Dietary Recommendations for the Management of Non-alcoholic Fatty Liver Disease (NAFLD): A Nutritional Geometry Perspective

Manuel Romero-Gómez, MD, PhD[1,2] Rocío Aller, MD, PhD[3] Franz Martín-Bermudo, MD, PhD[4,5]

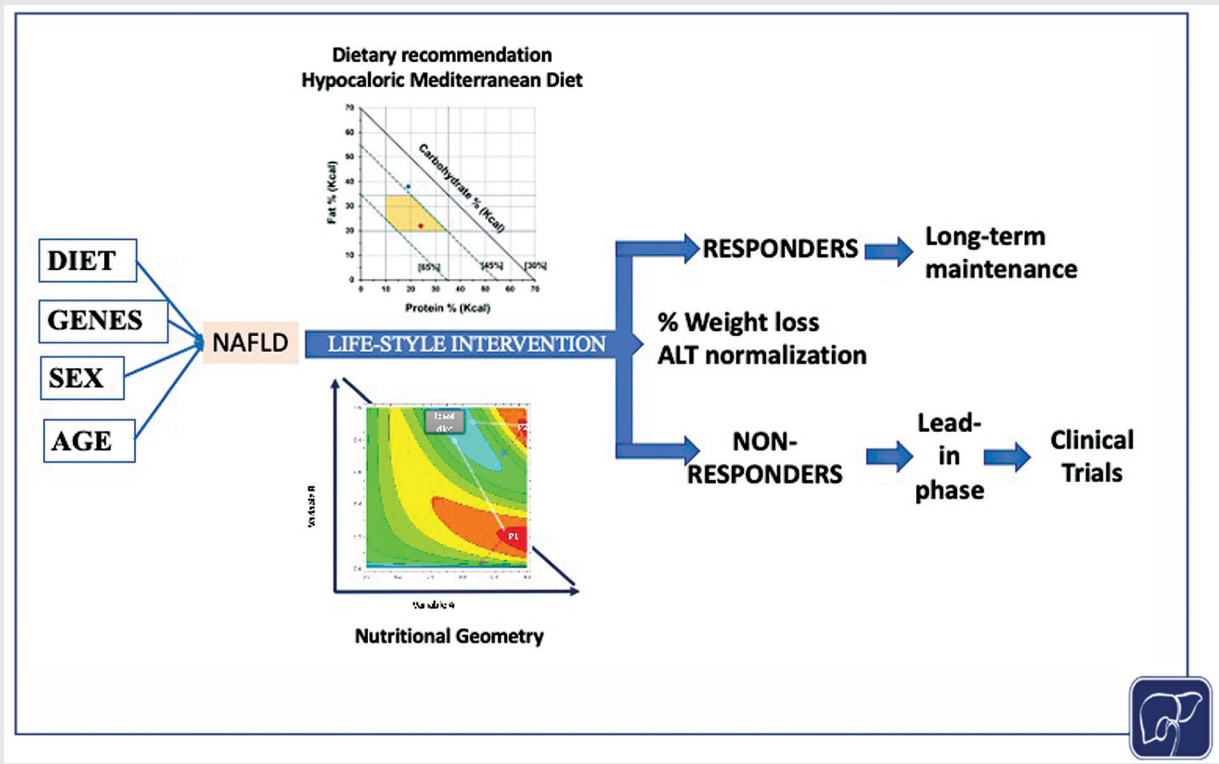
[1] Digestive Diseases Unit, Department of Medicine, SeLiver Group, Institute of Biomedicine of Sevilla (HUVR/CSIC/US), University of Seville, Hospital Universitario Virgen del Rocío, Seville, Spain
[2] Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBEREHD), Madrid, Spain
[3] Gastroenterology Department, Centro de Investigación de Endocrinología y Nutrición, Centro de Investigación Biomédoca en Red de Enfermedades Infecciosas (CIBERINF), Facultad de Medicina, University of Valladolid, Hospital Clínico de Valladolid, Valladolid, Spain

Address for correspondence Manuel Romero-Gómez, MD, PhD, Digestive Diseases Unit, Planta Baja, Hospital General, Hospital Universitario Virgen del Rocío, Avda Manuel Siurot s/n 41013, Sevilla, Spain (e-mail: mromerogomez@us.es).

[4] Centro Andaluz de Biología Molecular y Medicina Regenerativa-CABIMER, Universidad Pablo de Olavide, Universidad de Sevilla, Consejo Superior de Investigaciones Científicas (CSIC), Sevilla, Spain
[5] Centro de Investigación Biomédica en Red de Diabetes y Enfermedades Metabólicas Asociadas (CIBERDEM), Madrid, Spain

Semin Liver Dis

Graphical Abstract



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Abstract

Diet could be both culprit and solution of NAFLD. Dietary modifications have been associated with histological features improvement in NAFLD. The Western diet was related to a greater risk of disease progression while the Mediterranean diet (MD) could promote regression of histological lesions. Modifications in the nutrient composition seems to have lesser impact on NAFLD than dietary modifications. An intrinsic interaction between nutrients in the diet support a specific effect not seen when added separately. Dietary modifications should focus on promoting weight loss but also look for patterns that are able to promote histological improvement. Although several micronutrients' deficit has been related to NAFLD progression, prescribing these micronutrients' supplementation did not reach a positive impact. However, an enriching diet with specific nutrients could be useful, like olive oil supplemented in MD. Geometry of nutrition defines a framework to better understand the interaction between nutrients, foods, and dietetic pattern in the model of diseases and how we could approach taking into consideration the interaction between meals and disease features. After analyzing baseline diet and histological lesions, we could calculate the distance to optimal diet and to promote changes in lifestyle to reach all these goals. A standard MD menu would be recommended.

