Dietary Approach to NAFLD

15

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15.1 Introduction

Diet and physical activity belong to the key therapeutic options with regard to nonalcoholic fatty liver disease/nonalcoholic steatohepatitis (NAFLD/NASH) [1]. The burden of NAFLD has been dramatically growing in parallel with obesity, diabetes, and outbreaks of metabolic syndrome [2]. NAFLD has become the most common cause of chronic liver disease by representing a risk factor for cirrhosis, hepatocellular carcinoma, and liver transplantation [3], for extrahepatic manifestations such as cardiovascular [4, 5] and kidney disease [6], as well as for extrahepatic malignancies [7]. NAFLD encompasses a wide spectrum of conditions, ranging from simple steatosis to nonalcoholic steatohepatitis, which increases risk of getting cirrhosis and hepatocellular carcinoma. With the growing incidence of obesity, sedentary lifestyles, and unhealthy diet worldwide, an increased prevalence of NAFLD is

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being observed, with Europe witnessing between 20 and 30% of cases [8]. Thereby, it has now been recognized as a major public health problem.

Dietary habits and nutrients are the most important contributing factors to the development, progression, and treatment of nonalcoholic fatty liver disease and the associated metabolic comorbidities. In general, a hypercaloric diet, particularly one rich in trans-fats, saturated fats, cholesterol, and fructose-sweetened drinks, appears to increase visceral adiposity and stimulate lipid accumulation in the liver as well as progression of nonalcoholic steatohepatitis. However, the reduction of calorie intake and supplementation with monounsaturated omega-3 fatty acids [9] have preventive as well as therapeutic effects. In addition, fiber, coffee, green tea, and olive oil could be protective nutrients against NAFLD [10].

Based on the available data, a weight loss of at least 3–5%—achieved by having a hypocaloric diet alone, or in combination with exercise and modifications of lifestyle—generally reduces liver steatosis. However, according to the European Association for the Study of Liver Disease (EASLD) 2012 guidelines, a weight loss of up to 10% is required in order to improve cases of liver necroinflammation. Promrat K. et al. [11] performed one of the most relevant studies where it was found that a loss of at least 7% of body weight, due to changes in diet and lifestyle, improves all of the histological parameters in patients diagnosed with NAFLD. Maintaining a long-term adherence to the diet is an important factor for achieving this objective. In addition, a healthy diet has benefits beyond weight reduction in patients with NAFLD irrespective of whether they are obese or of normal weight [12]. Therefore, nutrition is as an important cornerstone in the prevention and treatment of nonalcoholic fatty liver disease, and patients with NAFLD should receive individualized dietary recommendations.

15.2 Effect of Different Nutrients on NAFLD

15.2.1 Effect of Dietary Fatty Acid Composition on NAFLD

Monounsaturated fatty acids (MUFAs), unlike saturated fatty acids (SFAs), do not worsen insulin sensitivity [13]. For example, MUFAs did not affect insulin sensitivity in the KANWU study [14] or in the more recent 24-week RISCK study [15], in which subjects were randomized to consume either a diet high in SFAs or another diet high in MUFAs. This study concluded that decreased insulin sensitivity was secondary to the content in SFAs but not in MUFAs. Nevertheless, other studies suggest that MUFAs are beneficial in cases of NAFLD and even propose mechanisms. These studies indicate that the effects of MUFAs may be explained by their participation in the regulation of insulin-sensitizing gene expression [16] and in reducing inflammation [17], as well as by their inhibitory effects on nuclear factor kappa B (NF-kappa B) [18]. In another study, MUFAs were shown to reduce the expression of genes related to hepatic lipogenesis, gluconeogenesis, and sterol regulatory-element binding protein (SREBP) in obese rats [19]. Further studies are needed to elucidate the role of MUFAs in NAFLD as well as its optimal dosage.

PUFAs are other fatty acids involved in NAFLD, specially omega-3 fatty acids. Intake of omega-3 supplements leads to improvement in cases of fatty liver. Despite the marked heterogeneity between various studies, omega-3 supplements have been shown, in several clinical trials, and as summarized in a meta-analysis [20], to reduce fat in the liver as measured by ultrasound, MRI, and biopsy. In addition, these lead to improvement in liver enzymes.

