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REVIEW ARTICLE

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The role of nutrition in non-alcoholic fatty liver disease: Pathophysiology and management

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Abstract

A healthy diet together with physical activity could induce weight loss and control the progression of non-alcoholic fatty liver disease (NAFLD). However, the composition of diet has not been clearly established. Macronutrients such as saturated fatty acids (SFA), trans-fats, simple sugars and animal proteins have a harmful effect on the liver. On the other hand, monounsaturated fats (MUFAs), polyunsaturated (PUFAs) omega-3-fats, plant-based proteins and dietary fibres are considered to be beneficial to the liver. The impact of specific micronutrients is less well-known. Nutrients are part of the food we eat. Food makes up our meals, which compose our dietary patterns. Non-alcoholic fatty liver disease patients usually follow Western diets which are rich in soda, frozen junk food, juice, red meat, lard, processed meats, whole fat dairy foods, fatty snack foods, take-away foods, cakes and biscuits and poor in cereals, whole grains, fruit, vegetables, extra virgin olive oil (EVOO) and fish. On the other hand, the Mediterranean diet (MD) is beneficial for NAFLD even when it is iso-caloric or there are no changes in body weight. A new approach, called 'nutritional geometry' considers the importance of integrating nutrition, animals and the environment. The goal of this approach is to combine nutrients and foods in a model to understand how food components interact to regulate the properties of diets affecting health and disease. The use of algorithms developed by artificial intelligence (AI) to create a personalized diet for patients can provide customized nutritional counselling to prevent and treat NAFLD.

KEYWORDS

artificial intelligence, dietary guidelines, macronutrients, micronutrients, nutritional geometry, personalized nutrition

1 | INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a major health problem because of its high prevalence. Non-alcoholic fatty liver disease is associated with obesity, insulin resistance, type 2 diabetes mellitus (DM2), hyperlipidemia, hypertension and metabolic syndrome.[1] Non-alcoholic fatty liver disease covers a wide pathological spectrum ranging from steatosis to steatohepatitis (NASH) progressing to different degrees of liver fibrosis, cirrhosis and hepatocellular carcinoma (HCC). At present there is no clear consensus on the pharmacological treatment of NAFLD, however, it is clear that therapeutic approaches should focus on lifestyle modification. Diet and exercise interventions remain the

Abbreviations: AI, artificial intelligence; DASH, Dietary Approach to Stop Hypertension; DHA, docosahexanoic acid; DM2, type 2 diabetes mellitus; EPA, eicosapentanoic acid; EVOO, extra virgin olive oil; MD, Mediterranean diet; MUFA, monounsaturated fatty acids; NAFLD, non-alcoholic fatty liver disease; NASH, Non-alcoholic steatohepatitis; PUFA, polyunsaturated fatty acids; SFA, saturated fatty acids.

first line of therapy and studies have shown that a healthy diet and weight loss in the early stages of NAFLD could be sufficient to control disease progression.[2] However, despite clear evidence that dietary interventions are effective, the extent and the composition of the diet has not been clearly established. Moreover, patients often fail to follow dietary interventions. Thus, simple, multidisciplinary, nutritional guidelines are needed that target the disease mechanisms. In addition, recent findings increasingly support an approach involving personalized nutrition and the role of artificial intelligence (AI) in this. Thus, the purpose of this review was to analyse the role of nutrients in the pathophysiology of NAFLD, focusing on the design of tailored diets.

Key points

- Dietary modifications have been shown to be effective in controlling non-alcoholic fatty liver disease (NAFLD).
- Modifications in the composition of specific macro- or micro- nutrients in the diet are not a central point.
- The Western diet is associated with a greater risk of disease progression in NAFLD while the Mediterranean diet with an improvement in NAFLD.
- Nutritional geometry can be an excellent tool to study the relationships between the various aspects of diet and NAFLD pathophysiology.
- The use of algorithms developed by artificial intelligence for personalized nutritional counselling would be useful to prevent and treat NAFLD.

