

Systemic Inflammation in Chronic Obstructive Pulmonary Disease: May Diet Play a Therapeutic Role?

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Abstract

Chronic obstructive pulmonary disease (COPD) is a significant and rising global health problem. It is a complex disease with genetic, epigenetic, and environmental influences characterized by progressive airflow limitation, chronic inflammation in the lungs, and associated systemic inflammation. No effective cure for COPD exists to date and research into new therapies will be essential if this disease is to be managed in the future. Obesity with the metabolic syndrome and malnutrition represent two poles of metabolic abnormalities that may relate to systemic inflammation. The metabolic syndrome is present in almost 50% of COPD patients. Instead, peripheral skeletal muscle dysfunction is an established systemic feature of COPD. Malnutrition varies from 20% to 50% in patients with COPD. Reduction in body weight by more than 10% of the ideal weight is an independent negative prognostic factor in COPD. We assume that in patients with COPD and concurrent alteration of nutritional status at least three factors play a role in the systemic inflammatory syndrome: the severity of pulmonary impairment, the degree of obesity-related adipose tissue hypoxia, and the severity of systemic hypoxia due to reduced pulmonary functions. Further research should elucidate the complex relationship between obstructive lung disease and systemic inflammation and oxidant stress, as well as the role of systemic inflammation in coexisting conditions, such as obesity and malnutrition. In this scenario, diet is a modifiable risk factor for COPD that appears to be more than an option to prevent and modify the course of COPD. Mounting evidence from human studies and experimental investigations have shed new light on the relationship between diet, lung function and COPD development, showing protective or harmful role of certain foods, nutrients and dietary patterns on pulmonary function and COPD development. In particular, beneficial effects on lung function and COPD development have been described for dietary antioxidants including vitamins and polyphenols, mainly from fresh fruits and vegetables, n-3 polyunsaturated fatty acids (PUFA) as well as dietary patterns rich in these constituents, possibly through antioxidant and anti-inflammatory mechanisms. A better understanding of dietary influences on COPD will hopefully lead to design more effective and personalized approach for the nutritional prevention and treatment of this disabling condition.

Keywords: Chronic obstructive pulmonary Disease; Obesity; Malnutrition; Inflammation; Oxidative stress; Diet; Antioxidant; Polyunsaturated fatty acid

Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by progressive and irreversible airflow limitation, impaired quality of life and increased mortality. It is the fourth-leading cause of chronic morbidity and mortality worldwide. Prevalence is projected to increase due to smoke exposure and the changing age structure of the world population. It is accompanied by chronic inflammation of the airways and lung parenchyma [1]. Several pathogenetic processes are involved in COPD development and progression, including oxidative stress, inflammation, protease/antiprotease imbalance, alteration of immune responses and cell proliferation, apoptosis, and cellular senescence [1]. Although COPD primarily affects the lungs, comorbidities such as chronic heart failure, cardiovascular disease, depression, diabetes, muscle wasting, obesity, weight loss, lung cancer, and osteoporosis can frequently be found in patients with COPD, and are considered to be part of the commonly prevalent non pulmonary sequelae of the disease [2,3]. Several studies have found that systemic inflammatory markers, such as high-sensitivity C-reactive protein (hs-CRP) and cytokines, are higher in patients with COPD when compared with subjects without COPD, and are related to mortality in COPD patients [4,5]. However, the origin of systemic inflammation in COPD is still under debate. A question arises whether systemic inflammation is the result of a local inflammation spill-over of the lung to the systemic compartments or a systemic component of COPD, not necessarily related to the local

inflammatory processes in the lung [6,7]. Systemic inflammation is considered a hallmark of COPD and one of the key mechanisms that may be responsible for the increased rate of comorbidities, including cardiovascular events, malnutrition or obesity, muscle dysfunction, and and osteoporosis [7].

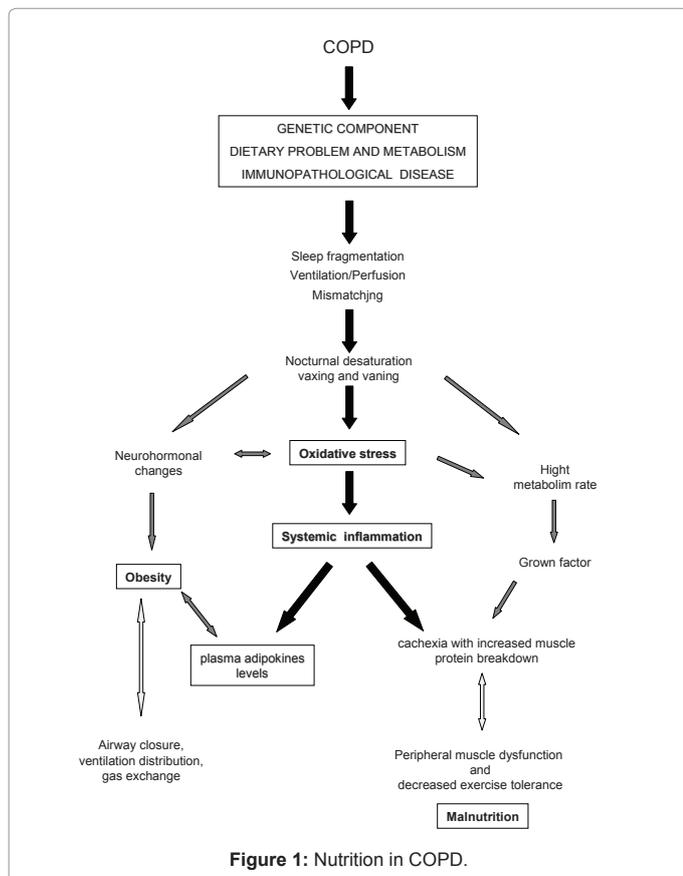
COPD pathogenesis has not yet been fully elucidated. In particular, the immunological mechanisms that initiate and maintain COPD process remain to be fully unravelled. Recently, nutritional status has been associated with respiratory failure in COPD with complex interplays between environmental and genetic factors [8] (Figure 1). Studies have shown that malnutrition served as negative prognostic factor in COPD. Conversely, diet could play a protective or a harmful role regarding COPD prevention and management [9,10].

