Biomedicine & Pharmacotherapy 163 (2023) 114753

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha

Review

Practical dietary advices for subjects with alpha-1 antitrypsin deficiency

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ARTICLE INFO

Keywords:
Alpha-1 antitrypsin deficiency
Chronic obstructive pulmonary disease
Dietary advice

ABSTRACT

Congenital alpha-1 antitrypsin deficiency (AATD) is a rare inherited disorder caused by the mutation of the SERPINA1 gene on chromosome 14. At pulmonary level, AAT deficiency leads to an increased risk of chronic obstructive pulmonary disease (COPD) and emphysema, starting from the third-fourth decade of life. At hepatic level, some variants of the allelic, in particular PI*Z, cause a conformational change of the AAT molecule, which polymerizes within the hepatocytes. Excessive hepatic accumulation of these abnormal molecules can lead to liver disease in both adults and children, with clinical presentation ranging from cholestatic jaundice in the newborn to abnormal blood indices of liver function in children and adults, up to fatty liver, cirrhosis and hepatocarcinoma. Nutritional interventions in AATD aim to provide the necessary calories, stop protein catabolism, prevent and treat malnutrition as in the case of common COPD, and even take into account any liver disease that is a distinctive trait, compared to common COPD. Actually, there is a lack of formal research regarding the effects of specific nutritional recommendations in patients with AATD, proper eating habits may help to preserve lung and liver function. For practical dietary advice in patients with AATD and COPD, recently a food pyramid proposal has been published. It has been observed that there is a marked overlap between AATD liver disease and obesity-related liver disease, suggesting shared molecular basis and, therefore, similar nutritional strategies. In this narrative review dietary advice for all possible stages of liver disease have been reported.

1. Introduction

Congenital alpha-1 antitrypsin deficiency (AATD) is a rare inherited disorder caused by the mutation of the SERPINA1 gene on chromosome 14; transmission is co-dominant, both alleles are expressed and each contribute 50% to the total amount of alpha-1-antitrypsin (AAT) [1]. Affected individuals can be homozygous (two copies of the same pathological allele), compound heterozygotes (two different pathological alleles) or simple heterozygotes (one pathological and one healthy allele). AAT is an acute phase protein that acts mainly as a protease inhibitor and whose function is essential to protect tissues from proteolic damage. Its deficiency can lead to an imbalance between protease and antiprotease activity, with an increased risk of developing both lung and liver diseases [1,2].

At pulmonary level, AAT deficiency leads to an increased risk of chronic obstructive pulmonary disease (COPD) and emphysema, starting from the third-fourth decade of life. The risk of pulmonary impairment is high in homozygotes but is also present in the intermediate deficit (heterozygotes), in case of exposure to environmental risk factors, in particular to cigarette smoke [3].

In presence of moderate to severe COPD obstruction and / or emphysema, a body mass index (BMI) < 25 kg/m2 has been consistently associated with an increased risk of mortality compared to overweight and even obese patients (BMI> 25 kg/m2 and BMI> 30 kg/m2

Abbreviations: AAT, alpha-1-antitrypsin; BMI, body mass index; COPD, chronic obstructive pulmonary disease (COPD); AATD, alpha-1 antitrypsin deficiency (AATD); FFM, fat free mass; FFMI, fat free mass index; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; RBP, retinol-binding protein.

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https://doi.org/10.1016/j.biopha.2023.114753
Received 18 November 2022; Received in revised form 18 April 2023; Accepted 20 April 2023
Available online 27 April 2023

respectively) [4–6]. This prognostic advantage of increased BMI in COPD, also known as the "obesity paradox", could be related to the direct effect of adipose tissue on lung mechanics [7] or it could be an epiphenomenon related to still unknown aspects of the disease that they confer both a reduced risk of mortality and a preservation of fat mass and / or FFM. It is still unclear whether excess fat or conserved FFM contributes to the survival advantage, but it is known that a low fat free mass index (FFMI) (<10th percentile), independent from BMI and fat mass, represent a strong predictor of mortality [8].

At hepatic level, some variants of the allelic, in particular PI * Z, cause a conformational change of the AAT molecule, which polymerizes within the hepatocytes. Excessive hepatic accumulation of these abnormal molecules can lead to liver disease in both adults and children [9], with clinical presentation ranging from cholestatic jaundice in the newborn to abnormal blood indices of liver function in older children and adults, up to fatty liver, cirrhosis and hepatocarcinoma (odds ratio for cirrhosis of 8.3 with a 95 % confidence interval [CI]: 3.8–18.3 and for HCC of 5.0, 95 % CI: 1.6–15.8) [10].

At present, there is no specific treatment for AAT deficiency induced liver disease. Treatment for progressive liver injury is supportive, including attention to adequate nutrition and prevention of disease complications. Commonly, children and adults with AAT-related liver cirrhosis remain clinically stable and live relatively unaffected lives for many years. Moreover, available data indicates that children with cirrhosis usually have normal growth, development, and anthropometric measurements. Such patients should be advised to abstain from alcohol consumption, and should be nutritionally supplemented with fat-soluble vitamins [11].