Keywords

- dietary recommendations
- geometry of nutrition
- food intake
- Mediterranean diet

Dietary Recommendations for the Management of NAFLD

Diet and exercise interventions remain the first line of therapy and several studies have shown that a healthy diet and weight loss in NAFLD could be sufficient to control disease progression.[1] NAFLD is a complex, dynamic, heterogeneous entity that encompasses a wide spectrum of histological lesions ranging from simple steatosis to steatohepatitis, fibrosis, cirrhosis, and hepatocellular carcinoma.[2] The prevalence of NAFLD has been estimated on 25% of European population. Considering the burden of the disease together with the risk of progression NAFLD has become an important public health problem.[3] In this review, we mainly focus on a new approximation defined as nutritional geometry to study the role of foods and diets in NAFLD. We then discuss the dietary recommendations and the importance of providing a dietary framework than can form part of a comprehensive management strategy for NAFLD. Finally, we discuss the role of Mediterranean diet (MD) in this strategy.

Dietary habits and nutrients together with age and gender are the most important contributing factors to the development and progression of NAFLD and the associated metabolic comorbidities.[4] NAFLD showed a sexual dimorphism related to different dietary patterns between males and females across age groups. However, a link between both conditions remains elusive.[5] In general, a hypercaloric diet, particularly one rich in trans fats, saturated fats, and cholesterol, and fructose-sweetened drinks, appears to increase visceral adiposity and stimulate lipid accumulation in the liver and progression to steatohepatitis and fibrosis. On the other hand, reduction of calorie intake coming from these foods, and supplementation with monounsaturated fatty acid (MUFAs) have preventive and therapeutic effects. In addition, fiber, coffee, green tea, and olive oil could be also protective factors for NAFLD development and progression.[6] Thus, we should encourage patients to increase intake of beneficial foods and avoid these dangerous foods (►**Table 1**).

The main aim of dietary intervention should be weight loss. Losing enough weight could improve histological features of NAFLD. A progressive percentage of weight loss seems to be needed to improve steatosis and steatohepatitis ($> 7\%$)[7] and fibrosis ($> 10\%$).[8] However, some patients could not improve liver histology despite losing weight and some patients could regress fibrosis or steatohepatitis features despite not losing weight. Indeed, dietary modification could improve liver diseases beyond caloric restriction. Moreover, increasing physical activity could rise muscle mass and weight loss could be hidden promoting an overall improvement of liver condition without apparent weight loss.[9] The maintenance of a long-term adherence to the diet is extremely important to achieve this objective. Mental disorders like anxiety and depression could impact on the progression of disease and response to lifestyle intervention.[10]

Nutrients are contained in the foods and the intake of a variety of foods is important to prevent the development of NAFLD.[11] Using dietary questionnaires, patients with NAFLD have been shown to consume fewer fruits and vegetables, cereals and grains than healthy subjects; but a higher intake of cooking oils, candy, pastry, desserts, salty food, soft drinks, red meat, processed and ultra-processed foods.[12] The effect was independent of saturated fat and cholesterol intake[13] (►**Table 2**). Reduction of saturated fat intake with subsequent weight loss has been associated with improvement of NAFLD. The ratio of polyunsaturated (PUFA)/saturated fatty acid (SFA) intake within patients with NAFLD was lower than healthy population. SFAs promoted lipolysis and increase fat storage by enhancing free fatty acids uptake. Moreover, SFA enhanced glucose-dependent insulinotropic polypeptide

Table 1 Macronutrients in NAFLD

Macronutrients	Mechanism	Food source	Recommendation
Whole grains[62]	Reduced energy intake. Modulation of gut microbiota, effects of specific phytochemicals, satiety	Cereals	Recommended
Simple carbohydrates[11]	De novo lipogenesis, excessive growth of bacteria in the small intestine	Fructose, refined carbohydrates (sucrose, honey, and syrup)	Discouraged (< 10 g/d)[a]
Saturated and animal proteins[12]	Hepatic fatty acids uptake. High content of sodium, presence of preservatives, additives and trans-fats. Insulin resistance: hyper-insulinemia. Dysregulated lipolysis	Red meat, butter, dairy products, vegetable oils (coconut, palm) processed foods (sausages, desserts)	Discouraged
Trans Fat[63]	Hyperinsulinemia, liver fat accumulations and sever hepatic necroinflammation	Partially hydrogenated vegetable oil, desserts	Discouraged
MUFAS and PUFAS (Olive oil)[16]	Peroxisome proliferator-activated receptors (PPARs) activation, which stimulates free fatty oxidationand decreases inflammation, insulin resistance and the expression of genes involved in hepatic denovo lipogenesis	Olive oil, advocates, nuts and nut oils, pumpkin seeds, and flaxseeds	Moderate consumption is recommended (high caloric content)
Omega 3[64]	Antioxidant/anti-inflammatory properties (activation of PPARs): reinstatement of insulin sensitivity. Inhibitory effects on nuclear factor kappa B (NF-kappa B)	Seafood, eggs, and meat	Moderate consumption is recommended
Omega 6[65]	An excess related to cardiovascular disease, cancer, inflammatory and autoimmune diseases	Vegetable oils (canola and cotton-seed), cereal grains, dried fruits (walnuts, pine nuts, peanuts, almonds, hazelnuts, and pistachios)	Increase omega-6/omega-3 ratio of 1–2/1
Animal proteins (meat and processed meat)[66]	Higher intakes of red meat, processedred meat, are risk factors forMAFLD/MAFLD-related cirrhosis. High intake of total meat,processed and unprocessed red meat and nitrite from processed meat was associatedwith liver disease-related mortality	Beef, lamb, andpork	< 50 g/wk[a]
Vegetable proteins[67]	An increase in hepatic lipid oxidation through an increase in energy expenditure. Prevent bacterial translocation and stimulate host immunity	Whole grains, cereals, seeds, nuts, legumes, vegetables, peas, and soybeans	Recommended (400 g/d)[a]
Prebiotic, probiotic, fiber[68]	Modulation of microbiota. Body weight reduction, improved glycolipid metabolism	Non-digestible carbohydrate found in garlic, asparagus, leeks, onions, cereals, yogurt	Recommended

[a]WHO-recommended healthy dietary pattern (Diet, nutrition and the prevention of chronic diseases. World Health Organization technical report series, 2003;916:i–viii, 1–149, backcover).