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The Early Origin of COPD/COPD as an Immunopathological Disease

Scientific evidence is getting stronger that some immunopathological events may play an important role in the development of the disease, but they remain to be fully unravelled. Accurate detection of the early stages of COPD/emphysema has proven difficult. Data indicates that a narrowing and destruction of the terminal bronchioles (airway remodelling) precedes emphysema formation. Macrophages are also present in emphysematous tissues, but the role of macrophages and neutrophils in the maintenance of chronicity, tissue damage or repair remains to be elucidated. Certainly, macrophages are strongly linked with COPD, and are correlated with the degree of bronchial obstruction and inflammation. Data indicates that macrophages isolated from COPD patients release higher levels of inflammatory mediators, such as chemokines, cytokines and proteases, whilst having a reduced capacity to phagocytose particles. Neutrophils are another major cell type associated with COPD. In particular, neutrophil elastase (NE) has been shown to influence cigarette smoke-induced emphysema [11].

The balance between neutrophil and macrophage recruitment, clearance and effector function, remains at the core of COPD pathogenesis [12]. Another study provides compelling evidence that IL-1 α is central to the initiation of smoke-induced neutrophilic inflammation and suggests that IL-1 α /IL-1R1-targeted therapies may be relevant for limiting inflammation and exacerbations in COPD [13]. More recently, microbiological techniques demonstrated that the lungs are not sterile and documented changes in the lung microbiome in several lung diseases. Nevertheless, the role of the lung bacterial microbiome in COPD pathogenesis and progression remains

undefined. In summary, there is the need to consider, in a systematic, anatomically-correlated fashion, both the lung microbiome and the host inflammatory response when studying COPD [14].

As a point of interest, it should be noted that systemic inflammation has failed, so far, to show substantial correlations with airway obstruction [15,16], whereas a connection has been reported between local inflammatory processes and airway obstruction [17,18]. COPD often accompanied by other chronic diseases, that are also associated with systemic inflammation, such as chronic heart failure, diabetes, and arteriosclerosis [19]. Alternatively, increased levels of inflammatory mediators in the blood of COPD patients may stem from extrapulmonary cells (circulating leukocytes, endothelium or muscle cells). A particular problem in COPD patients with marked alveolar wall destruction is intermittent and continuous hypoxia. A significant inverse correlation between arterial oxygen tension (PaO₂) and circulating tumor necrosis factor (TNF)- α and soluble TNF- α receptor (sTNF-R) levels in patients with COPD has been reported [20]. Similarly, a significant relationship between reduced oxygen delivery and TNF- α levels in the peripheral circulation has been shown [21]. It has been suggested that systemic inflammation may partially explain the heterogeneity of COPD phenotypes, such as loss of lean body mass and the higher prevalence of comorbid disorders such as coronary heart disease, depression and hypertension [22,23]. Future prospective studies should investigate whether these markers will give important prognostic information in relation to disease progression and severity in COPD.

Energy Imbalance and Metabolism Changes in COPD: Impact of Obesity in COPD

In normal subject, 60–70% of the total daily energy expenditure (EE), which is the energy needed for basic life processes, is expended for the basal metabolic rate (BMR) [24]. In COPD patients, resting energy expenditure (REE) has been showed to be 15–20% above the predicted values due to the increased energy required for breathing [25,26]. The total EE is increased in COPD patients because of mechanic disadvantage and metabolic inefficiency due to hypoxaemia, which together with systemic inflammation and oxidative stress may be determinants in alteration of metabolic status, that in turn can alter dietary intake [27,28]. A correct management of COPD can reduce EE and improves the hyperinflation and respiratory mechanical efficiency. This could reduce oxygen uptake for breathing and increased oxygen availability for peripheral tissues with improvement of hypoxemia [29–31].

Lung tissue hypoxia is another mechanism that can contribute to systemic inflammation in COPD. The nocturnal desaturation–re-oxygenation waxing and waning sequence is a typical pattern coupled with the majority of respiratory events. This sequence leads to oxidative stress with production of reactive oxygen species (ROS) [32]. A number of studies have suggested that it may result from “overspill” of inflammatory mediators from the lungs and pulmonary circulation, while others have failed to find any correlation between measurable pulmonary and circulating inflammatory mediators [33]. One potentially important source of inflammation in obese patients with COPD with nocturnal hypoxaemia is white adipose tissue. In patients with COPD, obesity is characterized by an absolute abundance of fat mass (FM), similar to other diseases associated with excessive adiposity. The prevalence of obesity is the highest among patients with milder forms of the disease (GOLD Stages 1 and 2), and the lowest in patients with the most severe lung function impairment in Stage 4 [34]. Marquis et al. [35] demonstrated the presence of one or more components of the

metabolic syndrome in almost 50% of COPD patients. High adiposity and fat tissue accumulation impair pulmonary functions and exercise performance. Obesity and the presence of metabolic syndrome are related to increased insulin resistance in overweight and obese COPD patients [36].

The study by Bolton et al. [37] suggests that insulin resistance is aggravated by both high BMI and increase in circulatory inflammatory mediators, such as interleukin (IL)-6 in these patients. Indeed, inflammatory mediators (TNF- α , IL-6, and leptin) were significantly higher, while plasma adiponectin levels were reduced in the presence of excess weight in COPD patients. Chronic low-grade adipose tissue inflammation in obesity may represent a specific response to relative hypoxia of adipose tissue [38]. Several factors may contribute to cell hypoxia within adipose tissue in association with high adiposity: (a) blood flow per unit of adipose tissue mass is reduced in obese humans resulting in decreased blood supply to the tissue; and (b) large adipocytes are further from the vasculature than the normal diffusion distance for O₂. Adipose tissue hypoxia has detrimental effects on cell metabolism and function, as evidenced by studies in vitro and animal models. Studies in vitro have shown that hypoxia results in enhanced TNF- α production, increased expression of plasminogen activator inhibitor (PAI)-1, and reduced adiponectin and peroxisome proliferators-activated receptor gamma (PPAR γ) expression [39,40].

On the other hand, obesity-related hypoxia evokes local inflammatory response within adipose tissue per se, and systemic hypoxia likely contributes to the adipose tissue inflammation. If so, elevated circulating levels of inflammation-related proteins may reflect also spill-over from the adipose tissue to the systemic circulation in patients with COPD and concurrent obesity.