Nutritional interventions in AATD aim to provide the necessary calories, stop protein catabolism, prevent and treat malnutrition [12] as in the case of common COPD, but must take into account any liver disease that is a distinctive trait compared to common COPD. For this reason, two types of indications were reported: one for subjects with lung disease only, the other for patients with both lung and liver disease.

2. Methods

The present narrative review was performed following the steps by Egger et al. [13] as follows:

Configuration of a working group: three operators skilled in clinical nutrition (one acting as a methodological operator and two participating as clinical operators). 2. Formulation of the revision question on the basis of considerations made in the abstract: “the state of the art on dietary practical advices for subjects with AATD. 3. Identification of relevant studies: a research strategy was planned on PubMed (Public MedIine run by the National Center of Biotechnology Information (NCBI) of the National Library of Medicine of Bathesda (USA)) as follows: (a) Definition of the keywords (alpha-1 antitrypsin deficiency; AATD; BMI; diet), allowing the definition of the interest field of the documents to be searched, grouped in quotation marks (”. ”) and used separately or in combination; (b) use of: the Boolean (a data type with only two possible values: true or false) AND operator, that allows the establishments of logical relations among concepts; (c) Research modalities: advanced search; (d) Limits: time limits: papers published in the last 20 years; humans; adults; languages: English; (e) Manual search performed by the senior researchers experienced in clinical nutrition through the revision of reviews and individual articles on dietary practical advices in patients with AATD published in journals qualified in the Index Medicus. 4. Analysis and presentation of the data extrapolated from the “revised studies” were collocated in tables; in particular, for each study we specified the author and year of publication and study characteristics. 5. The analysis was carried out in the form of a narrative review of the reports.

3. Nutritional state and AATD

To date, there are only 3 studies on the nutritional status in patients with AATD, two of which have shown that low BMI is correlated with poor survival [14,15].

These studies have been reported in Table 1.

The European Society for Clinical Nutrition and Metabolism (ESPEN) defines malnutrition as a combination of one or more of these indicators: involuntary weight loss, low BMI or reduced muscle mass; associated with one or more of these characteristics: reduced food intake or the presence of inflammation due to chronic diseases [16].

The BMI is part of the "BODE" index (BMI, Obstruction, Dyspnea, and Exercise capacity) which is widely used to predict mortality in COPD patients. This index is calculated by adding BMI, degree of airway obstruction (measured by evaluating FEV1, volume of air exhaled during the first second of a maximum forced expiration), severity of dyspnea (assessed with the Medical Research Council Questionnaire, modified or mMRC) and exercise tolerance (assessed by measuring the distance covered in the 6-minute walk test). The score can range from 0 to 10. The BMI in the BODE can give a score of 0 if greater than 21 kg/m2 or 1 if less than or equal to 21 kg/m2. The higher the BODE, the higher the mortality [17]. In COPD, in fact, several observational studies have shown how a low BMI was associated with poor prognosis, regardless of the level of respiratory compromise [4,18–20] and to an increase in both morbidity and mortality from all causes of 40 % [21].

FFMI is used in patients with normal weight and underweight COPD to determine the amount of FFM and represents the value of FFM adjusted for age and sex (FFMI = FFM/height2). Low values of FFMI are considered to be those below the 10th percentile, which correspond to an FFMI < 17 kg/m2 for males and < 15 kg/m2 for females [22]. The gold standard for the assessment of body composition is densitometry (Dual X-ray absorptiometry, DXA); if not available, body composition can be estimated by bioimpedance analysis.

Finally, about monitoring, patients with AATD should be screened for malnutrition approximately every 6–12 months or at the time of routine visits, assessing if there is a weight loss (90 % lower of ideal body weight) or BMI ≤ 20. Nutritional support is strongly recommended in individuals who exhibit involuntary weight loss and in normal weight patients but who are malnourished.

Plasma concentrations of some proteins secreted by the liver, such as albumin, prealbumin and RBP are considered a marker of visceral protein reserve and therefore, their changes represent markers of malnutrition [15].

Finally, given the higher prevalence of hypovitaminosis D in severe COPD, in patients with cirrhosis [23,24] and malnourished patients, screening for vitamin D deficiency appears useful [25].

The study by Seersholm and colleagues, evaluating mortality as a function of BMI, has examined 342 patients from the Danish registry of the AATD in Copenhagen (a registry that has existed since 1978 and is continuously updated), followed over a period of about 7 years [14]. The subjects were divided into two groups according to whether the BMI was less than or greater than 20 kg/m2. Subjects (n = 90) with BMI < 20 kg/m2 were defined as ’underweight’. The results showed that mortality was significantly higher in the underweight group of patients (with a risk ratio of 1.6), regardless of lung function (FEV1), smoking, gender and age.