15.2.2 Effect of Types of Carbohydrates on NAFLD

It seems clear that excess presence of carbohydrates in a diet increases the level of calories, and this may cause the increase in liver fat content which is found in many comparative studies. However, doubts do exist when one considers the type of carbohydrates. According to existing studies, fructose consumption increases visceral adipose tissue, hypertriglyceridemia, and insulin resistance, which is sufficient to warrant, as a clinical recommendation, a reduction in its consumption for patients with NAFLD. The most common sugar found in fruits is sucrose, while corn syrup (which has a high fructose content) is most common in nonalcoholic beverages. Sucrose consists of 50% fructose and 50% glucose. In a recent study done with healthy subjects, the authors observed an increase in liver enzymes in the subjects consuming 25% of sucrose as part of their total daily intake of calories [21]. In another study, it was found that patients with fatty liver disease consumed fructose syrup twice as much as those without NAFLD (365 kcal vs 170 kcal) [22]. In another study, it was shown that patients who received a high-calorie fructose diet had increased deposition of liver fat as compared to the control group [23]. A four-week, randomized, double-blind, and controlled intervention study [24] showed that the reduction of fructose in the diet of Hispanic-American adolescents with NAFLD caused an improvement in several important factors related to cardiovascular risks, in insulin sensitivity, in C-reactive protein, and in low-density lipoprotein oxidation. However, a recent meta-analysis of 21 interventions concluded that there was lack of enough evidence required to draw conclusions about the effects of fructose or saccharose in nonalcoholic fatty liver disease. Therefore, no evidence was found to recommend the avoidance of their consumption. Thus, the literature review by Chung et al. [25], based on a systematic review and meta-analysis, shows that there is a lack of enough evidence which is necessary to draw conclusions regarding the effects of fructose, as compared with sucrose consumption, in nonalcoholic fatty liver disease. Although a difference between fructose and glucose or the direct role of fructose has not been shown in studies aimed at quantifying the content of liver fat, a study monitoring an isocaloric fructose diet (25% of total daily caloric intake for 10 weeks), as compared to a glucose diet, found that it did impair insulin sensitivity [26].

In spite of studies comparing the effects of macronutrients on liver fat content and insulin have some limitations, we can draw a series of conclusions:

– Hypocaloric diets which are poor in fats and carbohydrates reduce liver fat content, while overfeeding based on hypercaloric diets increases it.
– Low-fat and high-carbohydrate diets, as compared to high-fat and low-carbohydrate diets, appear to decrease liver fat content and improve insulin sensitivity. The deleterious effects of high fat content appear to be due to the presence of SFAs, while MUFAs could be beneficial and recommendable in the diet of patients diagnosed with NAFLD.
– Hypercaloric high-carbohydrate diets increase the liver fat content, but there are no convincing data to conclude that fructose is worse than glucose, even though the metabolism of fructose appears to have comparatively more harmful effects on the liver.

The influence of genetic differences in patients with NAFLD, who maintain different diets, has not been systematically studied.

15.2.3 Fiber and NAFLD

Patients with NAFLD have a poor fiber intake. It has been shown that the mean daily fiber intake of these patients is almost 50% lower than that of healthy people [27]. Recently, Cheng and colleagues demonstrated the relationship between dietary fiber intake and hepatic lipid content in cases of NAFLD. They showed that fiber intake was inversely associated with hepatic fat fraction and intrahepatic lipid [28].

15.2.4 Effects of Micronutrients on NAFLD

Vitamin E. This vitamin acts on oxidative stress and is a free radical eliminator, with an antioxidant action that leads to radical chain reactions such as lipid peroxidation. Vitamin E is thought to act on tissue growth factor TGFß1, peroxisome proliferator-activated receptors (PPAR), apoptosis, and helps in the regulation of involved genes. Lavine et al. [29], in the most extensive clinical trial on pediatric patients, found no significant differences between the placebo and vitamin E groups with regard to the improvement of alanine aminotransferase levels. However, more resolution of NASH was seen in the vitamin E group as compared to the placebo group; this was mainly attributed to the improved ballooning of hepatocytes, but there were no differences in steatosis or lobular inflammation between the two groups. Hasegawa et al. [30] selected 12 adult patients with biopsy-proven NASH and administered vitamin E (300 IU/day) to them for 12 months, observing the improvement in cases of liver inflammation and fibrosis as well as in serum transaminases. Since these initial studies, randomized clinical trials with vitamin E have been performed in the context of NAFLD. A comparison between these trials is difficult due to the variation in selection criteria, different doses of vitamin E, and unclear formulations of vitamin E that may affect its bioavailability. In the clinical trial PIVEN [31], which is the largest documented clinical trial, vitamin E was administered orally, at a dose