Even in the absence of COPD, obesity is associated with small airways dysfunction, decreased chest wall compliance, V/Q mismatch, and increased peripheral oxygen consumption, all potentially leading to relative hypoxemia. Risk of sleep-disordered breathing and consequent nocturnal hypoxemia correlates with the degree of obesity [41], and in extreme cases morbid obesity can lead to profound alveolar hypoventilation, with chronic hypercapnic respiratory failure. Dysregulated ventilatory control is another factor contributing to the occurrence and persistence of hypoxemia in COPD patients [42].

According to some studies, the link between COPD and obesity/metabolic syndrome, in association with pleiotropic character of most inflammatory mediators, could suggest the existence of a physiologically and clinically relevant cross-talk between the lungs and adipose tissue. Although such a concept has not yet been directly studied in detail, several findings suggest that this hypothesis is worth further exploration. First, receptors of two typical adipocyte-derived cytokines, leptin and adiponectin, are expressed in peripheral tissues, including the lung [43-44]. Interestingly, increased leptin expression in bronchial mucosa was observed in patients with COPD, in association with airway inflammation and airflow obstruction [45].

Moreover, leptin receptor polymorphisms were linked to the decline in pulmonary functions, thus leptin receptor is considered a novel candidate gene for COPD [46], whereas adiponectin may attenuate allergen-induced airway inflammation and hyperresponsiveness, suggesting its potential protective role within the airways [47].

Cross-Talk between Nutritional Depletion and COPD

Research into the pathogenesis of pulmonary cachexia to alleviate progressive disability has been the subject of intensive research during

the past decade. The prevalence of malnutrition in patients with COPD has been reported to be between 20% and 50% [48,49]. Malnutrition strikes pulmonary function with adverse effects and with reduced physical capacity [50]. Malnutrition in COPD has also been shown to have a negative impact on the immune system and to increase the morbidity and mortality risk [51]. Mortality of COPD patients and occurrence of acute exacerbation requiring hospitalization are frequent in underweight patients with malnutrition [52]. During hospitalization, patients with COPD are more likely to lose weight due to increased metabolic demand for respiratory mechanical disadvantage, and have a greater risk of new infectious exacerbations. Landbo et al. [53] described that in mild to moderate COPD the best prognosis was found in normal weight or overweight subjects, whereas in severe COPD overweight patients were associated with a better survival. These patients may be somehow protected from weight loss because of higher energy reserves [54,55]. Some studies have shown that dietary intervention in patients with COPD increased energy intake and body weight [56,57], improved pulmonary function, enhanced exercise capacity [58]. However, a Cochrane review, including 11 studies, showed that nutritional support had no significant effects on anthropometric parameters, lung function or exercise capacity in patients with stable COPD [59].

Experimental research rapidly advances our understanding of the molecular regulation of muscle protein synthesis and breakdown, providing new leads for nutritional and pharmacological modulation.

Muscle wasting should be considered as a serious complication in COPD and other chronic illnesses with important implications for survival. Increased muscle protein degradation is a key feature in muscle cachexia [60]. Extracellular protein degradation is mediated by acid proteases, such as cathepsins and hydrolases, while intracellular proteins can be hydrolyzed by the calcium-dependent calpains, which are activated after muscle damage. Finally, the most important proteolytic processing is represented by the muscular injury and loss of ATP that determines the cachexia muscle. This process may be activated by cytokines, glucocorticoids, acidosis, inactivity, or low insulin level [61]. This affects exercise tolerance, leads to disability and causes poor quality of life, as well as adversely influencing the outcome of these patients. The muscle weakness is predominantly in the lower limbs, due to gait-related limitation from dyspnoea. The possible role of systemic inflammation in nutritional depletion in COPD is based on descriptive data and correlation analyses [62]. There are data on the role of hypoxemia in the pathogenesis of respiratory cachexia [63]: many patients have hypoxia, which has been shown to stimulate the production of inflammatory mediators and to contribute to the development of malnutrition in COPD patients. The hypermetabolism demonstrated in patients with COPD may be caused by the release of inflammatory mediators, such TNF- α and IL-1 β . Leptin is a protein that regulates caloric intake and body weight [64]. A schematic interpretation of the problem is that malnutrition in COPD is the result of an interaction between inflammatory factors, systemic and local factors, such as physical inactivity, ROS, acidosis, leading to an imbalance between anabolism and catabolism.

How to Intervene: Potential Preventive Avenues from Diet

COPD prevalence is dramatically increasing worldwide, and thus management of COPD is currently considered a major health issue. Several therapeutic strategies, including smoking cessation, pharmacological interventions and rehabilitation programmes, are implemented in COPD patients with the aim at improving quality of life,

decelerating lung function decline and preventing major complications. Nutritional support has been recently emerged as a valuable tool in the management of COPD patients at risk of malnutrition, suggesting that at least some of the adverse functional consequences of severe COPD are reversible by nutritional support [65].

With regard to COPD prevention, the most important public health message remains smoking cessation [66]. However, not all smokers develop COPD, suggesting that other factors, including genetic and lifestyle influences, are also involved. Diet is an important modifiable risk factor for obstructive lung diseases including COPD [67], and could play a role in modulating the impact of adverse environmental exposures on the lung. Furthermore, body composition is influenced by diet choice, physical activity, and genetic factors. Changes in diet over the past few decades (with decreased consumption of fruits, vegetables, whole-grains, and fish) have been suggested to contribute to the increased prevalence of obstructive lung diseases, including COPD [68].

Epidemiological evidence have been accumulating to ascertain the nutrients, foods and/or dietary patterns able to impact on COPD development and progression, and to modulate disease intermediate pathophenotypes, such as inflammation and oxidative damage. Data are mixed and not conclusive, but provide important evidence of an association between specific dietary intakes and respiratory health and, in particular, COPD.

Diet and Pulmonary Function: Evidence from Epidemiological Studies

Compared with other chronic diseases with similar burdens on quality of life and health-care costs, such as cancer and coronary heart diseases, less is known about how lifestyle factors other than smoking, such as diet, influence pulmonary function and the development of COPD. Most of the observational epidemiological evidence have focused on associations with intakes of individual nutrients and foods or food groups, either cross-sectionally or longitudinally [66].