In the study by Piitulainen the aim was to investigate the nutritional status of patients with severe AATD and emphysema by measuring total body protein (measured by in vivo neutron activation analysis of nitrogen), fat free mass (FFM) estimated from total body potassium measurement, respiratory muscle strength was studied by maximal inspiratory pressure (PImax) and maximal expiratory pressure (PEmax) and skeletal muscle strength by handgrip test [15].

Plasma concentrations of albumin, transthyretin, otherwise known as prealbumin, and retinol-binding protein (RBP) were analyzed as biochemical markers of nutritional status. The study, conducted on 15

Table 1
Studies on the nutritional status in patients with AATD.

First author, year	Study design	Inclusion criteria	Exclusion criteria	Number of subjects (M-F)	Outcomes	Results
Seersholm, 1997	Observational	Pi-type ZZ or with serum level of a-antitrypsin of less than 12 μmol/l	/	342 from the Danish a-Antitrypsin Deficiency Register in Copenhagen, aged 45.5 ± 10.7 years	Mortality of a-antitrypsin-deficiency patients PiZ as a function of body mass index (BMI) with control for FEV1	The underweight patients had significantly higher mortality in the two groups with the lowest FEV1% predicted. Low body weight is an independent predictor of mortality
Piitulainen, 2002	Case control	PiZZ phenotype, FEV1 < 50 % of the predicted value and FEV1/vital capacity (VC) ratio < 50 %.	Any disease other than COPD influencing nutritional status (eg, thyroid gland dysfunction, malignancy, connective tissue disease, diabetes mellitus), neuromuscular disease, severe left heart failure, hypoxemia with Pao2 < 8.0 kPa, continuous oxygen therapy, and treatment with diuretics or oral corticosteroids	15 subjects with AATD and emphysema (7 M aged 55 ± 14 years; 8 F aged 55 ± 7 years); 18 healthy control (9 M aged 54 ± 7 years; 9 F aged 56 ± 8 years)	Nutritional status and muscle strength in patients with severe AATD	Patients with emphysema and severe AATD show lower total body protein and plasma transthyretin (may indicate early signs of malnutrition), compared with healthy control subjects, while no significant differences were found in body weight and BMI. Concerning skeletal muscle function, significant decrease of handgrip strength test is observed only in the female patients. Maybe skeletal muscle dysfunction appears in a later stage of malnutrition than respiratory muscle dysfunction.
Dawkins, 2003	Observational, prospective	PiZ phenotype	/	256 subjects with AATD	The predictive potential of several parameters, including BMI and computed tomography (CT), for mortality in patients with severe AATD	BMI is not a predictor of mortality. CT scanning predicts respiratory and all-cause mortality in a1-antitrypsin deficiency and appears to be superior to lung function. parameters, especially FEV1

patients with AATD (7 males and 8 females) and 18 healthy controls, revealed a reduced level of total body protein and a reduced plasma concentration of prealbumin, which could be prime indicators of malnutrition, in subjects with AATD with emphysema. Indeed, the plasma concentration of prealbumin is considered a more sensitive marker of malnutrition than the plasma concentration of albumin. Concentrations of albumin and RBP, on the other hand, did not differ between the two groups. Furthermore, there were no significant differences in body weight and BMI between the two groups [15].

The advantage of analyzing plasma proteins in evaluating nutritional status is represented by the fact that concentrations are not influenced by body weight. The disadvantage is that the plasma protein concentration can be affected by other clinical conditions than malnutrition. The plasma proteins mentioned above are synthesized in the liver and their concentration can be affected by concomitant liver disease, as can occur in liver cirrhosis, a known complication in individuals with AATD-related liver disease. In general, the mean concentrations of prealbumin and RBP are slightly lower in patients with AATD than in the other groups.

In contrast to the previous 2 studies, the study by Dawkins, conducted over 5 years in 256 patients with AATD (PiZ phenotype), showed that, in this specific group of patients, BMI is not a predictor of mortality [26].

Probably these different results depend on the different phenotypes studied in the 3 studies.

4. Nutritional advice in patients with AATD and COPD

The results of the studies currently available in the literature, although they do not consider body composition (lean mass and fat mass) but only the BMI, are very important as they confirm that even in patients with AATD there is a bidirectional relationship between malnutrition and mortality, as is in patients with lung diseases [14,15]. On the one hand, it has been shown that individuals with low weight show a greater air entrapment at the alveolar level and a reduced gas exchange capacity [12]; on the other hand, malnutrition was found to be extremely common in COPD patients, especially in those with emphysema. The prevalence of underweight in COPD ranges from 25 % to 40 % [27], with 25 % having moderate to severe weight loss and 35 % having extremely low FFM, calculated using specific formulas that take into account gender and disease state [18]. Prevalence increases with disease severity [8] and is clearly associated with emphysema [28].

Observational studies in COPD also suggest that emphysema represents a particular phenotype associated with musculoskeletal impairment, but the underlying mechanisms remain unclear [29–31].

COPD patients with underweight or low FFM are more prone to bone mineral density (BMD) loss than overweight patients [12,28,32]. As reported by the European Respiratory Society (ERS), prevalence data varies from 5 % to 60 % depending on the diagnostic methods used, the population considered and the severity of the disease [33].