(GIP) release. In patients with NAFLD, a saturated fat intake promoted an increase of GIP response prolonging its action over time and resulting in liver disease progression.[14] On the other hand, a higher intake of saturated fats correlates with a deterioration of glutathione metabolism toward an oxidative state.[15] MUFAs induced a more favorable plasma lipid profile, with a reduction in oxidized low density lipoprotein (LDL), LDL-cholesterol, and triglycerides, and a lower total cholesterol/high density lipoprotein ratio. The substitution of dietary saturated fats by MUFAs or PUFAs improved lipid profiles, and thus health status. In a recent review, it has been concluded that MUFAs in the diet may be useful but further studies in humans are needed to determine their beneficial effect in NAFLD.[16] A 24-week intervention study (RISCK study), in which subjects were randomized to consume a diet high in SFAs or another diet high in MUFAs, concluded that decreased insulin sensitivity was secondary to the content in SFAs, but not to MUFAs.[17] Moreover, cooking meat at high temperatures for a long period could be an important factor. Extra virgin olive oil (EVOO) is a protective food and exerts its healthy effects through MUFAs (especially oleic acid) and phenolic compounds. In addition, it is more

Table 2 Micronutrients in NAFLD

Micronutrients	Mechanism	Food source	Recommendation
Vitamin E[69]	Acts on tissue growth factor TGFß1, PPAR and apoptosis, as well as in regulation of involved genes	Vegetable oils, nuts and seeds, leafy vegetables and in cereals	Recommended[a]
Vitamin C[70]	Antioxidant action	Nuts, seeds, plant oils, fruits, and vegetables	Recommended
Vitamin D[71]	Immune modulation, anti-inflammatory action, cell proliferation and differentiation	Fatty fish, such as trout, salmon, tuna, and mackerel, as well as fish liver oils	Recommended
Vitamin A[72]	Increase hepatic mitochondrial β-oxidation	Carrots and green leafy vegetables (such as spinach) or retinyl esters from rich animal sources like eggs, fish, and liver	Recommended[a]
Choline[73]	Increased hepatic mitochondrial β-oxidation. Along with various B vitamins (i.e., folate, vitamin B12, vitamin B6, and riboflavin), choline is required for the metabolism of nucleic acids and amino acids, and for the generation of the universal methyl group donor, S-adenosylmethionine (SAM)	Eggs and animal proteins	Recommended[a]
Polyphenol[74]	Antioxidant, anti-inflammatory, antimutagenic, and immunomodulatory action. Inversely associated with the presence of MAFLD	Berries, nuts, whole grains, fruits, as well as in tea, coffee, red wine, and beer	Recommended
Coffee[75]	Regular consumption of coffee with caffeine may significantly reduce liver fibrosis in patients with MAFLD		Recommended two to three cups of filtered coffee without sugar
Iron[76]	Although an essential nutrient in multiple cellular processes and erythropoiesis, an excessive amount of iron is commonly observed in patients with MAFLD	Swiss chard, spinach, lentils, chickpeas	Recommended[a]
Cupper[77]	Copper deficiency is observed in human-MAFLD and is associated with insulin resistance, steatosis, and an accelerated progressionof NASH	Legumes, nuts, potatoes (potatoes), and organ meats (kidneys, liver)	Recommended[a]
Zinc[78]	Zinc deficiency initiates insulin resistance, iron overload, and hepatic steatosis, which follows the impairment of zinc homeostasis caused by chronic liver disease	Meat, eggs, seafood, legumes	Recommended[a]

Abbreviations: MAFLD, metabolic associated fatty liver disease; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; PPAR, peroxisome proliferator-activated receptors.
[a]It is recommended not to exceed the amounts according to the RDA.

resistance to cook and does not oxidize easily. It has been suggested that EVOO should be included in the diets of NAFLD patients since it reduces insulin resistance (IR), total cholesterol, and triglycerides, thus inducing downregulation of lipogenic genes.[18] In a randomized, double-blind clinical trial, the consumption of 20 g/d of olive oil improved fat infiltration in the liver in patients with NAFLD.[19] Moreover, in animal models, EVOO supplementation improved steatosis, inflammation, and fibrosis.[20] Finally, a randomized trial in prediabetic patients with an isocaloric diet rich in EVOO, reported a decrease in liver fat and an improvement in both hepatic and total insulin sensitivity.[21] The impact of dietary consumption of fatty acids has been addressed in a recent systematic review. In four case–control studies, a significantly lower PUFA intake was reported and in another two studies, a higher consumption of MUFAs and SFAs was observed in NAFLD patients. In 18 randomized control trials testing supplementation of n-3 PUFA, an improvement of transaminases, steatosis, and fibrosis was reported in two-thirds of them. N-3 PUFA supplementation was associated with weight loss in five studies, improvement of glycaemia in six studies and lipid profile in 11 studies.[22]

Because people consume different amounts of different food groups and there are a limited number of large clinical trials, the impact of different foods is unclear in some cases. For example, dairy products, coffee, and rice. The results of studies on the consumption of dairy products were inconclusive in relation to NAFLD, while those on coffee were

contradictory. A remarkable protective effect of coffee consumption has been reported in the prevention of liver cancer in patients with NAFLD.[23]