2 | INFLUENCE OF DIETARY MACRONUTRIENTS ON NON-ALCOHOLIC FATTY LIVER DISEASE

Several studies have confirmed the role of specific macronutrients in the onset and progression of NAFLD. However, it is very difficult to separate the role of each separate macronutrient, in relation to the amount of energy provided, their proportion in the diet and the food they contain. The macronutrient composition of a diet is associated with NAFLD/NASH, independent of energy intake. Macronutrients such as saturated fatty acids (SFA), trans fats, simple sugars (sucrose and fructose) and animal proteins damage the liver. These modulate the accumulation of triglycerides and antioxidant activity in the liver, which affects insulin sensitivity and postprandial triglyceride metabolism.[3] In contrast, monounsaturated fatty acids (MUFA), PUFA ω3 fats, plant-based proteins and dietary fibres appear to be beneficial to the liver.[2]

2.1 | The role of fats

We can distinguish three types of fats at a nutritional level, saturated, monounsaturated and polyunsaturated. Despite a general consensus that the intake of saturated fats should be reduced, the issue of dietary fatty acid composition remains controversial. The SFA diet was associated with a marked increase in liver fat, probably because of an increase in de novo liver lipogenesis and an increase in lipolysis of adipose tissue. In contrast, unsaturated fat intake was associated with a decrease in lipolysis, preventing the accumulation of fat in the liver.[4] The SFA diet has also been linked to impaired glutathione metabolism and an increase in oxidative stress, which leads to the progression of NAFLD.[5] However, at present, it is not clear whether different sources of SFA (for example, dairy vs meat) can have different effects on liver fat content. On the other hand, it is also important to consider that the effects of saturated fats seem to depend on a patient's genetic background.[6] The specific effects of trans fats on the human liver have not been adequately evaluated because most studies have been performed in mice models.

Studies on MUFA have reported different, sometimes contradictory conclusions. This may be because of both differences in methodology and the origin of MUFAs. A negative relationship between MUFA consumption and the progression of NAFLD has been reported, mainly in cross-sectional studies in which the origin of MUFA was not considered. On the contrary, studies in which extra virgin olive oil (EVOO) was the source of MUFA suggest that its intake could improve fatty liver. In addition, a randomized controlled study in DM2 patients[6] showed that a MUFA-enriched isocaloric diet, induced a significant reduction in liver fat compared to a diet high in carbohydrates and fibre. In addition, the consumption of 20 g/day for 12 weeks in hypocaloric diets attenuated the degree of fatty liver in patients with NAFLD. However, it is difficult to isolate the effects of MUFA from other components (polyphenols), present in EVOO and the importance of the hypocaloric diet.[7]

Polyunsaturateds, including mainly ω3 and ω6 fats have also been evaluated in the progression of NAFLD in particular the essential PUFAS, α-linolenic acid (ALA; ω3) and linoleic acid (LA; ω6). LA is metabolized to arachidonic acid (AA; 20:4 n-6), and ALA is metabolized to eicosapentanoic acid (EPA; 20:5 n-3) and docosahexanoic acid (DHA; 22:6 n-3). The metabolic products of AA are proinflammatory, prothrombotic and proaggregatory. On the other hand, EPA and DHA modulate the liver's lipid composition, increasing anti-inflammatory mediators and decreasing insulin resistance.[8] In fact, low EPA and DHA liver values could tilt the balance towards liver fatty acid lipogenesis, instead of fatty acid beta-oxidation Figure 1.

Therefore, the ratio ω6/ω3 fats plays an important role in increasing the prevalence of chronic metabolic diseases (mostly a ω6/ω3 imbalance). Nevertheless, a double-blind randomized trial showed that a long-term hypercaloric diet rich in ω6 PUFA intake prevents liver fat accumulation in overweight individuals.[4]

Several clinical trials have addressed the potential benefits of omega-3 PUFAs on NAFLD/NASH. A systematic review and meta-analysis of controlled intervention studies on the effects of ω3 PUFAs in NAFLD patients[9] indicates that supplementation with ω3 decreases liver fat content and the steatosis score. However, the effects of ω3 supplementation on improving severe liver injury markers,