One reason for this association is the presence of common risk factors such as aging, smoking, underweight, sarcopenia, and physical or functional limitation. Furthermore, systemic inflammation, the use of systemic corticosteroids and the high prevalence of vitamin D deficiency, which are frequently observed in the most severe stages of COPD, unequivocally contribute to further loss of bone and muscle mass [34–36].

The reasons for the link between underweight and increased mortality in COPD remain to be clarified, but several hypotheses have already been put in place to explain this relationship, among the following: weakness of the respiratory muscles, impaired gas exchange, deficit of immune system [37] and loss of lean mass [8].

Furthermore, malnourished patients with lung disease show a greater number of exacerbations, which lead to a more rapid reduction in FEV1 and a worse quality of life [38].

To better understand the pathogenesis of malnutrition in COPD, several factors need to be considered:

• metabolic changes and caloric intake: in these patients the basal metabolic rate is increased, mainly due to the increased work of breathing [39–41].

• Although there is a need for a higher caloric intake, this remains insufficient as there is a reduced tolerance to general physical activity and consequently also poor resistance during food intake [42], there is a tendency towards depression and dyspnea which tends to be accentuated during meals [43]. In addition, the chronic inflammatory state that characterizes COPD also leads to an imbalance of chemokines, with an increase in pro-inflammatory cytokines, in particular IL6, which acting centrally, leads to a reduction in appetite [44].

• Tissue hypoxia: the increased oxygen demand, given by the increase in respiratory work, is not supported by cardiac output which is reduced in proportion to the severity of the pulmonary obstruction [45]. Under these conditions the body maintains blood flow to critical sites such as the heart, central nervous system and respiratory system, while peripheral tissues, including skeletal muscles, develop hypoxia and nutrient deficiencies, useful for maintaining muscle mass [46].

• Oxidative stress: in these patients, at the level of the muscle fiber cells of the peripheral districts, there is a functional change with a reduction in the oxidative phenotype and consequent reduction in energy efficiency, greater predisposition to oxidative stress and further muscle loss [47].

• Drugs: the same corticosteroids, used in the treatment of COPD patients, can contribute to the depletion of FFM, as they inhibit protein synthesis and promote protein catabolism, despite increasing appetite. This effect on muscle, "glucocorticoid-induced myopathy", is dose dependent and occurs for doses greater than 60 mg/day [47,48].

There are several therapeutic options both pharmacological and non-pharmacological to counteract the different pathophysiological factors of malnutrition in COPD and AATD.

As for depression, chronic physical illness is associated with significant emotional vulnerability disturbances. Some studies suggest that anxiety and depression are common comorbidities in the individuals with alpha-1 antitrypsin deficiency (AATD). Many aspects of the AATD contribute to the deterioration of the quality of life. According to most of the studies, anxiety and depression remain overlooked in case of AATD individuals [49]. The 2019 GOLD COPD guidelines stress that both anxiety and depression are common comorbidities in COPD leading to poor prognosis [50]. Even when diagnosed, treatment at times is omitted for various reasons. The utility of a pharmacological approach to treat depression as a comorbidity in COPD remains unclear. Recent literature found the use of serotonergic antidepressants to be associated with small increases in morbidity and mortality among older individuals with COPD [51].

Non-pharmacological interventions such as nutritional interventions can exert positive effects on both the pathology and the quality of life of patients and have therefore been considered in the management of patients with COPD for a long time [52].

In conclusion, while the importance of nutrition in the management of COPD patients has now been established, it is not yet clear whether the indications differ for patients with AATD, justifying the need for further studies in this regard. In the meantime, pending nutritional guidelines specifically dedicated to patients with AATD, the lifestyle interventions of these patients should be modulated according to the different clinical phenotypes that can be encountered in AATD (clinical picture characterized more by pulmonary pathology, or with contemporary presence of lung and liver disease). As previously stated, within the same genotype, the clinical presentation can be extremely heterogeneous and depends on both genetic and environmental factors. For these reasons, nutritional support should be individualized as much as possible, setting the indications "tailored" to the individual patient [53].

For the time being, referring to what has been demonstrated so far in COPD patients, those subjects who develop only AATD-related pulmonary disease should follow the general recommendations provided for COPD [54].

Therefore, a cross-cutting approach is recommended, which includes both general and nutritional interventions.

The general interventions include [55]:

- Reduction of respiratory effort by optimizing lung function. This reduces caloric needs and energy costs and also increases the patient's adherence to exercise.

- Regular exercise: this not only stimulates the appetite, but also improves the effectiveness of nutritional therapy.

Nutritional interventions aim to provide necessary calories, stop protein catabolism, prevent and treat malnutrition [12].

Specifically, the dietary intake should be normocaloric for normal weight and overweight subjects (BMI between 18.5 and 30 kg/m2), high calorie for malnourished subjects or at risk of malnutrition (BMI <18.5 kg/m2) and low calorie for subjects suffering from obesity. (BMI> 30 kg/m2). The dietary pattern should contain a high percentage of lipids (up to 50 %) and have a limited intake of carbohydrates (about 30 %), compared to what is indicated for healthy subjects [56].