of 800 IU/day for 96 weeks, and thereby, it was confirmed that vitamin E has a beneficial effect on patients with NAFLD, through improved serum biochemical indices and favorable changes in the liver biopsy. The long-term effect of vitamin E, as well as its effects on prevention of cirrhosis and long-term survival, remains unestablished. Since some meta-analyses have reported an increase in mortality with high doses of vitamin E [32], attention should be paid to administration of long-term high doses of vitamin E. Furthermore, it has been shown that the addition of another potent antioxidant, such as vitamin C, has not altered the antioxidant effects of vitamin E [33].

Vitamin D. There is epidemiologic evidence indicating that NAFLD and vitamin D deficiency often coexist. The epidemiological data shows that low levels of serum 25(OH)D are associated with NAFLD [34]. The first study to show the association between biopsy-proven NAFLD and vitamin D levels was published by Targher et al., which demonstrated that vitamin D concentrations were lower in subjects diagnosed with NAFLD as compared to matched controls. In addition, vitamin D levels were able to predict the histological severity of NAFLD [35]. In general, the different published studies suggest that patients with NAFLD are more likely to be deficient in vitamins. It seems that the metabolic, anti-inflammatory, and anti-fibrotic properties of vitamin D could be responsible for the possible impact of vitamin D on the progression of NAFLD. Nevertheless, the limitations of the studies (such as different methods used for NAFLD diagnosis, variability in defining vitamin D deficiency, and the employment of different techniques to measure vitamin D levels), the limited number of studies done on human subjects, and the lack of consensus with respect to defining the optimal levels of vitamin D make it premature to recommend vitamin D supplementation for the specific treatment of NAFLD.

Minerals. In general, a progressive deterioration in homeostasis of certain minerals is seen in patients with NAFLD, which may reflect the greater oxidative stress and inflammatory status. In particular, certain minerals such as copper, selenium, and iron have been studied in order to further investigate their possible contribution to the development and treatment of diseases such as NAFLD [36].

It has been observed that high-fructose diets may cause copper deficiency. In rats, fructose consumption alters the metabolism of copper, and copper deficiency may be due to the fact that fructose inhibits its absorption through the intestinal epithelium. In addition, copper deficiency and fructose appear to act synergistically: they accelerate the accumulation of liver fat as well as liver damage [37]. Selenium is a trace mineral that is incorporated into proteins in order to make selenoproteins, which are important antioxidant enzymes. This antioxidant property of selenoproteins helps to prevent cellular damage by free radicals. In this regard, it has been observed in experimental models that selenium supplements cause a decrease in the expression of TGF-β1-induced collagen, IL-8 production, as well as overexpression of antioxidant enzymes [38]. Considering that within both in vitro and in vivo studies, selenium supplements have shown a potential effect on the reduction of oxidative stress, it is important to take into account their potential clinical implications in subjects diagnosed with liver disease. However, a cross-sectional study has shown that increase in the levels of plasma selenium is associated with the elevated

prevalence of NAFLD [39]. Iron has been widely implicated in the pathogenesis of NAFLD and represents a potential target with respect to treatment. For example, hyperferritinemia is generally associated with NAFLD and liver damage, while iron depletion by procedural phlebotomy, in patients with a mild overload of iron, could benefit lifestyle changes by the normalization of liver enzymes and insulin resistance [40]. In addition, iron depletion overregulates glucose uptake, and increases insulin receptor expression and its signaling in hepatocytes within both in vitro and in vivo studies [41], while iron supplements in diet cause dyslipidemia and lead to insulin resistance. However, further studies are needed to evaluate the potential for iron depletion therapy in patients diagnosed with NAFLD.