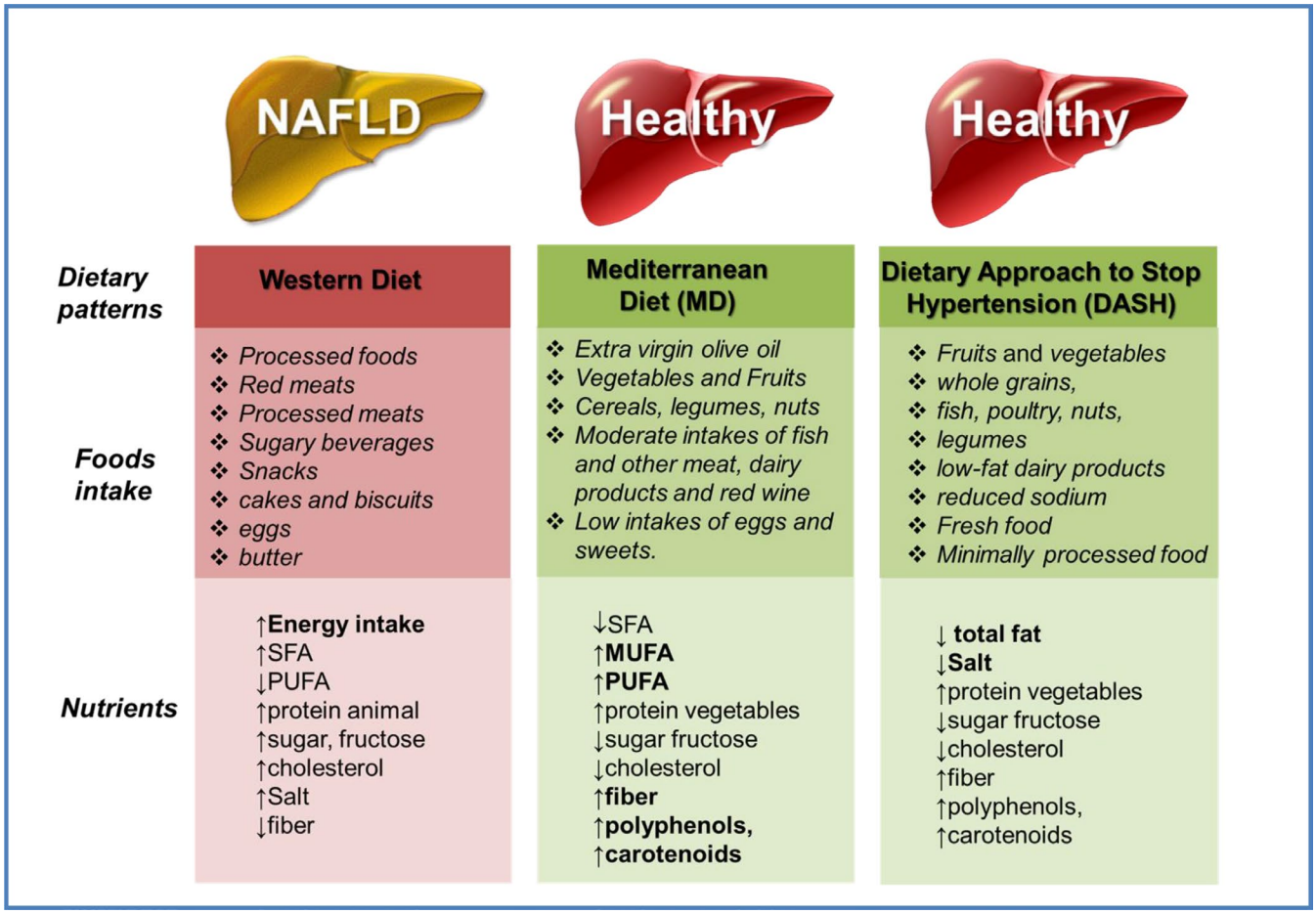

FIGURE 1 Non-alcoholic fatty liver disease (NAFLD) dietary patterns/food/nutrients chart. The Western diet is associated with NAFLD. This type of diet contains excessive amounts of refined and processed foods, red meat, processed meat, sugary drinks, snacks, cakes, biscuits, eggs and butter. It involves an excess of calorie consumption, saturated fats, animal protein, sugar, cholesterol and salt. The Mediterranean diet has beneficial effects on NAFLD. This diet is based on the high intake of extra virgin olive oil, vegetables, fruits, cereals, nuts and legumes; moderate intakes of fish and other meats, dairy products and red wine and low intakes of eggs and sweets. So, it provides a large amount of monounsaturated fatty acids, polyunsaturated fatty acids, vegetable proteins, fibre and antioxidants; and low amounts of sugar, cholesterol and saturated fats. Dietary approach to stop hypertension has beneficial effects on NAFLD. This diet is rich in fruits, vegetables, whole grains, fish, poultry, nuts, legumes and low-fat dairy products; it has low levels of sodium, added sugars and fat. Finally, this diet emphasizes on the consumption fresh food. This diet provides low intakes of total fat, salt, sugar and cholesterol; and high intakes of vegetable protein, fibre, and antioxidants.

such as inflammation and fibrosis are not well-established. It is important to consider that the controversial results on ω3 could be because of differences in methodology, the duration of the nutritional intervention, levels of intake, their sources, the EPA/DHA relationship, the chemical composition of ω3 and the patient's genetic background.[10]

The contribution of dietetic cholesterol in NAFLD is not clear. Certain nutritional studies suggest that high-cholesterol diets are involved in the development of NAFLD.[3] However, the same studies show that patients had high fat intake Figure 1.

2.2 | Role of carbohydrates

In the past twenty years, there has been substantial evidence to confirm the adverse metabolic effects of over consumption of simple carbohydrates. However, studies have cast doubts on the real role of monosaccharides and disaccharides when they are naturally contained in foods in NAFLD. On the contrary, numerous epidemiological studies have presented convincing evidence that there is an association between added sugars (sucrose, fructose and high fructose corn syrup) and NAFLD.[11] Overall, the dietary source of monosaccharides and disaccharides is essential to determine their effect on NAFLD.