The choice of fats should be addressed to polyunsaturated fats, preferably of the omega-3 series (we recommend 4 portions of fish per week and 30 g per day of nuts and oil seeds). The supply of antioxidants should be constant, guaranteed above all by the use of extra virgin olive oil (2–3 portions per day of 10 ml each), from nuts (rich in vitamin E) in the portion of 30 g per day, from 5 portions of fruit and vegetables every day, in particular citrus fruits, kiwis, red fruits, peppers, tomatoes, spinach, broccoli, lettuce due to the high content of vitamin C and from foods of animal origin, such as meat (3 portions per week of white meat, 1 portion per week of red meat), milk (milk and 1 portion of yogurt each day, 1 portion of cheese twice a week), eggs (2 portions per week), legumes (2–3 servings per week) and fish (4 servings per week) for the high content of zinc and selenium [56].

In addition, the fiber must be well represented, in the amount of at least 25 g per day, with whole grains,

The protein content must be significantly present to prevent or treat muscle loss. In the first case, the protein intake must be 1–1.2 g/kg/body lost, while in the second case the proteins must be equal to 1.5 g/kg / body lost with a specific leucine intake equal to 2.5–2.8 g (meat, cheese, fish, eggs) [56].

The calcium content must cover the estimated requirement (1000 mg for adults, 1200 mg for postmenopausal women), to prevent osteoporosis, through the daily consumption of calcium-rich water (2 liters), milk, yogurt and biweekly consumption of cheeses. It will also be necessary to evaluate the possibility of starting a specific supplementation with Vitamin D in case of proven deficiency or insufficient levels [56].

The need to include a food for special medical purposes, so called oral nutritional supplement (ONS) specific for the disease with a quantity of lipids higher than that of carbohydrates, will have to be assessed individually, in case the diet alone is not sufficient to meet the nutritional needs [56].

5. Nutritional advice in patients with AATD and hepatopathy

Concerning patients who also show liver disease, it has been observed that there is a marked overlap between AATD liver disease and obesity-related liver disease, suggesting shared molecular basis and, therefore, similar nutritional strategies [10].

In the study by Wang et al., published in the journal Hepatology in 2019, the contribution of a particular DNA methylation (5-methylcytosine [5mC]) to the heterogeneity of AATD-related liver disease was examined, as this methylation responds to environmental and genetic signals and its deregulation is an important factor involved in the onset

of liver disease. This methylation was compared between different groups of subjects who presented: normal liver, hepatic steatosis, early stage AATD liver disease and with the complications of cirrhosis and hepatocellular carcinoma. This comparison showed substantial overlap between the groups with AATD liver disease, AATD cirrhosis and obesity / fatty liver disease. Among all the subjects analyzed, the group with the most AATD-like liver disease driver was the group with obesity / fatty liver disease. In summary, a strong epigenetic link has been identified between AATD-related liver disease and that caused by obesity [10].

Moreover, it has been revealed that the presence of metabolic syndrome is the strongest predictor of hepatic fibrosis in AATD. The overall prevalence of fatty liver disease was 40 % higher in the AATD patients studied in the study, compared with an expected prevalence of 20 % – 30 % in the general population. Obesity (understood as BMI $\geq$ 30) was present in only 26.6 % of the study cohort, while at least 37% of the general US population is considered obese. These data suggest that individuals with AATD may experience greater overall susceptibility to metabolic diseases and fatty liver disease, despite BMI within normal limits. Based on the genetic investigation in the study, it appears that part of this susceptibility is governed by changes in DNA methylation shared between individuals with AATD and those with obesity-related fatty liver disease [10].

Taken together, the data provided by Wang and colleagues reveal that epigenomic variations can modulate what is considered a monogenetic disease and that molecular epigenetic signatures within this mutationally homogeneous group may allow for better stratification of patients for liver disease risk [10]. Therefore, it is likely that by identifying the epigenetic signatures that reflect the main differences in AATD liver disease, these could translate into prognostic markers for monitoring the progression of liver disease in these patients.

Regarding the dietary indications to be provided in the case of patients showing AATD-related liver disease, there are currently no specific guidelines. However, the liver damage to which the disease leads (from steatohepatitis to cirrhosis) is comparable to that of other liver diseases, therefore the ESPEN guidelines, although not specific for this type of pathology, provide a useful list of recommendations, to be associated with the previous ones [57].

6. Non-alcoholic fatty liver disease (NAFLD) and non alcoholic steatohepatitis (NASH)

Nutritional recommendations for overweight and obese NAFLD patients are comparable to current guidelines for the dietary management of obesity. Lifestyle changes, including a low-calorie diet and physical exercise, that guarantee a moderate weight loss (at least 7 %), with consequent reduction of the accumulation of hepatic fat, is recommended [58,59]. Bariatric surgery, if the previous strategies fail, must be considered [60].