15.2.5 Other Food Components

Caffeine. Caffeine acts on the signaling pathways which lead to reduction of the activity of the connective tissue growth factor: it is considered to be an important stimulator of liver fibrosis. Many of the cytoprotective antioxidant effects of coffee are thought to be independent from the actual caffeine and are due to other ingredients such as flavonoids and polyphenolic compounds with antioxidant activity. A recent meta-analysis showed that although total caffeine consumption is not related to the prevalence of NAFLD, regular consumption of coffee with caffeine may significantly reduce liver fibrosis in patients with NAFLD [42]. Considering the potential benefits of coffee, we recommend its regular consumption in patients with NAFLD while pointing out that consumption of coffee with caffeine is recommended, but caffeine alone is not. However, the recommended dosage has not been established.

Polyphenols. They form part of a very large family of plant-derived compounds comprising an extensive variety of chemical structures. They are included in many kinds of food items, especially ones with vegetal origins. There exists a considerable amount of evidence indicating the hepatoprotective effects of these biomolecules, unless they are in cultured cells and animal models. The proposed mechanisms of action include reduced fatty acid and triacylglycerol synthesis, increased fatty acid oxidation, and a decrease in oxidative stress and inflammation [43]. To date, their optimal dose and the concomitant length of the treatment period is not known, but the obtained data seem to indicate that nutritional intervention studies could demonstrate their importance in the prevention and treatment of NAFLD.

Prebiotics and probiotics. In recent years, we have seen a growing interest regarding the benefits of prebiotics and probiotics in different diseases and specifically in the NAFLD. Patients with NAFLD have a dysfunctional microbiota [44], and this may promote the progression of NAFLD through rupture of the mucosal barrier of the small intestine and bacterial translocation to the systemic circulation, which leads to systemic inflammation, increased cytokines, and insulin resistance [45].

A recent meta-analysis [46] suggests that probiotics improve transaminases, total cholesterol content, TNF-α, and insulin resistance. Moreover, Wong et al. showed that patients with NASH (demonstrated with biopsy), when treated with probiotics, had significantly lower intrahepatic triglyceride content, waist circumference glucose, and lipid levels [47]. However, there is not enough evidence to recommend use of probiotics in NAFLD. In addition, its possible translation to clinical practice may be limited by the reduced number of studies, the variations in the probiotic strains, the doses, and the variable duration of the intervention period used in the different published studies. However, by virtue of their good safety profile (except in immunosuppressed patients), further studies would be required to analyze their role in NAFLD.

15.3 Food and NAFLD

Macronutrients, micronutrients, bioactive compounds, and other components are part of the food that people eat. In addition, the mechanisms by which certain nutrients may influence the disease are not completely understood. For this reason, rather than nutrients, it is important to analyze the role of food in the pathophysiology and treatment of NAFLD. In the following paragraphs, we will focus on the food items that have been associated with NAFLD in both negative and positive ways.

15.3.1 Meat

In general, high intake of meat is related with glucose intolerance, insulin resistance, and a higher risk of type 2 diabetes [48]. All of these factors are involved in NAFLD pathogenesis. However, a high intake of processed meat has been recently associated with an increased risk of NAFLD [49]. In addition, it has been found that people with NAFLD consume more meat, of all types, than healthy people. The potential explanation for this could be: (1) it has a high level of saturated fats and cholesterol; (2) in many cases, it contains preservatives and additives, and (3) people with high intake of meat usually follow a “Western” dietary pattern.

15.3.2 Fatty Fishes

There are studies that have found associations between a high intake of these fishes and a reduced risk of NAFLD [50]. Allard et al. showed that the total PUFA intake of patients with NASH was below the recommended level [51]. The majority of these fishes (pilchards, sardines, mackerel, trout, salmon, herring, and tuna) are rich in omega-3 PUFAs.

15.3.3 Olive Oil

Most studies, which have been done with rodents, have shown a reduction in total lipid and phospholipid levels and in animals whose diet was supplemented with olive oil, as compared to SFAs [24]. Conversely, Rums et al. [52] observed increased liver steatosis in rats who were overfed with olive oil, as compared with corn oil or echium oil. However, it is important to note that the olive oil group had no evidence of oxidative stress or necrosis, as was shown in the liver biopsies from the other groups. Park et al. [53] showed a downregulation of genes associated with liver lipogenesis and a reduced expression of proinflammatory cytokines, providing information on the mechanism by which olive oil reduces oxidative stress in the liver. Finally, a recent study has shown that mice who were fed with a high-fat diet, rich in extra virgin olive oil, showed a decreased hepatic damage, possibly via an anti-inflammatory effect in adipose tissue, along with modifications in the lipid composition of liver and signaling pathways [54]. Therefore, olive oil may be recommended for patients with NAFLD only when it is consumed as part of a low-fat diet, e.g., a Mediterranean diet pattern. The role of olive oil supplements, as well as their use with other food items, requires further research, specifically to clarify the dose and formulation that may be more effective in the treatment and prevention of fatty liver.

