Is there any Consensus as to what Diet or Lifestyle Approach Is the Right one for NAFLD Patients?

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Abstract
In this article, we review the current concepts about the pathogenesis of hepatic steatosis and non-alcoholic steatohepatitis and evaluate the existing diets in the context of this knowledge and the available literature. The intent is to enable clinicians to evaluate the diets of non-alcoholic fatty liver disease (NAFLD) patients and make rational decisions based on this perspective - in the absence of controlled trials - to help their patients. Finally, a tailored approach for the dietary treatment of NAFLD is offered as a way to optimize the dietary management of this condition.

Key words
Non-alcoholic fatty liver disease – non-alcoholic steatohepatitis – diet – hepatic steatosis – type 2 diabetes – insulin resistance.

Abbreviations
NAFLD: non-alcoholic fatty liver disease; T2D: type 2 diabetes; IR: insulin resistance; HS: hepatic steatosis; NASH: non-alcoholic steatohepatitis; FFA: free fatty acids; TG: triglycerides; DNL: de novo lipogenesis; TNF- α; tumor necrosis factor α; SFA: saturated fatty acids; MUFAs: monounsaturated fatty acids; TC: total cholesterol; PUFAs: polyunsaturated fatty acids; DHA: docosahexaenoic acid; EPA: eicosapentaenoic acid; PPAR: peroxisome-proliferator activated receptor; SREBP: sterol regulatory element binding protein; GI: glycemic index.

Introduction
The rising incidence of obesity in today’s environment is associated with many obesity-related health complications, including cardiovascular disease, type 2 diabetes (T2D), hyperlipidemia, hypertension, and non-alcoholic fatty liver disease (NAFLD) [1–4]. This constellation is also recognized as the metabolic syndrome and is characterized by underlying insulin resistance (IR). NAFLD or generally speaking hepatic steatosis (HS) is defined as the accumulation of lipids, primarily in the form of triacylglycerols in individuals who do not consume significant amounts of alcohol (<20 g ethanol/day) and in whom other known causes of steatosis, such as certain drugs and toxins, have been excluded [5]. The spectrum of NAFLD includes simple fatty liver, non-alcoholic steatohepatitis (NASH), characterized by inflammation, apoptosis, ballooning degeneration, Mallory hyaline, fibrosis, cirrhosis post NASH, hepatocellular carcinoma and advanced liver disease, which leads to liver-related death [5-10].

Given the close relations between obesity, the metabolic syndrome, and the development of NAFLD, it is not surprising that many NAFLD patients have multiple components of the metabolic syndrome, whether or not they are overweight or obese. Insulin resistance is present in and is a significant predictor of NAFLD and NASH in most patients [11], even the ~ 10–15% of patients who are not overweight [12, 13]. NAFLD is a multifactorial disease that involves a complex interaction of genetics, diet, and lifestyle, all of which combine to form the NAFLD phenotype. A cornerstone of the management strategy in such patients with fatty liver is the use of diet to decrease body weight, and improve glycemic control, dyslipidemia and cardiovascular risks as well.

There is a bewildering array of diets that have been recommended for the prevention and treatment of all of the components of the metabolic syndrome. Their utility for the treatment of NAFLD remains mostly unknown. It is also important to note that cognitive-behavioral approaches, in addition to dietary modification, are necessary for the long-term success of dietary and lifestyle interventions.
NAFLD pathophysiology and diet

Dietary effects on whole-body metabolism and its regulation via effects on hormones, transcription factors, and lipid metabolic pathways are considered to play a central role in NAFLD. Insulin resistance is currently thought to be a key factor in the development of both NAFLD and NASH [14]. Many studies have shown an association of insulin resistance with NAFLD and NASH on the basis of impaired glucose tolerance or impaired fasting glucose [15–18]. Despite elevated insulin concentrations, adipose tissue fatty acid flux was not suppressed in NAFLD patients [18], which indicated the presence of peripheral insulin resistance.

In most patients, overnutrition or inappropriate diet are thought to lead to chronically elevated glucose, insulin, and free fatty acids (FFAs) concentrations in the blood. Both excessive carbohydrate intake (Fig. 1) and excessive fat intake (Fig. 2) could play a role in increasing blood glucose, FFAs, and insulin concentrations, independently or together. These dietary conditions (Fig. 3) contribute to resistance to insulin-stimulated glucose uptake at the level of the adipose tissue and skeletal muscle as well as resistance to the insulin-mediated suppression of triglycerides (TG) hydrolysis in adipose tissue [18]. Glucose uptake in the liver is not insulin dependent, and increased glucose concentrations in the blood lead to increased glucose uptake by the liver. Insulin-mediated stimulation of de novo lipogenesis (DNL) leads to an increased conversion of glucose to fatty acids [19].