There is no solid evidence to support a particular composition of the lowcalorie diet for exclusive use in patients with NAFLD/NASH. Indeed, the beneficial effects are obtained regardless of whether the diet is low in lipids or low in carbohydrates [61].

For normal weight patients, it seems plausible to recommend exercise for the improvement of steatosis and insulin resistance, as demonstrated for overweight and obese patients [62–65].

Studies [66–70] have shown that the Mediterranean diet has beneficial effects on body weight, insulin sensitivity, steatosis and hepatic fibrosis. Although there is no evidence regarding the preventive effect of the Mediterranean diet on the onset of NAFLD, this is associated with a lower severity of liver disease in patients with NAFLD [69], even without weight loss [71].

A reduction of the consumption of fructose-sweetened beverages is recommended, although the available evidence, however, is not solid enough to draw conclusions regarding the specific effects of fructose, consumed as an ingredient in a normocaloric diet, in promoting NAFLD [72,73]. Once there are signs of liver disease of any etiology, abstinence from alcohol is suggested due to the higher relative risk of mortality for any dose taken [74]. Furthermore, in the presence of NAFLD or NASH the risks may be aggravated by the interaction with drugs taken in association with factors related to the metabolic syndrome.

The efficacy of vitamin E as an antioxidant in ameliorating the biochemical and/or histological abnormalities of NASH has been studied in a number of studies [75–77] and its use has been associated with an improvement in liver enzymes (decreased ALT, AST), and the states of steatosis, inflammation, ballooning and resolution of steatohepatitis. However, there is great heterogeneity between these trials in terms of study power, inclusion criteria, dosages and formulations of the vitamin E used, additional use of other antioxidants or other drugs, and histological data to evaluate outcomes. In the largest randomized controlled trial (PIVENS study) the improvement in AST levels and histology, with or without weight loss, was significantly greater in patients receiving oral vitamin E (800 IU per day for two years) compared to placebo (42 % vs 19 %) [78].

Nutritional supplements containing selected probiotics or symbiotics can also be used to improve liver enzymes.

Improvement in ALT, AST and gGT levels was observed in 30 NAFLD patients treated with 500 million Lactobacillus bulgaricus and Streptococcus thermophilus daily for 3 months, compared to placebo [79].

Lifestyle modification (weight loss and physical exercise) associated with the intake of a probiotic blend, containing 200 million Lactobacillus plantarum, Lactobacillus deslbrueckii, Lactobacillus acidophilus, Lactobacillus rhamnosus and Bifidobacterium bifidum, and prebiotics (3 g of fructosaccharides) demonstrated a decrease in intrahepatic triglycerides and serum AST [80].

In another study conducted in 52 patients with NAFLD, the intake of a symbiotic, containing 200 million Lactobacillus casei, Lactobacillus rhamnosus, Streptococcus thermophilus, Bifidobacterium breve, Lactobacillus acidophilus, Bifidobacterium longum, and Lactobacillus bulgaricides (fructigaricides) and lactobacillus bulbs taken twice daily for 28 weeks in addition to lifestyle modification revealed a reduction in blood levels of ALT, AST, gGT, CRP and inflammatory cytokines, greater in the treated group compared to placebo [81].

Symbiotics have been shown to be effective in improving AST, inflammation markers, HOMA-IR, serum endotoxin, and histology of NASH with 24-week administration of Bifidobacterium longum with fructo-oligosaccharides associated with lifestyle modification, versus modification alone lifestyle [82].

In addition, the intake of 300 g per day of a probiotic yogurt containing Lactobacillus acidophilus La5 and Bifidobacterium lactis Bb12, for 8 weeks, also improved liver enzymes in patients with NAFLD [83].

Enteral nutrition (EN) or parenteral nutrition (PN) should be administered to NAFL / NASH patients with severe intercurrent illness, when oral nutrition alone is inadequate, not practicable or contraindicated.

Nutritional strategies for patients with NASH are summarized in Table 2.

7. Cirrhosis

It should be recommended to take three to five meals a day and a snack based on carbohydrates or proteins (both substrates of gluconeogenesis) in the late evening. The latter, regardless of the composition or type of formulation used, is useful for shortening periods of fasting, thus being a promising strategy for reversing the anabolic resistance and sarcopenia of cirrhosis [84].

Patients should receive an energy intake of 30–35 kcal per kg body weight (bw) per day [85].

In general, the caloric requirements of patients with compensated cirrhosis are not higher than healthy individuals [85]. Furthermore, during the course of the disease, cirrhotic patients tend to spontaneously reduce their food intake [86]. Those with hypermetabolic cirrhosis or advanced cirrhosis with complications can increase energy expenditure

Table 2
Nutritional strategies in non-alcoholic steatohepatitis (NASH):.

