured by a stadiometer to the nearest 0.1 cm. body mass index (BMI) was calculated by dividing weight by height squared (Lee, 2013). Flexible tape was used to measure CC to the nearest 0.1 cm in a sitting position (Lee & Nieman, 2003).

Segmental fat mass, fat free mass (FFM) and lean body mass were assessed by segmental multi-frequency Bioelectrical Impedance Analysis (BIA) and InBody S10 analyzer (BioSpace Co., Ltd., South Korea) (Lee, 2013). Finally, by dividing FFM by height square, FFMI was obtained (Schols et al., 2014).

2.7 Muscle Strength Assessment

By using a hydraulic hand dynamometer (model MSD, Sihan, Korea) in sitting position, muscular strength was measured (Massy-Westropp, Gill, Taylor, Bohannon, & Hill, 2011). Mean of three measurements was calculated for both hands (Chen et al., 2014).

2.8 Biochemical Measurements

Blood samples were collected after 10–12h overnight fasting. After Blood centrifugation at 3000 rpm for 10 min, plasma was stored at -70 °c. For assessing serum albumin concentration, enzymatic method (commercial kit from Pars Azmun, Iran) by Auto-chemistry analyzer (BT1500; Biotecnica Instrument, Italy) was performed (Paleari et al., 2017). Moreover, antioxidant status via concentrations of Glutathione (GSH) in plasma was determined using colormetrically kit (ZellBio GmbH, Germany) (Hou, Li, Li, Liu, & Xu, 2018). Inflammatory factors including TNF-α and IL-6 were evaluated by an enzyme linked immune sorbent assay (ELISA) method, using Demeditec and IBL international kits (Sapey et al., 2009). MDA (thiobarbituric acid reactive substances) concentration was assessed by spectrophotometry method and expressed by μm per liter of plasma (Kluchova, Petrášová, Joppa, Dorkova, & Tkáčová, 2007).

Plasma vitamin C concentrations were determined using HPLC (high pressure liquid chromatography) method (Waters pump Binary 1525, USA) (Najwa & Azrina, 2017). Furthermore, serum magnesium levels were measured using photometric assays and standard kit (Ziest CHEN, Iran) (Schutten et al., 2019).

2.9 Statistical Analysis

Characteristics of participants were expressed in percentage, mean ± SD, interquartile range and percentile which analyzed by SPSS software, version 19.0 (SPSS Inc., Chicago, IL, USA). The relationship between

inflammation (TNF-α and IL-6) and associated markers (vitamin A, vitamin C, vitamin E, selenium, zinc, carbohydrate, fat, protein, energy intake, PUFA, MUFA, saturated fatty acids, legume, vegetables, dairy, fruits, grain, BMI, lean body mass, fat-free mass (FFM), FFM/height, BIA protein, FEV1(forced expiratory volume), CC (calf circumference), mean right and left handgrip strength, albumin, plasma vitamin C, Mg, GSH and MDA, SGA score, Kats Score, IADL, SGRQ total score, physical activity, duration and rate of smoking) was evaluated by stepwise linear regression model. For distinguishing the factors which may affect inflammation, variables such as Mg, vitamin C, carotenoid, zinc, selenium, vitamin A, vitamin E, PUFA, MUFA, saturated fatty acids, nuts, legumes, vegetables, dairy, fruits, grains, plasma vitamin C, Mg, GSH and MDA, FEV-1, duration and rate of smoking were entered as independent markers and stepwise model was performed. Moreover, to detect the relationship between inflammatory markers and variables that might be affected by inflammation, SGA score, Katz score, IADL, SGRQ total score, BIA protein, activity, BMI, segmental lean body mass, FFM, FFMI, CC, mean right and left handgrip strength were entered as independent variables and stepwise model was used for analysis. P value of <0.05 was considered significant and Shapiro-wilk test was used to assess the normality of the data.