Methods for dietary assessment vary across studies and include 24-h recall and food-frequency questionnaire, which gather data on average dietary intake during the preceding 24 h and months/years, respectively. Measurements of serum or urinary biomarkers of intake (e.g. serum levels of vitamins, urinary sodium, etc.) have also been used to assess dietary intake, but this method reflects recent but not long-term intake, the latter being the most relevant risk factor for chronic disease. An indicator of short-term intake may also not adequately correlate to chronic outcomes, such as decline in lung function. Of course, a crucial methodological issue in nutritional epidemiology remains the control for effects of potential confounding factors. Most well-designed studies assessed the relation between diet and COPD in multivariate models after adjustment for multiple confounding factors known to influence pulmonary function, including age, gender, body mass index, physical activity, intake of other nutrients, and most importantly tobacco exposure; in fact, smoking is a powerful risk factor for COPD and current smokers tend to eat unhealthy diet when compared with former smokers [67]. However, residual confounding from inadequate measurements or unknown variables may still be possible, and contributes to the inconsistencies often observed across studies.

Role of antioxidants

Over the last decades there has been a growing interest in the identification of nutrients or foods with antioxidant and anti-

inflammatory properties able to affecting adult lung function or COPD symptoms (Table 1). Many cross-sectional and, albeit limited, longitudinal studies reported a significant positive associations between lung function and dietary antioxidants, assessed as intake of fruits and vegetables, or intake of vitamins/non-vitamin antioxidants using dietary questionnaires or measurement of nutrient blood levels. Several studies consistently reported beneficial effects of a higher intake of fresh fruits against lung function decline [69-71], incidence of COPD [72], and COPD mortality [73]. In a prospective randomized trial, Keranis et al. [74] reported that COPD patients following a diet with a high intake of fruits and vegetables (≥ 1 portion/day) showed an annual increase in the forced expiratory volume in one second (FEV₁), the most widely used marker of pulmonary function and highly diagnostic of obstructive disease, compared with the control group following a free diet over 3 years. However, fresh fruit intake may be a marker of a healthier lifestyle, and other not checked nutrients may mediate the observed beneficial effects. Furthermore, assessment of blood, urine or exhaled breath condensate biomarkers of endogenous oxidative stress is generally lacking in most prospective longitudinal studies, thus limiting the possibility to more accurately select subjects more susceptible to antioxidant dietary regimens and to appraise the antioxidant efficacy of tested foods over time.

Fruits and vegetables contain high levels of antioxidants including vitamins C and E, carotenoids and flavonoids, that might explain their beneficial effects on respiratory function. Accordingly, higher intakes of vitamin C were associated with higher levels of FEV₁, and with a lower rate of decline in FEV₁ after a follow-up period of 9 years [75]. Protective effects on lung function have also been described for vitamin E, vitamin A, vitamin D, carotenoids, and flavonoids [76-81], thus supporting the antioxidant hypothesis. Interestingly, intakes of vitamin E, vegetables and olive oil, rich in antioxidants, have been shown to be inversely correlated with serum markers of oxidative stress [82]. Butland et al. [70] found a positive cross-sectional association between higher apple consumption (5 or more apples per week) and lung function (FEV₁), independent of vitamin E and vitamin C intakes, and most probably attributable to other antioxidant constituents of apples, such as flavonoids (e.g. quercetin).

Other significant associations of dietary intakes with respiratory health have been documented in the general population for consumption of wine and its main polyphenolic antioxidant resveratrol [83], for curcumin-rich curry diet [84], coffee [85], whole-grains [71], dietary fiber (especially from cereal and vegetable sources) [86], fish and n-3 polyunsaturated fatty acids (PUFA) [87-89].

In the Atherosclerotic Risk in Communities Study (IRAS), a population-based cohort study (10,658 participants), Nettleton et al. reported a cross-sectional positive association between regular (not decaffeinated) coffee intake and pulmonary function, as measured by Forced Vital Capacity (FVC) and FEV₁, suggesting a potential beneficial effect of coffee or some coffee constituents on lung function. This association was observed only in never smokers and long-term quitters, but not in current smokers [85]. Some biologic mechanisms have been invoked to explain the lack of coffee effects in current smokers, including the deleterious effects of smoking on the lung that might overwhelm the beneficial influence of coffee consumption on pulmonary function; by inducing the enzyme cytochrome P-450 1A2, smoking can also accelerate the metabolism and clearance of caffeine [90], a coffee constituent associated with an improvement in pulmonary function [91]; finally, the increased oxidative and inflammatory burden associated with smoking may have diluted or dampened the beneficial

effects by antioxidative and anti-inflammatory agents contained in coffee.

Observational studies reported an independent beneficial effect of a high whole-grains intake on lung function [70], and against mortality from chronic respiratory disease [92]. Part of the protective action by whole-grains is attributable to cereal fiber. Cross-sectional and longitudinal studies indeed found a negative association between total fiber intake, specifically cereal fiber intake, and lung function decline, COPD incidence and prevalence [86,93]. The potential beneficial effect was independent of other dietary factors influencing COPD, such as n-3 PUFA and cured meat [86]. Beyond fiber content, whole grains are also rich in phenolic acids, flavonoids, phytic acid, vitamin E, selenium, and essential fatty acids, which may additively or synergistically contribute to the documented beneficial effect on respiratory as well as nonrespiratory diseases by whole-grains.

Role of n-3 PUFA

Data on the effects of n-3 PUFA and fish intake on lung function and COPD are still inconsistent across studies [67] (Table 1). In a 25-year prospective study conducted in the Netherlands, the intake of n-6 PUFA was positively related to the incidence of chronic lung diseases

(defined as chronic productive cough, chronic bronchitis, emphysema, and asthma), but no relation between n-3 PUFA intake and the incidence of chronic nonspecific lung disease was observed [72]. However, some observational studies and feeding trials support significant benefits from increased consumption of n-3 PUFA-rich foods, in particular fatty fish, on respiratory function and COPD symptoms mainly among smokers [87-89,94]. A 8-week supplementation with n-3 PUFA (1200 mg alpha-linolenic acid [ALA, 18:3n-3], 700 mg eicosapentaenoic acid [EPA, 20:5n-3], and 340 mg docosahexaenoic acid [DHA, 22:6n-3]) reversed muscle wasting and improved the functional capacity in patients with moderate to severe COPD compared with placebo, as shown by improvements in peak exercise capacity and submaximal endurance time [94]. These results provide important new directions in nutritional rehabilitation programme in COPD patients.