Lifestyle intervention	Stop alcohol intake [74]. • in overweight and obese NAFL patients it is recommended a low-calorie diet (MD it is associated with a lower severity of liver disease and can improve steatosis and IS) and exercise with aimed weight loss of at least 7% [58, 59]. Consider Bariatric surgery if the previous strategies fail [60]. • in normal weight patients physical exercise can improve steatosis and IS [62–65].
Dietary supplements	Oral daily intake of 800 IU of alfa-tocopherol and selected probiotics or symbiotics supplements. [78–83].
Artificial nutrition (EN, PN)	In all patients with severe NAFL/NASH, EN and PN should be administered in severe intercurrent illness, when oral nutrition alone is inadequate, impossible or contraindicated [57]. • in NAFL/NASH patients with a BMI < 30 Kg/m2: – EN: use standard formulas with high energy density (≥ 1,5 Kcal/ml) – Consider PN when patients have to abstain from food temporarily for more than 12 h and administer 2–3 g/Kg/day of glucose i.v. When fasting period lasts longer than 72 h, total PN is required. Water soluble and fat-soluble vitamins as well as electrolytes and trace elements shall be administered daily from the beginning of PN in order to cover requirements. • in obese NAFL/NASH patients the target of EN or PN energy intake is 25 Kcal/kg/day and target protein is 2–2,5 g/kg/day.

NASH: non-alcoholic steatohepatitis, NAFLD: Non-alcoholic fatty liver disease, EN: enteral nutrition, PN: parenteral nutrition, MD: Mediterranean diet, IS: insulin sensitivity

[87,88]. Therefore, it is recommended to measure energy expenditure, by indirect calorimetry, whenever possible. It is not recommended to increase energy intake in overweight or obese cirrhotic patients.

With regard to protein intake, non-malnourished patients with compensated cirrhosis should take 1.2 g of protein per kg bw per day [85,89,90]. Malnourished and sarcopenic cirrhotic patients, including those with sarcopenic obesity, presenting with protein depletion, either due to a high catabolism of total body proteins, or to a reduced muscle protein synthesis, should consume 1.5 g of protein per kg bw per day, in combination. with physical exercise to replenish muscle mass [91–95].

An adequate protein intake is also important in cirrhotic patients with hepatic encephalopathy; in fact, there is no indication of protein restriction, which could induce an increase in protein catabolism [90, 96–98].

In patients with advanced cirrhosis, administration of oral branched-chain amino acid supplements (0.25 g per kg bw per day) is useful in order to improve event-free survival or quality of life [99–102].

As an alternative to the nighttime snack with carbohydrates or proteins, which has been found to be useful in patients with cirrhosis [84], the administration of an ONS after dinner or before bed can also be considered in order to reduce the duration of the night fasting [57].

Integration with micronutrients is useful in the prevention or correction of deficiency states [23]. Patients with cirrhosis may have deficiencies in water-soluble vitamins, particularly thiamine, and fat-soluble vitamins such as vitamin D [23,24].

According to previous studies, zinc and vitamin A supplements can indirectly improve food intake and nutritional status by improving dysgeusia [103,104]. In the first, in fact, cirrhotic patients who presented low serum levels of vitamin A, and some also of zinc, were less sensitive to taste and smell than the healthy control group. Oral intake of vitamin A (10,000 micrograms/day) for 4 weeks led to a significant improvement in the mean detection and mean thresholds of recognition for the bitter and salty taste and smell of pyridine, regardless of the state of the zinc [103]. In the second, in a group of 16 patients with cirrhosis, taste function was significantly improved during treatment with zinc (0.2 g of zinc sulfate, 3 times a day) for 6 weeks, compared to the placebo group [104].

Where the diet alone is not sufficient to meet the nutritional needs, the possibility of taking a specific ONS for the disease will be evaluated.

In patients who cannot be fed orally or who do not achieve nutritional goal through the oral diet, initiation of EN and subsequently parenteral should be considered if oral feeding and/or EN are ineffective or impractical.

Nutritional strategies for patients with cirrhosis are summarized in Table 3.

Table 3
Nutritional strategies in liver cirrhosis:.