15.3.4 Nuts

They show a great therapeutic potential in the treatment of patients with NAFLD by improving the lipid profile and decreasing liver steatosis and inflammation. However, no randomized clinical trials, aimed at evaluating their role in the histological liver parameters of humans, have been performed. Only longitudinal studies are available which show that consumption of nuts leads to decrease in transaminases within 3 months [55].

15.3.5 Tea

Although the potential protective effect of tea appears to be promising for patients with NAFLD, caution must be exercised because of the cases of hepatotoxicity that have been documented in people who consumed green tea [56]. Despite the recent interest in the antioxidant properties of catechins, which may provide a potential benefit, their good effects on patients with chronic liver disease [57] have not been determined. Although there are epidemiological and experimental data, based on tests in animal models, which demonstrate that tea was likely to mitigate the development or progression of NAFLD, the lack of high-quality clinical trials in humans, at present, means that consumption of tea cannot be specifically recommended for patients with NAFLD.

15.4 Implications of Diet on NAFLD

In almost all consensuses on dietary interventions for patients diagnosed with NAFLD that is associated with obesity, a low-calorie diet is recommended. It is well known that the energy content of the diet is the most important factor that influences liver fat content. Hence, reduction of calorie intake should be recommended to all patients with NAFLD who are overweight or obese [58]. In fact, hypocaloric diets are more effective than changes in diet composition. These data agree with the results of two studies [59, 60], where it was seen that two hypocaloric diets were effective in decreasing the transaminase levels and insulin resistance in obese patients with NAFLD, regardless of the composition of the diet. Calorie restriction, together with physical activity, is the best way to lose weight. A relatively low-calorie diet yields better results as compared to a very low-calorie diet.

Regarding the qualitative composition of the diet, the recommended proportions are as follows: 50–60% carbohydrates and 20–25% lipids. This proportion of carbohydrates in the diet may be considered appropriate to ensure compliance with the nutritional intervention. To achieve these macronutrient recommendations, attention should be also paid to the election of food items. To create a "high-quality healthy diet" that improves cases of liver steatosis, it is particularly important to avoid fructose and trans-fats present in soft drinks and fast food meals, as well as processed food. In addition, consumption of refined grains and fried as well as salty food items should be reduced as much as possible.

The importance of the food items which constitute up a diet has been shown in studies on the DASH (Dietary Approach to Stop Hypertension) diet and the Mediterranean diet.

The DASH diet is rich in fruits, vegetables, and low-fat or nonfat dairy. It also includes whole grains on the most part, along with lean meats, fish, poultry, nuts, and beans as well. It is high in fiber content and low to moderate in fat content. This diet was designed to reduce blood pressure, but it has been observed that it is also beneficial for patients with metabolic disorders, due to the fact that it improves insulin resistance, dyslipidemia, and chronic inflammation [61]. In this context, a recent publication shows that NAFLD patients who followed the diet for 8 weeks reduced their body weight, body mass index, alanine aminotransferase, fasting insulin levels, insulin resistance, triglycerides, and inflammatory markers [62]. The possible mechanisms for the protective role of the DASH diet could be the high intake of antioxidants, fiber, MUFAs, and PUFAs.