Foods with potential deleterious effects on lung function and COPD: the role of cured meat

Among potential deleterious foods, a statistically significant inverse association between frequent consumption of cured (bacon, hot dogs, and processed meats) and red meats and pulmonary function has been reported, in agreement with evidence of detrimental effects in other

Dietary factors	Study design	Outcome(s)	Results	Ref
Antioxidants and antioxidant-rich foods				
Fresh fruit (FFQ)	Prospective cohort study (7 years) in 2,171 British aged 18-73 years	FEV1	A more marked fall in FEV1 (107 ml; 95% confidence interval, 36 to 178 ml) in subjects with the greatest decrease in fresh fruit intake compared with those with no change.	[69]
Antioxidant vitamins, fruit, alcohol (diet history)	Prospective cohort study (25 years) in 793 middle-aged men in the town of Zutphen (the Netherlands)	Incidence of chronic nonspecific lung diseases	Fruit and alcohol intake were inversely associated with incidence of chronic nonspecific lung diseases. No association with intake of antioxidants	[72]
Antioxidant, fruit, vegetable and fish intake (diet history)	Prospective cohort study (20 years) in 2,917 men aged 50-69 years (Finland, Italy and the Netherlands)	COPD mortality	COPD mortality was inversely associated with fruit and vitamin E intake	[73]
Fresh fruit and vegetables	Prospective study (3 years) in 120 COPD patients randomized to either a diet rich in fruit and vegetables (intervention group) or a free diet (control group) (Greece)	FEV1	At the end of the study FEV1 increased in the intervention group compared with the control group	[74]
Magnesium, vitamin C, and other antioxidant vitamins (FFQ)	Cross-sectional and longitudinal (9 years) analyses in 2,633 adults aged 18-70 years (United Kingdom)	FEV1	Cross-sectional analysis: FEV1 was positively associated with vitamin C intake; longitudinal analysis: decline in FEV1 was inversely associated with vitamin C intake	[75]
Serum levels of carotenoids, vitamin A, and vitamin E	Longitudinal cohort study (8 years) in 535 young adults aged 20-44 years (France)	FEV1	β-carotene concentration was independently associated with FEV1 decline, with the steepest decline occurring in subjects with the lowest β-carotene levels at baseline (i.e., heavy smokers)	[81]
Wine and resveratrol (FFQ)	Population-based cross-sectional study in adults (the Netherlands)	FEV1, FVC, FEV1/FVC	Resveratrol intake was associated with higher FVC levels, and white wine intake with higher FEV1 levels and FEV1/FVC ratio	[83]
Cereal fiber (FFQ)	Prospective cohort study (6 years) in middle aged men and women (US)	COPD diagnosis	The intake of total fiber intake, and particularly cereal fiber, was associate with lower risk of developing COPD	[86]
Fatty acids				
Fish intake (FFQ)	Cross-sectional study in 6,346 men aged 45-68 years (Hawaii)	FEV1	Among smokers, lower decline in FEV1 was shown at high level of fish intake	[87]
Fish intake (FFQ)	Prospective cohort study (5 years) in 2,512 British men aged 45-59 years	FEV1	No association of fatty fish intake and FEV1	[70]
n-3 PUFA (capsules)	Intervention study (8 weeks) in 80 moderate to severe COPD patients randomized to 9 g n-3 PUFA or placebo daily (The Netherlands)	FEV1, FVC, exercise capacity	PUFA intervention had no effect on FEV1, but increased exercise capacity	[94]
Cured meat				
Cured meat (FFQ)	Prospective cohort study in middle aged 42,915 men (12 years follow-up) and 71531 women (16 years follow-up) (US)	COPD diagnosis	Frequency of cured meat consumption was positively associated with risk of newly diagnosed COPD (mostly among past smokers)	[97,98]

Table 1: Main findings from epidemiological studies of micro- and macro-nutrients and foods in relation to adult lung function and COPD.

Dietary factors	Study design	Outcome(s)	Results	Ref
"Meat–dim sum pattern" and "vegetable–fruit–soy pattern" (FFQ and PCA)	Longitudinal cohort study (5 years) in 52,325 subjects aged 45-74 years (China)	New onset of persistent cough with phlegm (symptoms of chronic bronchitis)	The meat-dim sum pattern was associated with increased incidence of cough with phlegm	[101]
"Prudent pattern" and "Western pattern" (FFQ and PCA)	Prospective cohort study in middle aged 42,917 men (12 years follow-up) and 72,043 women (6 years follow-up) (US)	COPD diagnosis	The prudent pattern was negatively associated with the risk of newly diagnosed COPD while the Western pattern was positively associated with the risk of newly diagnosed COPD	[102,103]
"Prudent pattern" and "traditional pattern" (FFQ and PCA)	Cross-sectional study in 1,551 males and 1,391 females with average age of 66 years (UK)	Primary outcome: FEV1; Secondary outcomes: FVC, FEV1/FVC, COPD	The prudent pattern was positively associated with FEV1 in male and females, and negatively with COPD in males	[104]
"Cosmopolitan pattern", "traditional pattern", and "refined food dietary pattern" (FFQ and PCA)	Longitudinal study (5 years) in 2,911 subjects aged 29-59 years; cross-sectional study in 12,648 subjects aged 29-59 years (the Netherlands)	FEV1, wheeze, asthma, COPD	The "refined food pattern" was associated with a greater decline in lung function over 5 years. The "traditional pattern" was cross-sectionally associated with lower FEV1 and an increased prevalence of COPD, the "cosmopolitan pattern" was associated with a small increased prevalence of asthma and wheeze	[105]

PCA: Principal Component Analysis

Table 2: Main findings from epidemiological studies of eating patterns in relation to adult lung function and COPD (see text for further details on the diets).

nonrespiratory diseases, including coronary heart disease and diabetes [95] (Table 1). Increased intake of cured meats was independently associated with an obstructive pattern of spirometry in a cross-sectional analysis in the third National Health and Nutrition Examination Survey [96], and with an increased risk of newly diagnosed COPD in both men and women in prospective cohorts [97,98]. These data suggest that health promotion activities should include specific advice on lowering cured meat consumption.