3. Results

3.1 Participants

Table 1. Characteristics of participants

Variables	N (%)
Age, years	
40-50	1 (1.63)
51-60	20 (32.79)
61-70	34 (55.74)
>70	6 (9.84)
Education	
Illiterate	11 (18)
Elementary	29 (47.6)
Intermediate	6 (9.8)
Diploma	10 (16.4)
>Diploma	5 (8.2)
Job	
Exposure to dust	19 (31.1)
Exposure to chemicals	15 (24.6)
Exposure to dust and chemicals	8 (13.1)
Driver	10 (16.4)
Other	9 (18.8)
Type of tobacco and opioid used [a]	
Cigarette	55 (90.16)
Opium	41 (67.21)
Hookah	7 (11.47)
Methadone	8 (13.11)
Heroin	2 (3.27)
Smoking status (cigarette and hookah) [a]	
Have already consumed	55 (90.16)
Now they consume	34 (55.73)
Never used	6 (9.83)
Age of onset of smoking, years	
9-20	27 (50)
21-30	14 (25.93)
31-40	8 (14.82)
>40	5 (9.25)
Years of smoking	
3-20	11 (20)
21-40	23 (41.82)
>40	21 (38.18)
FEV1	
Moderate	23 (37.7)
Severe	38 (62.3)

FEV1: Forced expiratory volume in 1second. [a] The percentages were reported to be over 100 because each individual might have multiple answers.

Table 2. Mean ±SD of variables of body composition, lung function, muscle strength, smoking status, plasma, SGA and quality of life questionnaires

Variables	mean±SD	Interquartile Range(IQR)	Percentile (25-75)
Body composition			
BMI, kg/m^2	21.02±2.89	3.85	19.35-23.20
Segmental lean body mass, kg	6.86±0.71	0.91	6.37-7.28
Protein BIA	9.21±1.14	1.35	8.45-9.80
Fat-free mass, kg	46.88±5.65	6.75	43-49.75
FFMI, kg/m2	16.65±1.48	1.81	15.87-17.67
Calf circumference, cm	31.32±2.46	3.50	29.75-33.25
Lung function			
FEV1, %	43.69±15.83	27	31-58
Muscle strength			
Mean handgrip Right, kg	22.49±6.24	7.01	18.66-25.66
Mean handgrip Left, kg	21.93±7.36	10	16.66-26.66
Smoking status			
Duration of consumption	35.43±13.96	21	25-46
Maximum amounts of cigarettes consumption per day	25.71±12.15	23.50	16.50-40
Blood analysis			
Albumin, g/dl	4.14±0.36	50	3.90-4.40
Vitamin C, µM/L	28.68±3.90	5.25	25.75-31
Magnesium, mg/dl	2.02±0.16	0.20	1.90-2.10
GSH, mM/l	189.21±39.14	62	159-221
MDA, µM/L	2.81±0.47	0.65	2.50-3.15
TNFα, pg/ml	27.40±10.18	16.66	19.01-35.67
IL-6, pg/ml	9.65±10.48	12.01	2.32 -14.33
Questionnaires			
SGA score	10.98±5.73	7	7-14
Katz index	5.45±0.94	1	5-6
I.A.D.L score	5.11±1.41	1	5-6
SGRQ, total score	15.08±27.32	9.77	0.57-10.34
SGRQ, impact score	13.57±26.04	6.02	0.53-6.56
SGRQ, activity score	16.74±30	3.70	0.59-4.30
SGRQ, symptom score	17.22±30.34	21.56	0.61-22.17

BMI: body mass index, BIA: Bioelectrical Impedance Analysis, FFMI: fat free mass index, FEV1: forced expiratory volume in 1second, GSH: glutathione, MDA: Malondialdehyde, TNF-α: Tumor necrosis factor. IL-6: Interleukin 6, SGA: subjective global assessment, I.A.D.L: Instrumental Activities of Daily Living, SGRQ: St. George's Respiratory Questionnaire.

Baseline background characteristics of 61 patients with moderate and severe COPD are summarized in table 1. Sixty-five percent of patients were older than sixty and only 24.6 percent of them had education level of diploma or more. Due to their job history exposure to dust and chemicals were 31.1 and 24.6 percent respectively. Almost 90 percent of patients had cigarette smoking and only 10 percent of them never smoked. The age of smoking initiation was less than twenty years in 50 percent of subjects and 80 percent of them had more than twenty years' history of smoking. Based on disease severity classification 38 percent had moderate and 62 percent had severe FEV1.