Mediterranean diet improves insulin sensitivity and achieves a significant reduction in steatosis (from up to 39 to 7%) with a low-fat and high-carbohydrate diet [63]. It is interesting to note that in this study, these changes were not secondary to weight loss. In addition, compared to similar diets with calorie restriction and low-fat content, adhesion to the Mediterranean diet is associated with improvements in lipid profile and insulin, reduction of ALT, and significant improvement in liver steatosis as determined by ultrasound. In another randomized clinical trial, it was

shown that the Mediterranean diet caused a benefit in cases of liver steatosis and insulin sensitivity, when it was maintained for a period of 12 months [64]. This benefit is postulated to be due to the content of olive oil in the Mediterranean diet, regardless of its calorie content. In a cross-sectional study conducted by our working group [65], it was found that adherence to the Mediterranean diet (assessed by a 14-item questionnaire) was associated with lower grades of steatosis and NASH in patients with NAFLD, as diagnosed through liver biopsy. Meta-analyses which assess the effect of the Mediterranean diet in NAFLD are unavailable, but this dietary pattern has demonstrated its effectiveness in surrogate markers of liver steatosis and insulin resistance. In conclusion, the Mediterranean diet is currently considered to be a healthy eating pattern with respect to many diseases which include metabolic syndrome, cardiovascular disease, and neoplastic diseases. In recent years, an interesting inverse association with NAFLD has been observed, which exalts the Mediterranean dietary pattern as a new therapeutic option for cases of NAFLD. Additional studies are needed to confirm these preliminary data and suggest the employment of a reliable and easy-to-use tool for measuring the benefits of adhesion to the Mediterranean diet in patients diagnosed with NAFLD. In addition, it is important to consider that the Mediterranean diet might be associated with a Mediterranean lifestyle, which could also have beneficial impacts with regard to NAFLD.

15.5 Geometry of Nutrition in NAFLD

Geometric Framework for Nutrition (GFN) is a new methodology of interpreting the ways in which nutrients, other dietary constituents, and their interactions influence physiology and health. Thus, it allows to relate nutrition with health outcomes and to move from molecular to ecological levels [66]. A recent study using GFN in mice shows that nutrient intake has a deep impact on appetite, growth, reproduction, aging, cardio-metabolic outcomes, health, obesity, immune function, and gut microbiota [67]. Thus, GFN could be used to improve the diet in order to get better health outcomes. At the end, it would allow us to design a diet containing precise amount of requisite nutrients/foods. Actually, GFN is being used in studies on humans, with promising results that allow one to focus on the dietary determinants of chronic diseases that are associated with obesity and aging [68].

Up till now, there is only one study, in aged mice, that employs GFN to associate nutrition with NAFLD. The study suggests that a low-protein/high-fat/low-carbohydrate diet increases the probability of having NAFLD. The authors also indicate that the composition of macronutrients may be as important as the energy content of the weight-loss diet. Currently, there are no GFN studies being undertaken on diseases of the human liver. Some pertinent limitations could be the slow progression of liver disease and the need to have liver biopsies in order to monitor the disease.

In the future, GFN will provide a unique tool by which to understand the multiple relationships among nutrition, diet, and health. The concomitant information will not only help to understand the causes of NAFLD but also to define nutritional interventions aimed at prevention and treatment of NAFLD.

15.6 Conclusions

In general, it can be considered that NAFLD is a disease that is caused by an unhealthy diet, which has become the main cause of liver diseases in Western countries. The majority of NAFLD patients follow hypercaloric diets laced with instances of overconsumption of simple carbohydrates and fats (mainly saturated fats), along with reduced intake of dietary fiber and food items rich in omega-3 supplements. The available scientific evidence for dietary and nutritional therapy of NAFLD strongly recommends, with a high quality of evidence, that reduction of body weight through a hypocaloric diet and exercise for a period of 3–12 months can improve liver function and the histology of NAFLD/NASH. A weight loss of 5–10% should be sought along with a 25% reduction in caloric intake of the normal diet for the patients' age and sex, in order to obtain a weekly weight loss of 0.5–1 kg. For improvement of NAFLD/NASH, it is recommended to give priority to energy optimization (lipid restriction) in terms of the proportions of food intake. In addition to calorie restriction, the composition—mainly macronutrients and micronutrients—of the diet and some specific food items may also improve the cases of NAFLD. Although the causality has still not been established, the data reviewed in this document suggest that the consumption of specific food items may modulate the risk of NAFLD and its progression to NASH, along with regulating the risk of other entities including metabolic syndrome. There is enough evidence indicating that patients may benefit from a moderate- to low-carbohydrate (40–45% of total calories) diet, coupled with increased dietary MUFA and n-3 PUFAs, and reduced SFAs. Moderate consumption of coffee, nuts, fatty fishes, and olive oil—all of which constitute a Mediterranean diet—appears to be safe in this context. However, the studies which assess their therapeutic role in patients with NAFLD/NASH are currently insufficient.