Relationship of eating patterns with lung function and COPD

Although many foods or nutrients are identified in relation to respiratory outcomes, the interest of nutritional epidemiology has shifted toward dietary patterns to address an overview of the diet. Some important issues in nutritional epidemiology have been indeed increasingly recognized. First, recommendations to increase or decrease a certain food or food groups instead of a certain nutrient represent a more practically relevant public health message, because it is easier to modify consumption of food or food groups rather than the intake of a nutrient. More importantly, an independent protective or adverse effect attributed to one nutrient can be difficult to be determined, because it may actually reflect the effect of other correlated constituents of the diet or an interaction between dietary constituents [99]. Foods or nutrients are not eaten in isolation but consumed in combination, in the form of dietary patterns, where additive/synergistic interactions among nutrients and foods occur and are accounted for. Therefore, considering diet by an overall approach instead of individual nutrients or foods would more comprehensively capture the complexity of dietary influences on COPD prevention. Moreover, the lack of benefit of vitamin supplementation on lung function and hospitalization for COPD [100] may indicate that observational associations between vitamin intake and respiratory function or COPD symptoms were confounded, either by other nutrients or by non-dietary lifestyle factors. An alternative plausible explanation may be that antioxidant regimens should be in the form of dietary patterns rather than individual nutrient to be effective, as demonstrated below.

While dietary patterns have been widely investigated in relation to cancer, cardiovascular diseases or diabetes, studies on dietary patterns and respiratory outcomes with relevance to COPD are sparse to date

[101-105] (Table 2). In some studies, principal component analysis was used to derive dietary patterns. A cohort study in Chinese Singaporeans found that the meat-dim sum dietary pattern (red meat, preserved foods, rice, noodles, deep-fried foods) was associated with an increased incidence of cough with phlegm [101], indicating a deleterious effect of a diet rich in meat, starchy foods, and high-fat dairy products on COPD. Two prospective studies in the US population identified two distinct major dietary patterns, the "prudent pattern", loaded by a high intake of fruits and vegetables, oily fish, poultry, whole-grain products, and low-fat dairy products, and the "Western pattern", characterized by a high consumption of refined grains, cured and red meats, desserts, French fries, and high-fat dairy products [102,103]. Both studies consistently found that the prudent dietary pattern was negatively, and the Western pattern positively, associated with the risk of self-reported newly diagnosed COPD in women [102] and men [103] after adjustment for several potential confounders, including multiple measures of tobacco exposures. In contrast with findings for COPD, the dietary patterns were not associated with the risk of adult-onset asthma [102]. In addition, the effect of each dietary pattern was stronger in men than in women [102,103], and the association between Western diet and COPD risk was stronger among lean (BMI ≤ 20) than normal, overweight and obese subjects [102]. Accordingly, a recent cross-sectional study in the UK population observed that a similar prudent dietary pattern was positively associated with lung function (FEV1), in males and females, and negatively associated with COPD prevalence in males. Associations in males were stronger among smokers than non-smokers [104]. In this study, although the "traditional" pattern was similar to the Western dietary pattern of other studies [102,103], it was not associated with any negative outcome, probably due to its relatively high fish and vegetables content [104]. In a large population from the Netherlands, McKeever et al. [105] identified three major dietary patterns, the "cosmopolitan pattern" (higher intakes of vegetables, fish, chicken, wine, and lower intakes of high-fat dairy products, added fat, added sugar, and potato), the "traditional pattern" (higher intakes of red meat, processed meat, potato, boiled vegetables, added fat, coffee, and beer and lower intakes of soy products, low-fat dairy products, tea, breakfast cereal, brown rice, pizza, juice, and fruit), and the "refined food dietary pattern" (higher intakes of mayonnaise, salty snacks, candy, high-sugar beverages, French fries, white bread, and pizza and

lower intake of boiled vegetables, whole-grains, fruit, and cheese). The Authors assessed the relation of the different dietary patterns to lung function (FEV₁) and symptoms of COPD cross-sectionally and to longitudinal change in FEV₁. When the diets were analyzed in relation to nutrients, the cosmopolitan diet was positively correlated with intake of alcohol, vitamin C, and beta-carotene, the traditional diet was positively associated with alcohol and total fat intake, and negatively with carbohydrate intake, the refined food diet was negatively associated with magnesium, fiber, and vitamin C intake [105]. None of the dietary patterns were associated with a decline in lung function over 5 years, although there was some evidence that a diet high in refined foods is associated with an increased decline in lung function. On the contrary, the traditional diet was associated with a lower lung function and a higher prevalence of COPD, while the cosmopolitan diet was associated with a small increased prevalence of asthma and wheeze [105]. The content in fruits, vegetables, whole-grains, and fish, which was high in the prudent diet and low in the Western diet along with a high content in red meats, may underline the opposite effects of these dietary patterns on lung function and COPD.

Although needing further confirmations, collectively these data provide important evidence that a prudent diet exerts beneficial effects, and Western diet detrimental effects, not only in nonrespiratory clinical settings, such as cardiovascular diseases and cancer [106], but also on respiratory outcomes and COPD. This information potentially contributes to improve public health messages for a healthier eating pattern, although such a lifestyle change would be challenging.

Potential Biological Mechanisms Underlying Effects of Dietary Intakes on COPD

Anti-inflammatory and antioxidant effects of diet

Inflammation and oxidative stress are involved in the pathophysiology of reduced pulmonary function and COPD development [107]. An increased production of ROS and reactive nitrogen species (RNS) as well as a decrease in antioxidant defences have been involved in COPD pathogenesis and may ultimately induce inflammatory responses through the activation of redox-sensitive transcription factors (e.g., nuclear factor[NF]- κ B), induction of autophagy and unfolded protein response [107]. In particular, NF- κ B plays a crucial role in the chronic inflammatory responses found in COPD, regulating the expression of genes for pro-inflammatory mediators (IL-1, IL-6, IL-8, MCP-1, TNF- α). Indeed, the number of NF- κ B-positive epithelial cells and macrophages increased in smokers and COPD patients, and correlated with the degree of airflow limitation [108]. Therefore, the associations between dietary intakes and pulmonary function are thought to be mediated, at least in part, by anti-inflammatory and antioxidant mechanisms.