Genes and Dietary Modification

Several single nucleotide polymorphisms in genes related to NAFLD have been found associated with results of lifestyle intervention. A significant percentage of patients do not achieve the expected results even after adequate adherence to treatment because nutrigenetic interactions might modulate the antioxidant status in NAFLD.[24] Polymorphism in patatin-like phospholipase domain-containing protein 3 (PNPLA3) (rs738409 [G]), with a 30 to 50% prevalence worldwide, increases the risk of steatosis and the risk of liver inflammation and fibrosis, cirrhosis, and hepatocellular carcinoma.[25] Patients with fatty liver disease bearing PNPLA3 polymorphism do not typically have IR.[26–28] Moreover, this polymorphism has also been associated with a higher reduction in liver fat content by diet therapy.[29] Besides, transmembrane 6 superfamily member 2 (TM6SF2) E167K variant (prevalence 15%), also confers susceptibility to NAFLD.[30] Carriers of this TM6SF2 polymorphism have an increased risk of NAFLD, but their circulating levels of triglycerides are normal or low and they do not develop IR. Therefore, in the context of these two polymorphisms, it is crucial to prevent liver disease from fat deposition more than the metabolic complications. Finally, when comparing the two types of hypocaloric diets, the polymorphism rs9939609 of the fat mass and obesity-associated protein (FTO) gene influenced weight loss, IR, and metabolic parameters. FTO variant rs9939609 was associated with weight loss in patients receiving PUFAs but not MUFAs. Finally, metabolic improvement was higher in carriers of allele A, with greater weight loss secondary to a hypocaloric diet rich in PUFAs.[31] In a case–control study, the combination of different genetic variants related to oxidative stress mechanisms (GSTT1, GSTM1, SULT1A1, CYP2E1, and CYP1A1) in patients with a high fruit/grilled food diet increased the risk of developing NAFLD.[32] On the other hand, the presence of the signal transducer and activator of transcription 3 (STAT3) in 189 rs2293152 G genotype was associated with more beneficial changes after a 24-week MD in an open-label study involving 44 patients with NAFLD.[33] Therefore, the interaction between nutrients and genes could explain this interindividual variability in the response to treatment and therefore personalized therapies based on genetic profiling could constitute a useful tool in the treatment of NAFLD.

The Geometry Framework of Nutrition in the Management of NAFLD

Dietary habits impact the pathophysiology, evolution, and treatment of metabolic-associated liver diseases. A realistic approach to analyze the role of diets in NAFLD would be to study what patients eat and then be able to give a dietary advice. However, this approach depends on a variety of individual dietary habits and to the fact that numerous dietary quality indices should be taken into account. It is now considered that food components interact at a high level of complexity to give rise to emergent properties of the diet, which are beyond the value that a particular nutrient and/or food could have. There is a mathematical model, nutritional geometry, that studies how nutrients and foods can be combined in a system that allows to know the interaction of foods to regulate the properties of diets that affect health. This mathematical model defines the relationships of different nutritional hierarchies (nutrient, food, and diet) with aspects related to health. The analysis of the food/meal/diet consumption in NAFLD patients using nutritional geometry may allow us to understand the multiple dimension existing between nutritional aspects and NAFLD. This type of analysis would allow us to know the dietary/nutritional starting point of patients and to generate predictive models that allow us to design personalized diets for patients, to prevent and treat NAFLD, since nowadays lifestyle modifications is the first therapeutic approach for this disease. It is now known that dietary habits are important factors in the development and progression of NAFLD. However, when trying to advice on the modification of dietary habits, these can vary in terms of the extent of these habits and their characteristics, since clinical guidelines very rarely go into this level of detail. A further problem to consider is that the patients' original dietary and lifestyle habits are not known. Indeed, nutritional recommendations for the management of patients with NAFLD aimed at solving these problems is an unmet need. There is a relationship between macro- and micronutrients consumption and NAFLD.[34] However, people eat foods, not nutrients, which in turn are part of dietary habits. Therefore, an approach would be to analyze the role of diets in NAFLD, since we would base ourselves on studying what patients eat and from there be able to give dietary advice. Apparently, this approach may seem easier and more suitable. Nonetheless, the variety of people's dietary habits is very high and various indexes of dietary quality would have to be considered, such as the energy density and the degree of diversity of the diet, the healthy dietary intake index, the diet quality index, or the MD adherence scale. To all of this, we can add that foods contain different nutrients, depending on the geographical areas and that foods are combined in meals, which differ according to cultures and meals constitute diets. Thus, diets are much more than the mere sum of nutrients and/or foods. The paradigm of simple nutrient model and its cause–effect relationship in a particular pathology is not adequate for metabolic disorders. Thus, it would be necessary to change the way of approaching the problem and give priority to the nutrient/food/food/diet relationship. In this sense, a methodology would have to be found to define and quantify the effects that different diets have on various relevant aspects of NAFLD. One way to do this could be to use the technique of nutritional geometry.

This concept was originally called nutritional ecology and was developed by Raubenheimer et al.[35] It is based on the idea that there is an integration between nutrition and animals and it seeks the dynamic interaction of organisms with their nutritional environment. The perspective tries to

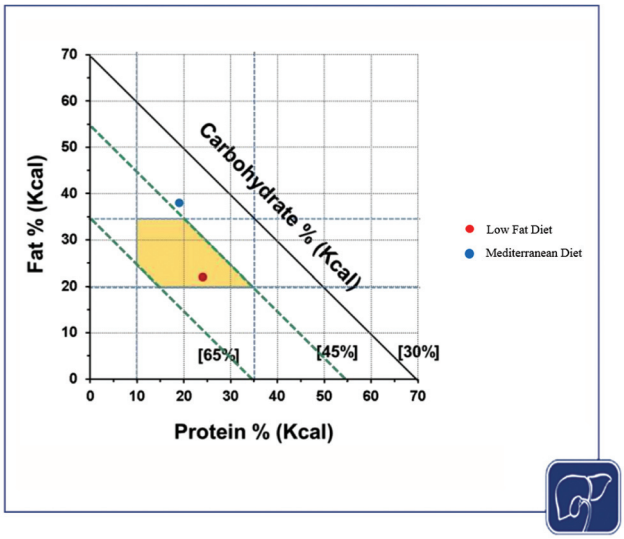

Fig. 1 Macronutrient composition of different diets following nutritional geometry analysis. Two different diets (Mediterranean diet and low-fat diet) corresponding to a nutrition intervention study in biopsy proved NAFLD patients. The polygon is an integrated representation of the macronutrient distribution range (protein = 10–35%, fat = 20–35%, carbohydrate = 45–65%) obtained from the Dietary Reference Intakes from the Food and Nutrition Board of the Institute of Medicine (FNB-IOM). Diet points falling within this yellow polygon are macronutrient balanced and diet points falling outside are macronutrient imbalanced with respect to the FNB-IOM.