Assessment of body composition, lung function, muscle strength, smoking status, blood markers, nutritional status and quality of life is reported as mean ± SD in table 2. Considering body composition subjects had mean of 21.02 kg/m^2 for BMI and 6.86 kg for segmental lean body mass. While the mean for fat-free mass and calf circumference were 46.88 kg and 31.32 cm respectively. Due to muscle strength assessment mean of right and left handgrips were reported 22.49 and 21.93 kg. In addition, Blood sample analysis showed that mean of albumin, vitamin C and IL-6 among patients was 4.14 g/dl, 28.68 µM/L and 9.65 pg/ml. The mean score of SGA and IADL score were 10.98 and 5.11.

3.2 IL-6, TNF-α and Associated Markers

The results in Table 3 showed that based on stepwise model intake of polyunsaturated fatty acids, vegetables and grains, right handgrip and Katz index were significantly associated with serum level of IL-6. Furthermore, variables such as intake of vegetables, left handgrip strength and Katz index were significant determinants of TNF-α ($P < 0.05$).

Table 3. Factors associated with IL-6 and TNF-α due to stepwise model.

Variables	IL-6		TNF-α	
	β (95% CI)	P [a]	β (95% CI)	P [b]
Polyunsaturated fatty acid (gr)	0.39 (0.18, 0.61)	0.001*	-	-
Vegetables (gr)	-0.1 (-0.02, -0.005)	0.006*	-0.02 (-0.03, -0.003)	0.022*
Grain (gr)	0.1 (0.00, 0.02)	0.048*	-	-
Right handgrip (kg)	-0.51 (-0.8, -0.23)	0.001*	-	-
Left handgrip (kg)	-	-	-0.34 (-0.64, -0.04)	0.025*
Katz index	-5.26 (-7.12, -3.41)	0.000*	-3.89 (-6.28, -1.5)	0.002

Vitamin A, vitamin C, vitamin E, selenium, zinc, carbohydrate, fat, protein, Energy, PUFA, MUFA, saturated fatty acids, legume, vegetables, dairy, fruits, grain, BMI, lean body mass, fat-free mass (FFM), FFM/height, BIA protein, FEV1(forced expiratory volume), CC (calf circumference), mean right and left handgrip strength, albumin, SGA score, Kats Score, IADL, SGRQ total score, physical activity, duration and rate of smoking were entered in the model as independent variables. *P < 0.05 considered significant.

3.3 The Interrelationship between Inflammatory Markers and Related Factors

Table 4. Factors affecting inflammation based on stepwise model

Variables	IL-6		TNF-α	
	β (95% CI)	P [a]	β (95% CI)	P [b]
Polyunsaturated fatty acid (gr)	0.39 (0.18, 0.61)	0.001*	-	-
Vegetables (gr)	-0.02 (-0.04, -0.008)	0.004*	-0.02 (-0.03, -0.003)	0.022*
Plasma vitamin C (µM/L)	-	-	-0.78 (-1.47, -0.09)	0.027*
MDA (µM/L)	6.90 (0.73, 13.07)	0.029*	-	-

Mg, vitamin C, carotenoid, zinc, selenium, vitamin A, vitamin E, PUFA, MUFA, saturated fatty acids, nuts, legumes, vegetables, dairy, fruits, grains, GSH, MDA, plasma vitamin C and Mg, FEV-1, duration and rate of smoking were entered in the stepwise model as independent variables. MDA: Malondialdehyde. *P < 0.05 considered significant.

Table 5. Effect of inflammation on study parameters based on stepwise model

Variables	IL-6		TNF-α	
	β (95% CI)	P [a]	β (95% CI)	P [b]
Right handgrip (kg)	-0.55 (-0.96, -0.13)	0.01*	-	-
Left handgrip (kg)	-	-	-0.40 (-0.78, -0.05)	0.025*
SGA score	-	-	0.85 (0.18, 1.52)	0.014*
Katz index	-4.47 (-7.45, -1.49)	0.004*	-	-

SGA score, Katz score, IADL, SGRQ total score, BIA protein, activity, BMI, segmental lean mass, FFM, FFM/height, CC, mean right and left handgrip strength were entered in the stepwise model as independent variables. SGA: Subjective global assessment. *P < 0.05 considered significant.

It is apparent from Table 4 that MDA levels, vitamin C plasma concentration, poly unsaturated fatty acid and vegetable intakes had significant roles in the occurrence of inflammation. In this regard vegetables intake affect IL-6 level negatively, while poly unsaturated fatty acid intake and MDA serum level had additive effect on it. Additionally, vegetables intake and serum vitamin C level inversely effected TNF-α.