Many foods associated with lung function protection, such as fruits, vegetables, and whole-grains, contain several vitamin and non-vitamin antioxidants, including polyphenols, which may prevent or reduce the airways and systemic oxidant/antioxidant imbalance observed in COPD [109]. Accordingly, with regard to diet as a whole, the Western diet (with a low content of antioxidants) has been shown to be positively associated while the prudent diet inversely associated with serum levels of inflammatory markers [110]. Some subgroups with particularly high levels of oxidative stress, including tobacco smokers, may be more likely to benefit from a higher dietary intake of antioxidants. In fact, a stronger association between intake of antioxidant-rich foods and better lung function has been observed among smokers [76,84,111]. Large experimental evidence indicates that dietary polyphenols

exert antioxidant, anti-aging and anti-inflammatory properties in different cells and tissues, such as the vascular endothelium, immune cells, and smooth muscle cells, at least in part through inhibition of cellular oxidative stress and inflammatory pathways including NF- κ B [112,113]. Resveratrol, a polyphenolic constituent of red wine, inhibits more potently than corticosteroids cytokine release from airways smooth muscle cells and alveolar macrophages of COPD patients [113]. Moreover, epidemiological data indicated that fiber intake, one important constituent of whole-grain foods, is associated with lower serum levels of C reactive protein and cytokines (IL-6, TNF- α), and higher level of adiponectin, an insulin-sensitizing adipocytokine with anti-inflammatory properties [114]. A recent randomised controlled trial in moderate-to-severe COPD patients found that increased fruits and vegetables intake was not associated after 12 weeks with significant changes in biomarkers of airway inflammation (IL-8 and myeloperoxidase) and systemic inflammation (C reactive protein) or airway and systemic oxidative stress (8-isoprostane) [115]. However, it may be possible that the sample size and the intervention period were not adequate to observe a substantial change in the measured biomarkers.

On the other hand, a diet rich in meat has of course several potential nutritional benefits but also some potential drawbacks, including the high content in cholesterol and saturated fatty acids, as well as nitrite preservatives in cured and processed meats. Nitrites generate RNS that can amplify inflammatory processes in the airways and lung parenchyma causing DNA damage, inhibition of mitochondrial respiration, and nitrosative stress [107]. Nitrites are also byproducts of tobacco smoke, thus nitrite generation may be one of the mechanisms by which tobacco smoke causes COPD. The combination of smoking and higher cured meat consumption is indeed associated with the highest risk of newly diagnosed COPD [98].

Protective mechanisms of n-3 PUFA

Beyond antioxidants intake, the lipid composition of the diet is of fundamental importance in inflammation and immune reactivity. In fact, n-3 PUFA and fish, the main food source of the n-3 PUFA DHA and EPA, have been emerged as potent anti-inflammatory factors with beneficial effects, and in most cases clinical applications, in several chronic inflammatory diseases including cardiovascular diseases, cancer, rheumatoid arthritis, diabetes, and also airway diseases [116,117]. Opposite effects have been described for n-6 PUFAs, including linoleic acid and arachidonic acid, mainly found in vegetable oils such as soybean, corn, and sunflower oils. The higher n-6/n-3 PUFA ratio, as is found in today's Western diets, has been often regarded as a potential contributor to the increased prevalence of inflammatory diseases. In a recent cross-sectional study involving 250 clinically stable COPD patients, higher dietary intakes of n-3 PUFA were associated with lower serum pro-inflammatory cytokine concentrations (e.g., TNF- α), while higher n-6 PUFA intake was associated with higher pro-inflammatory IL-6 and C reactive protein concentrations [118]. It has been recently found that shifting the PUFA supply from arachidonic acid to DHA significantly reduced the release of pro-inflammatory cytokines (TNF- α , IL-6, and IL-8) and increased the release of anti-inflammatory cytokine (IL-10) from human alveolar cells after endotoxin challenge [119]. However, in the study by Broekhuizen et al. [94], the positive effect of n-3 PUFA supplementation on the exercise capacity in COPD patients was not associated with a decreased systemic inflammatory response (CRP, IL-6, and TNF α), and was proposed to be mediated by PUFA-induced PPAR activation and subsequent increased muscle oxidative capacity. Of course, a beneficial modulation of local (lung

and muscle) chronic inflammation by PUFA intervention cannot be excluded and needs to be fully evaluated.

Potential biological mechanisms mediating protective effects by n-3 PUFA include, upon incorporation into cellular phospholipids, the production of anti-inflammatory and pro-resolving mediators from n-3 PUFA metabolism [112] (Figure 2). Usually esterified in the sn-2 position of the phospholipid, n-6 PUFA arachidonic acid as well as the n-3 PUFA EPA and DHA can be released through the action of phospholipase A₂ and metabolized through “orthodox” and “unorthodox” pathways. The “orthodox” pathway involves cyclooxygenase and lipoxygenase activity converting PUFA into eicosanoids, including prostanoids (PG), thromboxanes (TX), and leukotrienes (LT). Arachidonic acid is converted by cyclooxygenase into the 2-series PGs and TXs (including PGI₂-prostacyclin and TXA₂), and by lipoxygenase into the 4-series LTs (including LTB₄), which display potent pro-inflammatory, vaso- and broncho-constrictive and chemo-attractant properties. Increasing the content of n-3 PUFA in the diet causes a partial substitution of the n-6 PUFA, especially decreasing the relative proportions of arachidonic acid in the cell membranes. This causes a net decrease in the production of eicosanoids (because n-3 PUFA are worse substrates for the metabolizing enzymes) and favours the synthesis of generally less biologically active eicosanoids (PGs of the 3-series and LTs of the 5-series) [112]. In addition, some EPA- and DHA-metabolites via cytochrome P450 enzymes, which are highly expressed in the lungs, are potent vasodilators and bronchodilators and show anti-inflammatory properties [117].