While specific recommendations regarding their benefit or dosage are established, patients with NAFLD should be allowed to consume these food items as part of a general diet and physical exercise program.

The importance of adherence to the diet should be emphasized because weight loss and weight maintenance remain a considerable challenge for many individuals and most patients end up regaining weight after an initial weight loss [1].

Future studies are needed on bioactive food compounds, which are able to modulate the activation of the genes involved in lipogenesis, fibrogenesis, lipid peroxidation, and inflammation, thereby representing an attractive therapeutic approach for this condition (Fig. 15.1).

Hypocaloric Mediterranean diet for weight loss and NAFLD/NASH resolution

Early breakfast:

- 1 hypocaloric piece of fruit (avoid bananas, grapes, custard apple). The piece of fruit is preferable to juice.
- 1 skim yogurt or glass of skim milk.
- 1 coffee or tea with skim milk,without sugar.
- Sometimes (2-3 times per week), you could add a couple of biscuits of whole bread or half of a toast of whole bread with extra virgin olive oil (1 tablespoon), or margarine (10 gms), or wholegrain cereals without sugar (30 gms).

Midmorning:

- 1 infusion (tea, chamomile, or mint pennyroyal) or coffee with saccharinc an be taken several times per day, provided that they are taken without sugar.
- 1 hypocaloric piece of fruit, or 1 skim yogurt, or 3/4 nuts.
- Occasionally (1-2 times per week), you could add half of a vegetable sandwich or ham sandwich without cheese.

Lunch:

- 1 salad plate (lettuce, endives, tomato, pepper, onion, asparagus, mushrooms, cucumber, spinach, heart of palm, or little corncob) or cooked/grilled vegetables (cucumber, pepper, cauliflower, broccoli, cabbage, asparagus, mushrooms, spinach, chard, zucchini, eggplants, leek, green beans, beet, carrots, pumpkin, artichokes, potatoes, sprouts, pea, or broad beans with moderation) or vegetable soup.
- Cooked or grilled fish, chicken or turkey (without skin),or beef every other day. Oily fish should be included only once per week.

Fig. 15.1 Hypocaloric Mediterranean diet for weight loss and NAFLD/NASH resolution

- Sometimes (2-3 days per week), instead of fish or meat, you could eat a dish which consists of brown rice, wholegrain pasta, potatoes, and stewed vegetables without fat or sauce.
- Sometimes (2-3 days per week), instead of fish or meat, you could consume a dish made of legumes.

Snacks:

- 1 glass of orange juice (two pieces), or 1 hypocaloric piece of fruit, or 1 skim yogurt, or 3/4 nuts.
- 1 infusion/coffee.

Dinner:

- Vegetable soup, or salad, or cooked or grilled vegetables (which should be different from those consumed during lunch).
- Eggs (omelet or cooked, 2 whites and ½ yolk), or fish, or meat that are cooked or grilled, or seafood with shell or natural tuna.
- Sometimes you could add fresh cheese or Iberico ham without fat.
- Optional fruit·

When eating meat, try to avoid red meat (no more than 1 fillet each for 15 days) and choose white meat (chicken, turkey and rabbit). Water should be the principal drink in all meals. Extra virgin olive oil should be the main source of fat in all meals. The usual ways of cooking should be grilling or steaming in the oven. Avoid sauces.

In summary, total caloric intake should be adjusted to save between 500-1,000 kcal/day.

Mediterranean dietary pattern:

Carbohydrates: 45% to 60% of calories, preferably unrefined

Fiber: 20 to 40 g/day (5 to 15 g of soluble fiber)

Total fat: 20% to 35%.

Fig. 15.1 (continued)

Saturated fat: 7%

Polyunsaturated: 5% to 10%

Monounsaturated: 15% to 20%

Omega-3: preferably through intake of blue fish/nuts, 2 to 4 g/day

Cholesterol: 200 to 300 mg/day

Trans fatty acids: <1% of daily calories

Proteins: 20% of daily calories

Vitamin E: 800 IU/day (supplement)

Daily moderate consumption of coffee

Fig. 15.1 (continued)

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