find out how nutrients and foods can be combined in a model that allows us to know how foods interact to regulate the properties of diets that affect health. Ultimately, a mathematical model is established that defines the relationships of the various nutritional hierarchies (nutrient, food, meals, and diet) using the geometric model of the right-angle mixed triangle.[36] Typically, the model represents the macronutrients (fats, carbohydrates, and proteins) of foods in a three-dimensional way (►**Fig. 1**) and how this is combined at a higher level, such as meals and diets.[37] The levels of hierarchy may change depending on the issue to be addressed. Instead of macronutrients, we can choose foods, dishes, daily meals, or dietary habits. For example, for a specific diet, one could analyze the relationship between energy intake, protein, fat, and carbohydrate intake with a cardiometabolic phenotype and longevity.[38,39] Measuring these nutritional trade-offs is challenging because it requires to control potential confounding effects of energy intake and nutrient balance in determining the expression of traits (like for example steatosis or fibrosis). In this regard, only by controlling these confounding effects, it is possible to know the specific food that is important for the development of one trait. Another option that nutritional geometry allows is to set in a two- or three-dimensional plane how the diets of NAFLD patients are placed with respect to the nutritional recommendations issued by international organizations. Once we have a patient's diet on the plane, it is easier to identify where the problems are and to bring the diet back into line with the international recommendations (►**Fig. 2**). This approach allows us to make changes in the patient's diet that do not have to be very drastic, and therefore would be easier to follow, than if the patient's diet is completely changed. In other words, the idea is to use nutritional geometry to redirect patients' diets, facilitating adherence to the new diet.

Nutritional Geometry Applied to Acceptable Macronutrient Distribution Ranges

Based on the evidence suggesting a role in the onset of chronic diseases and taking into consideration the amounts needed to ensure an adequate intake of essential nutrients, different scientific institutions have developed what is called the acceptable macronutrient distribution range. One of the most validated is the one proposed by the Food and Nutrition Board of the Institute of Medicine (FNB-IOM)[40] In the bottom panel of ►**Fig. 2**, we have performed a nutritional geometry analysis, based on the values of macronutrient intakes of countries distributed in different geographical areas of the world. The macronutrient intake data were obtained from the countries' National Nutrition Surveys: Spain-ANIBES Study[41] China-Fifth National Nutrition Survey,[42] Japan-National Health and Nutrition Survey,[43] Italian National Food Consumption Survey (Italy-INRAN-SCAI 2005–06)[44] USA-NHANES 2009–2010,[45] Australian-Australian Health Survey[46], the UK National Diet and Nutrition Survey (NDNS),[47] German-NEMONIT[48], Mexico-Mexican National Health and Nutrition Survey,[49] Iran-Isfahan Cohort Study[50] and were expressed as mean energy contributions from fat, protein, and carbohydrate. For the nutritional geometry analysis, we used the right-angle mixture triangle methodology,[34] which allow us to represent three components (fat, protein, and carbohydrates) in two dimensions. The yellow polygon is an integrated representation of the FNB-IOM Acceptable Macronutrient Distribution Range and shows an estimated possible range of proportional macronutrient intake to avoid metabolic diseases. The diet points falling within the polygon are macronutrient balanced, and diets falling outside are macronutrient imbalanced with respect to the FNB-IOM Acceptable Macronutrient Distribution Range proposal. An advantage of considering diets in this way is that it provides a framework for understanding the functional relationship among macronutrient intakes. This is because many problems in nutrition concern the relationship among three mixture components (e.g., fat, protein and carbohydrate, in this case). In ►**Fig. 2**, we observe that diets of different regions of the world remain almost in the same vertical line. This means that people from different parts of the world, with different cultures and dietetic customs tightly regulate protein intake. As NAFLD prevalence changes across the world, this probably means that NAFLD development and progression are probably independent of protein consumption. On the other hand, what gets modified is their proportion of fat and carbohydrates intakes (horizontal and hypotenuse lines, respectively). In this regard, it has been suggested that macronutrient might be as important as the energy content of weight-loss diets, for NAFLD prevention and treatment.[51]

Recently, the concept of nutritional geometry is increasingly being used to generate graphs in which the expression