Numerous studies have found a positive association between the risk of NAFLD and high-fructose products (cakes, soft drinks and sugary snacks).[2] The liver is the primary site of fructose metabolism, with nearly 60% oxidation of fructose ingestion. Furthermore, fructose metabolization in the liver is much higher than that of glucose. The hepatic metabolism of fructose stimulates de novo lipogenesis in the liver, increasing liver fat.[12] The most recent meta-analysis of controlled clinical trials concluded that the isocaloric exchange of carbohydrates for glucose does not induce NAFLD. However, when

fructose is the source of a hypercaloric diet, patients with NAFLD have increased liver fat and plasma alanine aminotransferases.[13] In addition, Abdelmark et al[14] showed that in adult patients with NAFLD, an increase in fructose consumption increased fibrosis and swelling Figure 1.

The role of non-digestible carbohydrates (fibre) in NAFLD has not been extensively studied. A decrease in fibre consumption is thought to be related to NAFLD. The proposed rationale is that low fibre intake, along with other dietary patterns induces dysbiosis, which modifies the microbiota inducing endotoxemia, systemic inflammation, insulin resistance and liver inflammation and damage. An alteration of gut microbiota has been observed in NAFLD patients. Prebiotic intake has also been shown to improve liver phenotype in NAFLD patients (Figure 1).[15]

2.3 | Role of proteins

The role of protein intake in the development of NAFLD is unclear. Existing studies do not provide evidence for or against. This may be because of the methodology used in the different studies, the origin of the protein source used (vegetable or animal), as well as the foods containing it (Figure 1).

3 | CONTRIBUTION OF MICRONUTRIENTS TO NON-ALCOHOLIC FATTY LIVER DISEASE

Micronutrients are important for the development of NAFLD. To date, the micronutrients involved in NAFLD are zinc, copper, iron, selenium, magnesium, vitamins A, C, D and E and carotenoids.[16] The proposed mechanisms of action are their antioxidant, antifibrotic, immunomodulatory and lipoprotective effects.