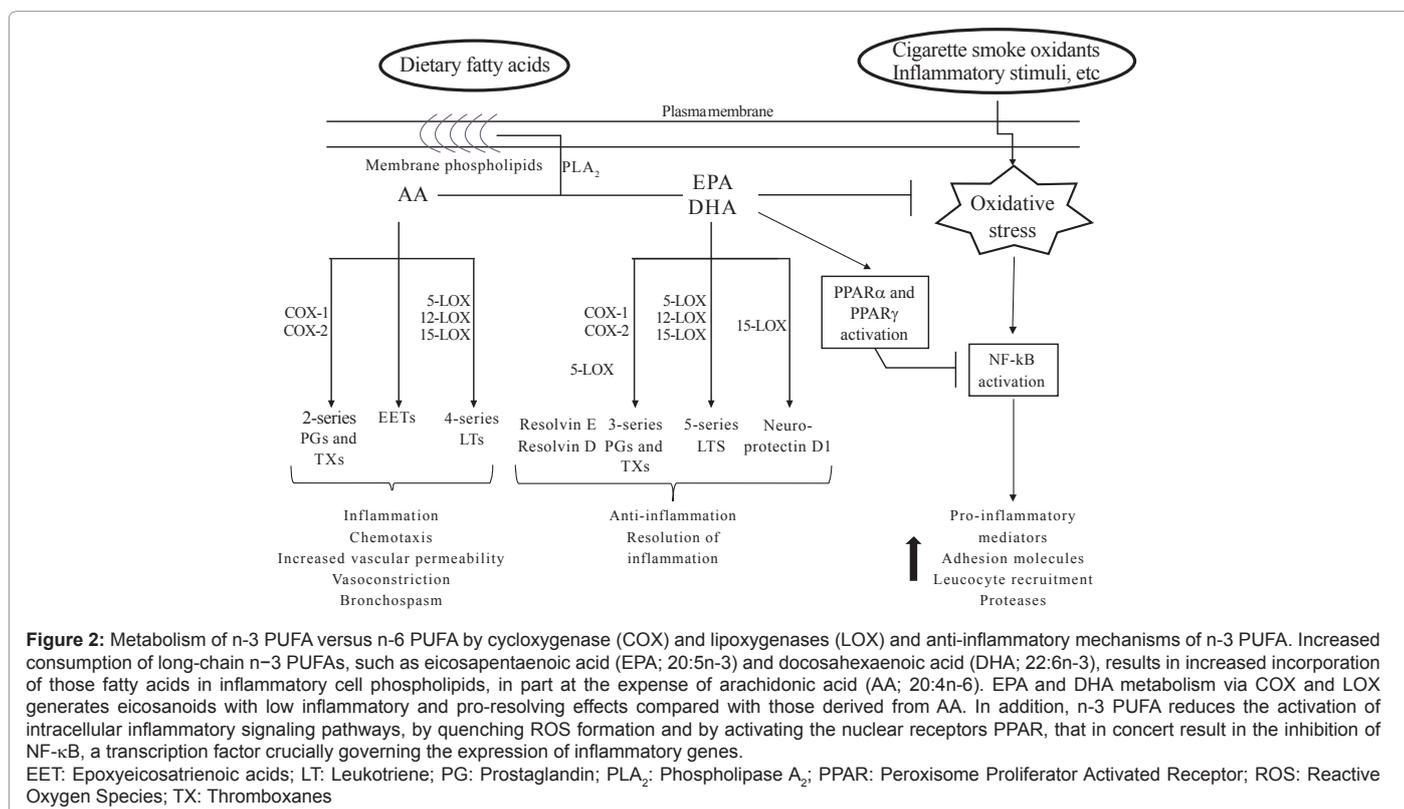
The “unorthodox” metabolic pathway of n-3 PUFA generates the so-called resolvins (E-series resolvins from EPA, and D-series resolvins from DHA) typically produced during the resolution of self-limited inflammation. These metabolites have been shown to have potent anti-inflammatory and pro-resolving effects without

being immunosuppressive [112], with a strong potential as a novel therapeutic strategy for the treatment of inflammatory lung diseases including chronic lung injury and COPD. Recently, resolving D1 has been reported to inhibit cigarette smoke-induced pro-inflammatory response in human lung cells in vitro and in a mouse model of acute cigarette smoke-induced lung inflammation by selectively activating specific anti-inflammatory pathways, including the inhibition of neutrophilic inflammation and the activation of a subset of anti-inflammatory, pro-resolving macrophages [120].

In addition to the production of bioactive lipid metabolites, n-3 PUFA anti-inflammatory mechanisms also include the direct modulation of the expression of genes involved in the pathogenesis of chronic inflammatory diseases, including adhesion molecules, cytokines, matrix degrading enzymes, cyclooxygenase-2 [112] (Figure 2). This effect mainly occurs via the regulation of nuclear transcription factors: indeed PUFA binds and activates PPAR, which controls lipid and glucose metabolism, and inhibits inflammatory responses in vascular and inflammatory cells; n-3 PUFA also reduces the recruitment of redox-sensitive proinflammatory NF-κB, which has been involved in the pathogenesis of lung inflammation [107]. An antioxidant effect has also been documented for DHA. Indeed, DHA reduced intracellular ROS production and the consequent NF-κB activation and inflammatory response in cultured endothelial cells, possibly by modifying lipid composition, and altering membrane lipid microdomains involved in cell signalling [112].

Conclusion

The possible role of systemic inflammation in common clinical manifestations of COPD, such as obesity and cachexia, warrants further investigations, which hopefully lead to the development of novel preventive and therapeutic strategies appropriately curbing



the underlying pathogenetic mechanisms. Epidemiological and interventional studies as well as biochemical and metabolic results provide compelling evidence for the existence of an impact of diet on COPD, mostly when interactive and sometimes synergistic effects among nutrients or foods potentially occur. From a mechanistic point of view, although not exhaustive, the present data indicate that modulation of inflammatory and oxidative burden may constitute an underlying mechanism plausibly underpinning physiologic effects of some effective dietary constituents, including antioxidants and n-3 PUFA, on COPD as well as on other inflammatory diseases. It seems plausible that a diet high in fish oils, fresh fruit and vegetables, cereal fiber and whole grains, and low in red meat, preserved and refined foods, saturated fatty acids, and sodium, may positively influence lung function, eventually preventing the development of COPD, and should be considered as part of a healthy lifestyle for the management of COPD. Interestingly, many characteristics of dietary patterns associated with improved lung function and COPD prevention are common to the so-called Mediterranean diet, characterized by elevated intakes of plant-derived foods, low to moderate amounts of dairy products and eggs, and only little amounts of red meats. This dietary pattern is low in saturated fatty acids, rich in complex carbohydrates, fiber and antioxidants, and has a high content of monounsaturated fatty acids and n-3 PUFA, which are primarily derived from olive oil and fish intake, respectively. Although the Mediterranean diet has consistently proven protective against pathological processes leading to cancer, cardiovascular disease [121] and respiratory illness as well [122], the specific relation to COPD has not been explored, and warrants further investigations. A more complete understanding of how dietary changes may impact on the pathogenesis of COPD will likely lead to a beneficial exploitation of such a knowledge in terms of nutritional prevention and management of COPD.

Authors' Contribution

Domenico Maurizio Toraldo has made a substantial contribution to the conception and design of the short communication while the analysis and interpretation of the resulting literature data of the nutritional status was made by Egeria Scoditti and Francesco De Nuccio was involved in drafting and revising the manuscript critically for important intellectual content and gave final approval of the version to be published.

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