Table 5 illustrate that serum level of IL-6 and TNF-α significantly affected some factors such as right and left

handgrip, SGA score, and Katz index. As findings shows, IL-6 had inverse relationship with mean right handgrip and Katz index. Moreover, TNF-α had significant negative role in mean left handgrip. On the other hand, TNF-α could negative affect on nutritional status according to SGA scores.

4. Discussion

The present cross sectional study explored the related factors to inflammatory status of COPD patients with moderate to severe conditions. We found that there is a significant association between IL-6, TNF- α and some dietary components, muscle strength, blood biomarkers, nutritional and functional status among patients.

Systemic inflammation and high circulating level of interleukins 6 (IL-6) and tumor necrosis factor alpha (TNFα) is thought to have an important pathogenic role in COPD (Agustí et al., 2012). Various dietary constituents possess different impacts on inflammation (Baldrick et al., 2012). Dietary components such as fatty acids had regulatory effect on immune response. Omega 3 and 6 polyunsaturated fatty acids metabolized by common enzymes by competitive interaction (Matsuyama et al., 2005). Omega 3 fatty acids have anti-inflammatory therapeutic properties, while a high proportion of omega-6 to omega-3 may contribute to different metabolic and immune disorders. Contrary to this, lower omega-6 to omega-3 ratio or higher intake of omega-3 may cause inhibitory effect on the similar conditions (Simopoulos, 2002; Noori et al., 2011). As the results of our study showed, higher intake of PUFA is associated with higher level of IL-6. Since the highest amount of oil consumed by participants was sunflower oil and it's the main source of omega 6, the association between PUFA intake and inflammation can be justified. Some evidences showed that high dietary intake of omega-6 fatty acid have inhibitory effect on inflammation-resolving role of the omega 3 fatty acids (Innes & Calder, 2018; Chavali, Zhong, & Forse, 1998).

Another component of dietary intake is vegetables which was inversely associated with IL-6 and TNFα plasma level in our study. Vegetables contain a variety of bioactive compounds such as polyphenols, vitamins, and minerals which have an inverse association with oxidative stress and inflammation. In this regard Holt et al. indicated in their cross sectional study that vegetable and fruits intake have beneficial effect on decreasing inflammatory and oxidative stress markers such as IL-6 and CRP (Holt et al., 2009). However, a study by Baldrick showed that intake of five or more serving of vegetables and fruits in patients with moderate to severe COPD didn't show significant efficacy on systemic inflammation and oxidative stress, that might be due to the different design of the study compared to the present study (Baldrick et al., 2012). Based on stepwise analysis we found that total grain consumption is associated with inflammatory markers. Various dietary factors such as high intake of simple sugars, different cereal grains and wheat are capable to activate pro inflammatory pathways by increasing intestinal permeability (De Punder & Pruimboom, 2013). As Masters et al. investigated the relationship between whole, refined grain intakes and inflammatory markers, plasma PAI-1 concentrations was positively related to intake of refined grain in diet (Masters, Liese, Haffner, Wagenknecht, & Hanley, 2010). It should be noted that the dominant form of Iranian cereal intake is refined grain instead of whole grain.

As evidences shows, alveolar macrophages in those with COPD have elevated releasing amount of ROS such as peroxides and superoxides especially during disease exacerbations which can develop related complications (Kirkham & Barnes, 2013). We concluded the inverse association between serum vitamin C and TNF-α level, and different studies confirmed our results and reported low vitamin C concentration in inflammatory conditions such as atherosclerosis and stroke (Langlois, Duprez, Delanghe, De Buyzere, & Clement, 2001; Sánchez-Moreno, Dashe, Scott, Thaler, Folstein, & Martin, 2004). On the other hand, an experiment by Hartel et al. indicated that 20 mM ascorbate had the ability to inhibit TNF-α and IL-6 production in monocytes (Härtel, Strunk, Bucsky, & Schultz, 2004).