Non-alcoholic fatty liver disease patients have been shown to have decreased levels of serum zinc, copper, vitamins A, C, D, E and carotenoids. Moreover, an iron and selenium excess have been reported to play a role in the severity of NAFLD.[16]

Lipid soluble vitamins have been linked to NAFLD, mainly low serum levels of vitamin A.[17] Because vitamin A may be beneficial, there are some concerns about supplementation. Vitamin A has many other effects. Treatment with vitamin E showed a decrease in transaminase levels and liver lobular inflammation, improved liver fibrosis and reduced steatosis.[18] Vitamin E supplementation is a common practice in NAFLD patients. Vitamin E has antioxidant effects and NAFLD patients present with increased oxidative stress. Nevertheless, vitamin E supplementation could have different side effects, including an increase in the risk of certain types of cancer or of hemorrhagic stroke, which are the key factors reducing its use in clinical practice.

A mix of micronutrients could be proposed to help in the treatment of NAFLD. However, the interactions between different vitamins and between vitamins and macro/micronutrients must be taken into consideration. Moreover, identifying the contribution of specific micronutrients is difficult because human diets are complex and vary and may not correspond to experimental dietary models. Thus, it is difficult to recommend diets with specific micronutrients.

4 | FROM MAJOR FOODS GROUPS TO DIETARY PATTERNS: EVIDENCE FROM NON-ALCOHOLIC FATTY LIVER DISEASE

4.1 | Relationship between food group intake and non-alcoholic fatty liver disease

Nutrients are contained in the foods that people eat, thus a more physiological approach is an analysis of the intake of food groups and their relationship with NAFLD. There is a general consensus that the intake of a variety of foods is important to prevent the development of NAFLD.[19]

The foods that are considered to be beneficial for the prevention and progression of NALFD are whole grain cereals, fruits and vegetables, fatty fish (mainly high in ω3) and EVOO. On the other hand, foods that are considered to adversely effect NALFD include red meat and processed meats, soda, processed foods, cakes and biscuits.[14] Patients with NAFLD have been shown to consume fewer cereals, grains, fruits and vegetables than healthy subjects. NAFLD patients have a higher intake of cooking oils, candy, pastry, desserts, salty food, spicy food, sauce, dressings and soft drinks.[20]

A recent study showed that patients with NAFLD had a higher intake of red and processed meats. The effect was independent of saturated fat and cholesterol intake.[21] Moreover, cooking meat at high temperatures for a long period could be an important factor.

Extra virgin olive oil is a 'protective' food and exerts its healthy effects through MUFAs (especially oleic acid) and phenolic compounds. It has been suggested that EVOO should be included in the diets of NAFLD patients since it reduces insulin resistance and blood triglycerides, thus inducing downregulation of lipogenic genes.[22] In a randomized, double-blind clinical trial, the consumption of 20 g/d of olive oil attenuated the fatty liver grade in NAFLD patients.[7] 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.[23]

Because people consume different amounts of various food groups and because of the limited number of large clinical trials, in some cases the impact of different foods are not clear, for example dairy products, coffee and rice. The results of studies on the consumption of dairy products were inconclusive in relation to NAFLD[20] while those on coffee were contradictory (Figure 1).

4.2 | Healthy dietary patterns help reduce the risk factors of non-alcoholic fatty liver disease

Another approach is to analyse the role of diet in NAFLD. In this case, data are based on habitual food consumption, which is therefore

more realistic. Western dietary patterns are often associated with the development of NAFLD independent of physical activity.[2] 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 the different foods found in the diet, the excess amount of calories are a risk factor for NAFLD.[1]

In the last decade, several studies have analysed the beneficial effects of certain dietary patterns on NAFLD, in particular the Mediterranean Diet (MD) and the dietary approach to stop hypertension (DASH).

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. 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.[24] Moreover, this diet may improve NAFLD without changing body weight, which is an important obstacle in lifestyle changes. To better confirm its beneficial effects, long-term trials with more patients with histological outcomes are required.