Oral nutrition	Nutritional counseling: • Three to five meals a day and a late snack evening (carbohydrates or proteins made) can minimize fasting periods and improve the total body protein patrimony [84]. • cirrhotic patients in conditions of increased energy expenditure (e.g. acute complications, ascites refractory) or malnutrition should take a greater amount of energy [87,88]. • It is not recommended to increase the energy intake in overweight or obese cirrhotic patients. In obese patients with cirrhosis should be implemented a lifestyle intervention with the goal to take advantage of the benefits of weight loss, including the reduction of portal hypertension [105]. Protein requirement: • Non-malnourished patients with compensated cirrhosis must take 1.2 g/kg/day of protein [78,82,83]. • Cirrhotic patients malnourished and/or sarcopenic must take 1.5 g/kg /day of protein in order to replenish protein assets [91,94]. • In cirrhotic patients with malnutrition and muscle depletion, oral diet should provide 30–35 kcal/Kg/day and 1.5 g/kg/day of protein [86]. • In cirrhotic patients with hepatic encephalopathy don't limit protein intake since it could induce an increased protein catabolism [98]. BCAA requirement: • Cirrhotic patients who are "intolerant" to proteins must take vegetable proteins or BCAA (0.25 g/Kg/day) orally to promote an adequate protein intake [106]. • In patients with advanced cirrhosis oral supplements BCAA (0.25 g/Kg/day) should be prescribed for a long time in order to improve the free events survival or the quality of life. Micronutrients / Low sodium diet: • Micronutrients must be administered for treat confirmed or clinically suspected deficits [23]. • When prescribing a low sodium diet (unpleasant to taste), it should be considered the risk of further reduction of spontaneous oral diet in front of a moderate advantage in the treatment of ascites. Pay attention to the low sodium diet palatability [107].
Artificial nutrition (EN, PN)	EN and PN: • In cirrhotic patients who cannot be orally fed or do not reach the nutritional goal through the oral diet, EN should be administered [57]. • In cirrhotic patients the PN should be used when oral feeding and / or NE are ineffective or impractical [57]. • In cirrhotic patients, nutritional intervention (oral, EN or PN) must be implemented according to current guidelines for non-cirrhotic patients [57]. • In cirrhotic patients, a nutritional intervention (oral or NE or NP) should be recommended for potential clinical benefit without an increase in adverse events [108]. EN tubes: • The positioning of the PEG is associated with a increased risk of complications related to ascites or varices and therefore can only be used in exceptional cases [109]. • Esophageal varices are not one absolute contraindication for positioning of a nasogastric tube [57].

BCAA: branched chain amino acids, EN: enteral nutrition, PN: parenteral nutrition, PEG: Percutaneous Endoscopic Gastrostomy.

8. Discussion

In the absence of specific nutritional guidelines for patients with AATD-related lung or liver disease or for patients presenting both AATD phenotypes, it seems useful to make use of the indications in the literature for the individual pathologies. In the case of AATD-related lung disease, the nutritional recommendations present in the literature for patients with COPD were reported, while in the case of patients with AATD-related liver disease, the international dietary guidelines of the ESPEN company were reported, which include indications for all steps of the liver damage that may be encountered in these patients. The case of patients presenting both pathological conditions (hepatic and pulmonary disease) at the same time is more complex, for which there is currently no resource in the literature. Given the lack of resources in this regard, the only alternative seems to be to use the indications provided in the text for subjects with COPD and AATD-related liver disease at the same time. To check whether these nutritional approaches are compatible and applicable in the same patient, we compared them. The main differences concern total energy intake and dietary fats and carbohydrates intake. In COPD patients the dietary intake should be normocaloric for normal weight and overweight subjects (BMI between 18.5 and 30 kg/m2), high calorie for malnourished subjects or at risk of malnutrition (BMI <18.5 kg/m2) and low calorie for subjects suffering from obesity. The dietary pattern in COPD patient should contain a high percentage of lipids (up to 50 %) and have a limited intake of carbohydrates (about 30 %) [56]. In NAFLD/NASH patients a lifestyle change is recommended, including a low-calorie diet for overweight and obese, but there is no solid evidence to support a particular composition of a low calorie diet, because the beneficial effects are obtained regardless of whether the diet is low in lipids or low in carbohydrates [61]. However studies [59–63] have shown that the Mediterranean diet has beneficial effects on body weight, insulin sensitivity, steatosis and hepatic fibrosis. In terms of calories, patients with cirrhosis should receive an energy intake of 30–35 kcal per kg body weight per day in normal weight cirrhotic subjects [78], not increasing energy intake in overweight or obese cirrhotic patients. There are no specific indications on diet composition.

It is recommended to evaluate case by case, developing a tailor-made approach for the patient based on specific needs and characteristics.

9. Conclusions

To date, there is a lack of formal research regarding the effects of specific nutritional recommendations in patients with AATD; proper eating habits may help to preserve lung and liver function. In this narrative review two types of nutritional indications were reported in relation to AATD phenotype: one related to subjects with lung disease only and the other for patients with both lung and liver disease. For practical dietary advice in patients with COPD AATD-related, a food pyramid for COPD subjects published has been used.

Since there are no specific guidelines for patients who also have AATD-related liver disease and who present with liver damage common to other diseases (such as that observed in the case of obesity) ranging from steatohepatitis to cirrhosis, the ESPEN guidelines have been reported for individual liver disease.

Further studies would be needed to define specific nutritional guidelines for all the phenotypic variants of AATD.

Funding

None.

CRediT authorship contribution statement

Mariangela Rondanelli: Conceptualization, Supervision, Project administration. Clara Gasparri.: Writing- Original draft preparation. **Claudia Razza**: Writing- Original draft preparation. **Cinzia Ferraris**: Writing- Reviewing and Editing. **Simone Perna**: Writing- Original draft preparation. **Ilaria Ferrarotti**: Writing- Reviewing and Editing, Project administration. **Angelo Guido Corsico**: Conceptualization, Project administration. All authors have read and agreed to the published version of the manuscript.

Declaration of Competing Interest

The author declare no conflict of interest.

Acknowledgments

None.

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