Recent studies have demonstrated that antioxidant capacity and peroxidation of lipids are disturbed in COPD patients compared to healthy ones. An elevation in level of lipid peroxidation products could result in reactive carbon production which malondialdehyde (MDA) is the most important one (Tug, Karatas, Terzi, & Ozdemir, 2005; Busch et al., 2017). This hyper production of ROS can cause oxidative damage to cell macronutrients and might lead to molecular mechanisms which can initiate pulmonary and systemic inflammation (Stanojkovic et al., 2011). It had been hypothesized that MDA can act as mediators of inflammation in diseases and can contribute to pathogenesis of inflammatory conditions (Busch & Binder, 2017). We found that MDA concentration could positively worsen IL-6 level. In line with our findings, Waseem et al. showed, MDA as a biomarker of oxidative stress, had higher amounts and negative correlation with FEV1 in COPD patients compared to the control ones (Waseem, Hussain, Ahmad, & Islam, 2012). In addition, Busch et al. indicated MDA accumulation had the ability to stimulate pro inflammatory cytokine secretion (Busch et al., 2017).

Measurement of handgrip strength is an indicator of muscle function. On the other hand, metabolism of skeletal

muscle could be effected by inflammation. Different experimental studies showed that increase of IL-6 or TNF-α could result in low protein synthesis in muscles, muscle mass breakdown, alteration of resting membrane potential of skeletal muscle that could cause poor contractile ability. These evidences support the hypothesis of muscle weakness due to inflammation (Norman, Stobäus, Gonzalez, Schulzke, & Pirlich, 2011; Norman, Stobäus, Kulka, & Schulzke, 2014). In this regard, we found low handgrip strength in correlation with inflammatory markers. As Hubbard et al. indicated low peripheral skeletal muscle function in COPD patients as a result of IL-6, TNF-α and CRP elevation in the elderly (Hubbard, O'Mahony, Savva, Calver, & Woodhouse, 2009). Moreover, Park et al. showed that after an intervention in postmenopausal women, handgrip strength was improved due to IL-6 reduction (Park et al., 2013). All of the aforementioned studies are in line with our results.

As we showed IL-6 and TNF-α are inflammatory markers which may aggravate nutritional status. Inflammation, hypercapnia, hypoxia and pharmacologic therapy in COPD patients can promote hypermetabolism and muscle proteolysis. Additionally decreased dietary intakes and anorexia are prevalent in this condition (Ezzell & Jensen, 2000). It has been observed that cachexia in these patients is related to soluble tumor necrosis factor and other cytokines (Schols, Buurman, Van den Brekel, Dentener, & Wouters, 1996). A study by Nascimento et al. demonstrated that malnutrition (SGA≥2) and inflammation are associated with disease severity and FEV1. This relationship might be a reflection of malnutrition association with inflammation and its impact on pulmonary dysfunction (Nascimento et al., 2004). In addition, Pitsiou et al. reported that serum level of TNF-α is elevated in COPD patients and it might be a contributing factor of weight reduction in these patients (Pitsiou, Kyriazis, Hatzizisi, Argyropoulou, Mavrofridis, & Patakas, 2002). The results of our study also confirmed these evidences.

Katz index is as an instrument to assess functional status which is about being independent in routine activities and daily living (Almagro et al., 2012), which was affected negatively by inflammation in present study. COPD might contribute to different complications such as weight, respiratory and skeletal muscle reduction, low exercise capacity, gas trapping, and low diffuse capacity. On the other hand, the systemic inflammation involved in COPD is a risk factor for cardiovascular disease including arrhythmias, sudden deaths, myocardial infarction and strokes which increase high morbidity and mortality (Sin & Man, 2006). So, people with COPD disease are suffering from its related complications, which may affect their daily activities and independency. As Almagro et al. indicated that mortality rate and comorbidities in COPD patients was associated with higher functional dependence (Katz index) (Almagro et al., 2012). Furthermore, based on Gonzalo-Calvo et al. study in elderly population up-regulation of inflammation was a predictor of functional dependency (de Gonzalo-Calvo et al., 2012).

It is essential to mention limitations of the study. Since considered exposures and outcomes were assessed simultaneously, no causal relationship could be obtained. In addition, despite the prevalence of the disease in women, they were not included in the study. However, as a strength this study may related factors were included in the stepwise models.

5. Conclusion

We found that some components of dietary intake (PUFA, vegetables and grain), oxidative stress biomarkers, muscle function and nutritional status can predict or result from inflammation in those patients with moderate to severe COPD, and this might predict an inter-relationship between inflammation and dietary or nutrition factors. Future studies should concentrate on therapeutic strategies to modulate inflammation and its related complications.

Acknowledgments

Conflict of interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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