The DASH diet, which was designed in the 1990s to regulate blood pressure, has also been found to have beneficial effects on NAFLD.[25] The DASH diet is rich in fruits, vegetables, whole grains, fish, poultry, nuts, legumes and low-fat dairy products. Moreover, there is reduced sodium, added sugars, as well as saturated and total fats. DASH emphasizes the consumption of minimally processed and fresh foods.

Both of these diets are probably beneficial because of their macro- and micronutrient components, but other aspects should also be considered. For example, the diet-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.[26] A recent study established a relationship between gut microbiota and NAFLD.[27] Thus, additional studies are needed to investigate the mediation of NAFLD and microbiota through diet (Figure 1).

5 | NUTRITIONAL GEOMETRY: A KEY CONCEPT FOR PERSONALIZED NUTRITION IN NON-ALCOHOLIC FATTY LIVER DISEASE

When studying the role of nutrition/foods/diets on metabolic diseases, the involvement of specific nutritional parameters of these diseases may be unclear. Moreover, the relationship between biology and environment is complex. Finally, foods are composed of a mixture of nutrients which are combined into meals to make up a person's diets and dietary patterns. Diets are known to be more than the sum of their components. As a result, the single-nutrient model paradigm (the relationship between a particular disease and a specific nutrient) is not a useful approach in metabolic diseases, and the large number and huge variety of nutrients, foods, diets and dietary patterns that constitute human nutrition must be taken into consideration. The level of focus must be changed to give priority to foods, diets and dietary patterns. A methodology that takes into account the interactions among nutrients in foods and diets and metabolic diseases should be developed. This methodology should define and quantify the effects of different diets on different health outcomes.

In response to this, the notion of 'nutritional ecology' has been developed[28] based on the idea that there is a dynamic interface between the organism and its environment from a nutritional point of view. The goal of this concept is to combine nutrients and foods into a model to understand the way food components interact to regulate the properties of diets affecting health. This is called 'nutritional geometry'.

This approach models the relationship of different levels of a nutritional combinatorial hierarchy (nutrients, foods, meals and diets) using the right-angle mixture triangle geometric model.[28] The model can use micronutrients, a combination of macro- and micronutrients, bioactive compounds or other food components. Usually, the model represents three-dimensional macronutrients (fats, carbohydrates and proteins) of foods and how to combine them into a meta-mixture: for example, meals and diets.[28] The levels of the hierarchy of meta-mixtures represented in the model can change depending on the question being addressed. Instead of macronutrients, we can choose foods, dishes, daily meals or dietary patterns. An important conclusion of studies using nutritional geometry is that the balance of macronutrients affects food, energy intake and various physiological functions in varied manners.[28] (Figure 2)

Some questions addressed by nutritional geometry are as follows: (a) how does dietary macronutrient balance relate to energy intake? (b) how does the range of energy intake relate to energy balance? (c) what is the relationship between dietary macronutrient ratios and total energy intake? (d) what is the relationship between dietary macronutrients ratios and socioeconomic status? and (e) how does dietary balance influence protein intake? Another unexplored issue that can be analysed by nutritional geometry is the quality of the macronutrients.

Thus, nutritional geometry accommodates multiple diet components with different animal models and particular health issues. There is only one study to date using nutritional geometry to evaluate the relationship between diet and NAFLD.[29] The authors found that the development of NAFLD increases during old age once carbohydrate intake is >25 kj/d. When protein intake >10 kj/d, the probability of avoiding NAFLD increases. Finally, the highest probability of suffering from severe NAFLD occurs with low-protein, high fat diets. Moreover, the authors concluded that the ratio and quality of macronutrients could be as important as the diet's energy content.