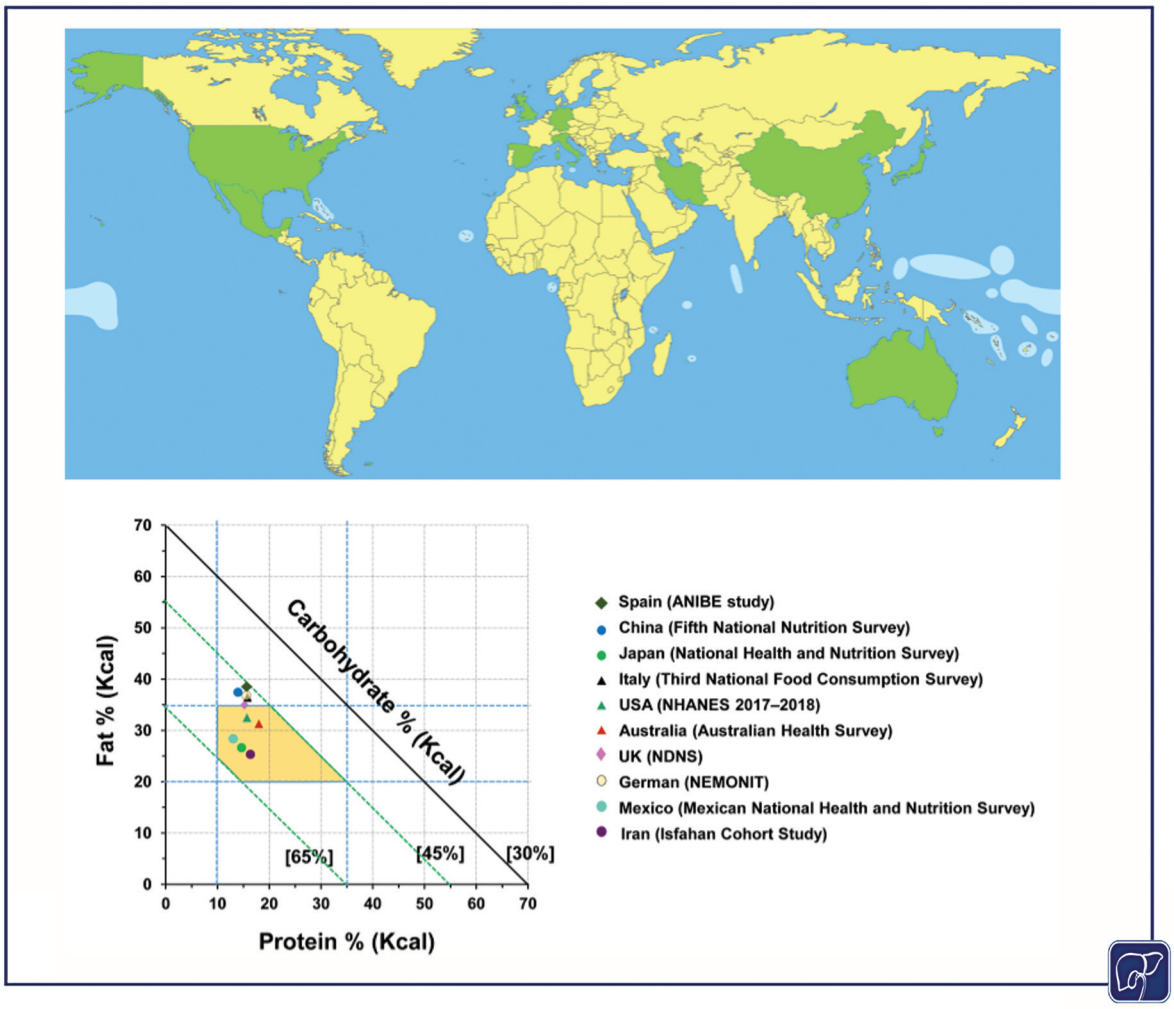

Fig. 2 Macronutrient composition of dietary intakes in different countries. The polygon is an integrated representation of the macronutrient distribution range (protein = 10–35%, fat = 20–35%, carbohydrate = 45–65%) obtained from the dietary reference intakes from the Food and Nutrition Board of the Institute of Medicine (FNB-IOM). Diet points falling within this yellow polygon are macronutrient balanced and diet points falling outside are macronutrient imbalanced with respect to the FNB-IOM.

of a phenotypic trait can be mapped onto a nutrient space defined by the intake of various nutrients or foods (►**Fig. 3**). This is a powerful approach that allows us to analyze the effects of nutrient, foods, and energy intake on the optimal expression of the traits we want to analyze. Nutritional geometry is beginning to provide key information on the nutritional factors underlying a wide variety of physiological phenomena.[37] Mammals generally have an internal clock that is involved in regulating the nutrients and energy they consume. There are several studies that show how animals adjust food intake to meet their specific macro- and micronutrient and energy needs and how this relates to the health/disease binomial.[51–53] This geometric approach provides a platform to visualize and analyze these interactions. Previous studies in mice and humans have shown that when the environment is not appropriate, the ingestion of protein-rich foods, regardless of their origin, is prioritized. This is known as the "protein leverage" hypothesis.[54] In this sense, it may happen, that trying to maintain a convenient protein intake, people could resort to high consumption of foods rich in carbohydrates and fats, given that this is the current food supply in developed societies. This can lead to consuming diets rich in calories, sugars, and fats, that contribute to the appearance of NAFLD. If the food supply is varied and contains a wide variety of nutrients, people tend to consume a variety of foods that allow us to cover all our daily requirements. This type of problem can be analyzed in a more effective way through nutritional geometry, since it allows the analysis of dietary modifications and their relationships with different NAFLD parameters through multidimensional representations in space, of nutrients, foods, and diets. The multidimensional diagrams that are created collect the individual data of each patient and represent the phenotypic features of the disease, as a function of the way they eat (►**Fig. 2**). In this regard, it is important that the feeding pattern is carefully collected so that the graphs represent accurate and reliable information. At this point, nutritional geometric analysis suggests that an important aspect to consider is not whether nutrients or foods are more important, but rather develop a mixed model to understand how the components of the foods we eat interact to determine the properties of diets that affect

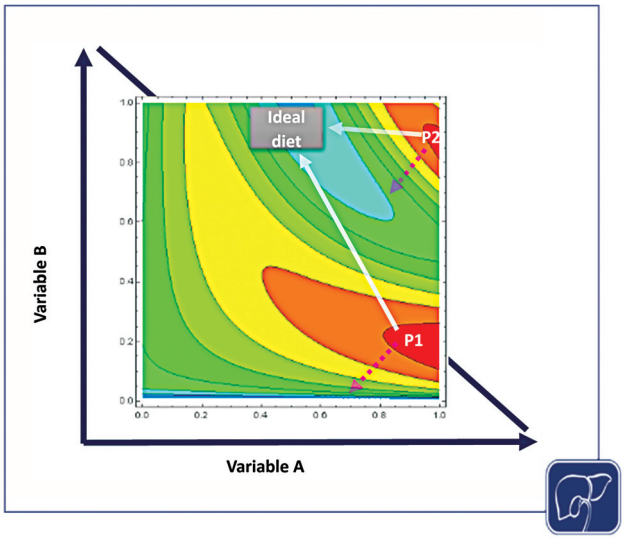

Fig. 3 Sample of analysis of different patient dietary scenarios with respect to a particular trait of NAFLD. The graph shows a possible simulation model, generated with nutritional geometry, in which two variables, which can be different macronutrients or dietary patterns, are plotted on the X and Y axes against a NAFLD trait such as the degree of fibrosis. The severity of fibrosis is represented by a color map, where hot colors (*red*) indicate more severity and cold colors (*blue*) less severity. Different patients (P1 and P2) with a high degree of fibrosis are placed in different positions on the X-Y plane. The arrows show the distance to go in dietary adjustment to improve fibrosis. The white arrows indicate the distance to ideal diet and the flashing pink arrows indicate the distance to a diet that is not considered ideal but is sufficient to improve fibrosis. As can be seen, the route toward the diet that achieves an improvement in fibrosis is shorter, illustrating that fewer modifications must be made in the diet of the patients and therefore greater adherence to the new dietary proposals could be achieved. This type of graphs allows to analyze the most harmful or adequate diets for each patient. Finally, for different patients, it would be possible to calculate the distance to most beneficial objectives and in which direction their diet should move.