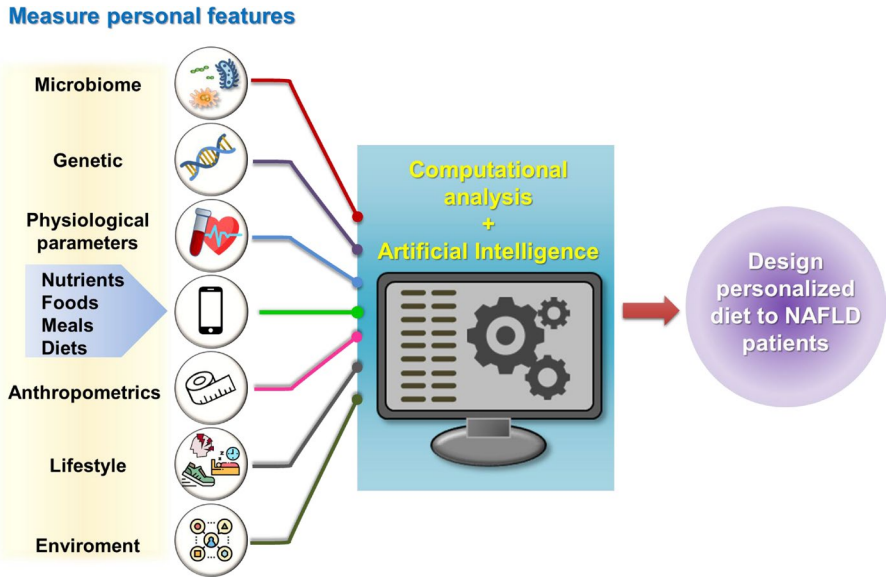

FIGURE 2 Personalized nutrition. With the advances in technology, big data analysis and artificial intelligence, we can design diets and dietary patterns in a personalized way according to the specific situation of non-alcoholic fatty liver disease patients
Source: Adapted from Zeevi et al.[30]

6 | LOOKING TO THE FUTURE: THE ROLE OF PERSONALIZED NUTRITION

Dietary guidelines are based on the assumption that diets affect everyone equally, without taking into consideration the heterogeneity and individuality of the metabolism, microbiota and lifestyle. Each person is unique and reacts differently to the same foods or dietary patterns. Zeevi et al[30] measured the postprandial glucose responses to 46.898 foods in 800 individuals and found a great variability in responses to the same foods. These data suggest that the use of general dietary recommendations may be limited. These authors developed a machine-learning algorithm based on these data that integrates several traits (blood parameters, dietary patterns, anthropometric values, physical activity and gut microbiota). This algorithm precisely predicted individual post-prandial glycemic values to real-life meals. This type of study will make it possible to develop more personalized diets to predict the potential role of nutrients/food/diets on the pathophysiology and progression of NAFLD and to design personalized nutritional interventions for more effective control of the disease (Figure 2).

7 | CONCLUSIONS

The relationship between nutrients/food/meals, dietary patterns and NAFLD has been extensively studied in the last decade. Research into the role of nutrition for the management of NAFLD patients is a major challenge. This is particularly important because lifestyle modifications including diet, exercise and weight loss have been found to be effective in controlling NAFLD. The long-term effects of calorie-restricted diets result in an improvement in several features of NAFLD. The specific macronutrient composition of the diet seems to be less important, although further studies are needed to clarify this issue. However, hypocaloric diets, either high fat/low carbohydrate or low fat/high carbohydrate intake are known to be equally effective in reducing liver lipids. The Western style diet is associated with a greater risk of NAFLD while the Mediterranean diet results in significant improvement in steatosis, even in the absence of weight loss. One important difficulty in the research of nutrition and NAFLD is the slow progression of the disease. Furthermore, prospective long-term trials with liver biopsies are required to monitor histopathological endpoints. Nutritional geometry could be an excellent tool in these cases to study the relationships between the various aspects of diet, nutrients and liver health. Models can be used to understand the multiple dimensions and relationships between nutritional issues and NAFLD. Another important contribution will be algorithms developed by AI to create a personalized diet for patients. Except for certain broad nutritional guidelines, the idea that there is no single optimal diet is gaining ground. In upcoming years, patients will probably wear devices to register data on what they eat. This information will be processed by deep learning and integrated by AI, with multiple data (physical activity, level of stress, sleep, microbiome, physiological constants, medications and genome) to provide customized dietary recommendations and personalized nutritional counselling, to prevent and treat NAFLD.

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CONFLICT OF INTEREST

The authors (GB and MRG) declare no conflict of interest.

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