metabolic liver disease. One of the ways that nutritional geometry does this is through the already mentioned right-angle mixture triangle method. Today there is only one study performed in rodents evaluating the relationship between diet and non-alcoholic steatohepatitis (NASH) using this approach. As indicated by Simpson et al,[55] the authors found that in rodents, with aging, the development of NAFLD increases when carbohydrate intake is higher than 1.5 g/d. Furthermore, when protein intake is higher than 0.60 g/d, the probability of NASH decreases significantly. Finally, the highest probability of severe NASH appears when diets low in protein and high in fat are followed. Moreover, the quality of macronutrients is more important than the energy content of the diet.

Therefore, the analysis of food/meal/diet consumption of NAFLD patients using nutritional geometry may allow us to understand the multiple dimension that exists between nutritional aspects and NAFLD. In addition, it could give us a robust research tool to unravel the effects of foods and diets, on phenotypic outcomes such as liver steatosis, inflammation, or fibrosis. This approach can also be applied to understand the complex network of nutrient sensing pathways, potentially identifying new targets for the development of drugs that could help prevent the liver disease progression. Moreover, this type of analysis would allow us to know the starting point of patients and generate predictive models that allow us to design personalized diets for patients, to prevent and treat NAFLD. Finally, nutritional geometry can be used to dissect other nutritional dimensions, such as consumption of simple sugars, fatty acid profile or the role of certain amino acids, in metabolic liver diseases. Mapping and analyzing how people respond to the intakes of different types of diets can help to define which diets may be more appropriate for different patients. This is important, since nowadays lifestyle modifications are the only therapeutic approach that exists for this disease.

Dietary Patterns from Western Diet to Mediterranean Diet

Healthy dietary patterns help reduce the risk factors of NAFLD. Western dietary patterns are often associated with the development of NAFLD independent of physical activity.[56] This diet is generally hypercaloric with inadequate intake of fruits, vegetables, whole grains, legumes, fish and low-fat dairy products and excessive refined and processed foods, alcohol, salt, red meats, sugary beverages, snacks, eggs, and butter. In addition to the role of different foods found in the diet, excess number of calories are a risk factor for NAFLD.[57] Nutrient's composition of MD and low-fat diet was shown on ►**Table 3**. In the last decade, several studies have analyzed the beneficial effects of MD in NAFLD. A good general definition of MD is the high intake of EVOO, vegetables including leafy greens, fruits, cereals, nuts and pulses/legumes, a moderate consumption of fish and other meats, dairy products and red wine and a low intake of eggs and sweets. Adherence to this diet is measured by a score of adherence that has been strongly related to the liver-nephro and cardiometabolic outcomes. At present, several studies (observational studies and short-term trials) have demonstrated that this type of diet is beneficial for NAFLD by improving liver status, in particular hepatic insulin sensitivity and lipid profile.[16] Moreover, this diet may improve NAFLD without changing body weight. To better confirm its beneficial effects, long-term trials with more patients with histological outcomes are required. MD is probably beneficial due to the combination of their macro- and micronutrient components. MD-induced modifications in gut microbiota could be an important factor. Inadequate changes in gut microbiota increase gut permeability and the translocation of bacteria and their products to blood. This induces endotoxemia, which has been found to contribute to liver inflammation in NASH patients.[17] A recent study established a relationship between gut microbiota and NAFLD.[58] Nutritional framework geometry could allow to explain controversies about the impact of olive oil or MUFAs on NAFLD depending on the type of diet the patients are following. Adding EVOO to MD impacts positively on the disease. A recent randomized controlled trial comparing two hypocaloric diets (1,500 kCal/d) MD versus low fat diet, demonstrated a similar ability to promote weight loss and

Table 3 Micro and macronutrients composition of a standard hypocaloric Mediterranean diet and low-fat diet

Macro-Micronutrient	Mediterranean diet	Low fat diet	RDI FESNAD
Kcal	1,540	1,503	
%E P	19.4	24	
%E HC	43	53	
%E G	38	22	
AGMI (g)	36	19	
AGPI (g)	12.5	6.3	
AGS (g)	11	8	
Vitamin A (μg)	813	1,173	700–600
Vitamin C (mg)	195	177.4	60–70
Vitamin D (μg)	3.2	4.5	5–7.5
Vitamin E (mg)	14.7	10.4	15
Vitamin B1 (mg)	2.9	1.5	1.2–1
Vitamin B2 (mg)	1.6	1.9	1.6–1.3
Vitamin B3 (mg)	19	23	18–14
Vitamin B6 (mg)	2	2.5	1.5–1.2
Vitamin B9 (μg)	357	347	300
Vitamin B12 (μg)	8	8.6	2
Ca (mg)	747	830	900
P (mg)	1,281	1,413	700
K (mg)	3,324	4,011	3,100
Mg (mg)	385	399	350–300
Fe (mg)	14	24	9–18
Zn (mg)	9.4	14.7	9.5–7
Se (μg)	15	28	55
I (μg)	14	24	150

Abbreviations: FESNAD, Spanish Federation of Nutrition, Food, and Dietetic Societies; NAFLD, non-alcoholic fatty liver disease; RDI, reference dietetic intake.
Note: Data were obtained from diets followed in a nutritional intervention study in biopsy proved NAFLD patients (Martin et al. Hepatology 2021).

improvement of liver stiffness measured by transient elastography. However, MD improved significantly total cholesterol levels, aspartate aminotransferase, and γ-glutamyl transferase together with APRI fibrosis score but not the hypocaloric low fat diet.[59] Intermittent fasting could be a pattern to be added to MD. A recent meta-analysis including 365 patients from six studies belonging to several patterns of intermittent fasting reported an improvement on liver function tests related to weight loss.[60] Nevertheless, alimentary disorders, like binge eating, should be avoided in this scenario despite not being associated with liver disease progression on obese people.[61] Recommended MD menu has been added in ►**Fig. 4**.

Conclusion

Dietary intervention could reach two main aims in clinical practice: (a) improving histopathological conditions in NAFLD mediated by weight loss and specific effect of dietary patterns; and (b) stratifying patients according to response to lifestyle intervention. It is mandatory to test lifestyle intervention in patients with NAFLD and checking how new foods with controlled calories could promote improvement of the liver. In patients where lifestyle intervention fails we should look for other therapeutic approaches focusing on drug therapy. MD emerged as more accepted and useful diet in the management of these patients. An itinerary should be designed to better explain the pathway for the patient considering the basic principles of geometry of nutrition. Lastly, nutrigenomic could be another source of information in the better management of these patients. Precision and personalized medicine in NAFLD included in the conceptual framework of geometry of nutrition could be used to design clinical studies to explore beyond the impact of nutritional manipulation to the interaction with others dietary components. Nutritional geometry could be a tool to improve the role of personalized medicine in diet and physical activity intervention supporting better patient stratification in our clinical practice.

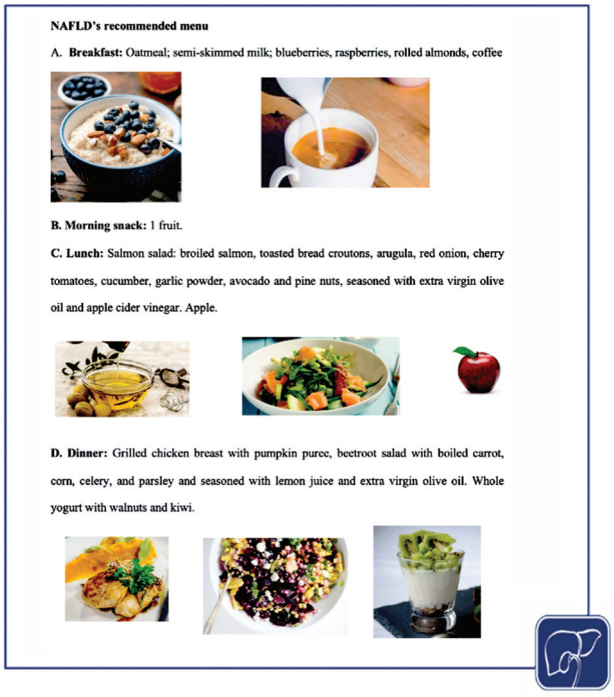

Fig. 4 Recommended menu to be adherent to Mediterranean diet. The exact portion size varies according to the energy needs of everyone as well as his or her level of physical activity. • Energy balance is the main driver of liver fat turnover; therefore, a maintenance diet based on these nutritional recommendations is important. • In non-overweight individuals with NAFLD, the same nutritional recommendations should be indicated, and the diet composition should be corrected, avoiding fructose and cholesterol.[79] • Prioritize the consumption of whole complex carbohydrates, such as brown rice, quinoa, and oatmeal, and limit or avoid refined starches, such as white bread and white rice.[80] • Substitute part of carbohydrates, especially refined carbohydrates, with animal-based proteins (chicken, turkey, rabbit, fish) and vegetables, such as legumes. • Include the consumption of fruits, vegetables, coffee, tea, nuts, seeds and extra virgin olive oil.[81] • Include most fats from unsaturated sources, such as olive oil (ideally extra virgin), nuts and seeds.[21] • Limit or avoid added sugars, whether sucrose, fructose, maltose, maltodextrin, or any syrup. To avoid liquid sugar, such as carbonated drinks or soft drinks, lemonade, juices, smoothies, and sugar added to tea and coffee.[82] • Partially or fully indigestible carbohydrates increase the production of short-chain fatty acids through fermentation by the colon and gut microbiota, which modulate whole-body insulin sensitivity through a variety of mechanisms.[62] • Proteins and amino acids could decrease intrahepatic triglyceride levels without weight loss through several mechanisms that affect metabolism, inflammation, oxidative stress, and intestinal epithelial barrier physiology. Specific dietary amino acids have also been shown to modulate various aspects of NAFLD pathogenesis, such as glucose homeostasis, fibroinflammation, and the integrity of intestinal epithelial barrier. Branched-chain amino acids (leucine, isoleucine, and valine) regulate certain aspects of hepatic metabolism such as insulin signaling and glucose regulation.[83] • The use of polyphenol-rich foods and other bioactive compounds may decrease inflammatory pathways involved in liver disease.[74] • In addition, unsaturated fats, such as n-3 or n-6 polyunsaturated fatty acids, or MUFA, have been shown to improve insulin sensitivity and lower intrahepatic triglyceride levels when substituted for saturated fats.[64] • Although emphasis should be placed on foods rich in unsaturated fats rather than saturated fats, there is some evidence that fermented dairy foods, including yoghurts, have a neutral or even protective effect against cardiovascular risk.[82]

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Conflict of Interest

M.R.-G. received consulting or speaker fee for: Abbvie, Alpha-sigma, Allergan, Astra-Zeneca, Axcella, BMS, Boehringer-Ingelheim, Gilead, Intercept, Inventia, Kaleido, MSD, Novo-Nordisk, Pfizer, Prosciento, Rubió, Siemens, Shionogi, Sobi, Zydus. Research Grants: Gilead, Intercept, Siemens.

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