Together, the increased concentrations of both glucose and FFAs in the blood contribute to excessive accumulation of neutral lipids in the liver. A study by Donnelly et al [20], using a multiple-stable-isotope labelling approach, showed that in NAFLD patients plasma FFAs were the primary contributors to the liver triacylglycerol content in the fasted state (50–70% of total fatty acids [FAs]) and to the lipoprotein triacylglycerol content in both the fed and the fasted state (50–75% of total FAs). Most of the plasma FFAs were from adipose tissue, which accounted for 70–90% of FAs in the fasted state and 50–70% in the fed state. The de novo synthesis of FAs from glucose, fructose, and amino acids was also dysregulated in NAFLD patients. DNL was elevated in the fasting state - accounting for 25% of liver and VLDL triacylglycerols compared with 5% in healthy individuals [21] - and failed to increase post-prandially. Moreover, this study showed that there were likely two distinct pools of FAs in the liver, which were handled differently. Plasma FFAs - representing mainly adipose-derived FAs - were thought to be part of a fast turnover pool that was preferentially incorporated into VLDLs, whereas FAs synthesized de novo were thought to enter a hepatic holding pool. Therefore, especially in the presence of peripheral insulin resistance, in which the flux of FAs from the adipose is not suppressed by insulin and plasma FFAs are persistently high, elevated rates of lipogenesis may be a significant source of accumulated triacylglycerol in the liver.

In healthy individuals, elevated lipid concentrations in the liver lead to increased VLDL production and secretion; however, in NAFLD patients, this increase in fat export via VLDL may be impaired or insufficient to prevent fatty liver [22]. Hypertriglyceridemia, low HDL concentrations, and small, dense LDL particles often result from an increase in the concentration, size, or both of circulating VLDL.
which together contribute to an increased risk of cardiovascular disease [24]. In NAFLD patients, blood lipid concentrations may be normal or elevated, and many patients have the atherogenic dyslipidemia associated with the metabolic syndrome, which includes high triacylglycerol, low HDL, and increased small, dense LDL [25].

The original “two-hit hypothesis” of NASH asserts that the accumulation of lipid in the liver (first hit) is followed by a cascade of prooxidative, hepatotoxic events (second hit), which are caused by an as yet unknown mechanism [26]. Mitochondrial dysfunction has been recently considered to be such an important hit [27].

There are several other mechanisms being investigated also. The increased secretion of tumor necrosis factor α (TNF-α) and other proinflammatory cytokines by adipocytes and infiltrating macrophages is thought to lead to chronic systemic inflammation (Fig. 4) as well as obesity-linked insulin resistance [28]. Elevated concentrations of circulating IL-6 have been documented in NASH patients [29] and have been implicated in the manifestation of fatty liver disease.

Dietary treatment of NAFLD

Because of the strong association of obesity and the metabolic syndrome across the entire spectrum of NAFLD, current recommendations for the treatment of fatty liver disease are aimed at weight loss and dietary modification [17, 30, 31]. For unknown reasons, sudden or quick weight loss achieved through dietary modification may lead to the progression of liver failure in some NAFLD patients [32]. On the other hand, weight reduction through surgical methods, even with quick weight-loss after surgery, has been successful in reducing disease progression [31, 33, 34].

A number of hormones which have important metabolic functions are produced by the gastric tissue. There is a potential connection between NAFLD, circulating inflammatory cytokines, and the serum concentrations of the hormones gene products in morbidly obese individuals undergoing bariatric surgery. Given the connections between the hormones gene products and inflammation, it could be hypothesized that the activity of the hormone gene is modulated by inflammatory cytokines and reflect the severity of NAFLD.

Despite the fact that weight loss and dietary and lifestyle changes are recommended as primary treatment for fatty liver, no specific guidelines exist pertaining to diet. Very few studies of the effects of different diets on NAFLD have been performed.

Effect of individual dietary components

Saturated fat

A recent study in a rat model of HS showed that saturated fatty acids (SFAs) promote endoplasmic reticulum stress as well as hepatocyte injury [35]. Accumulation of SFAs in the liver due to high-SFA or high-fructose diets led Fig 2. Fat metabolism in peripheral insulin resistance and fatty liver. Excessive or inappropriate dietary fat intake combined with peripheral insulin resistance (resistance to insulin-inhibited lipolysis in the adipose tissue), continued insulin-stimulated triacylglycerol (TG) hydrolysis via lipoprotein lipase (LpL), and many other possible genetic alterations in key lipid metabolic pathways tend to result in increased blood free fatty acid (FFA) concentrations. This leads to excessive skeletal muscle fat accumulation and increased liver concentrations of TG and cholesterol esters (CE). High blood TG concentrations in the form of VLDL tend to accompany this condition and can induce cholesterol ester transfer protein (CETP) activity, which results in an increased transfer of TG from VLDL to HDL and a subsequent increase in HDL clearance and decreased HDL concentrations. β-ox, fatty acid β-oxidation; Chylo, chylomicron; FC, free cholesterol; sm/d, small density.
to an increase in markers associated with endoplasmic reticulum stress and liver dysfunction. This, along with ample evidence associating high-SFA intakes with an increased risk of cardiovascular disease [36, 37], suggests that the intake of dietary saturated fats should be limited in NAFLD patients. However, what saturated fat intake should be recommended?

A randomized, double-blind, crossover study examined the effects of three diets in 86 free-living healthy men: a control diet (38% fat with 14% SFAs), the National Cholesterol Education Program Step I diet (30% fat with 9% SFAs), and the National Cholesterol Education Program Step II diet (25% fat with 6% SFAs) [33]. Although both reduced-fat diets decreased LDL, they also decreased HDL and increased plasma triacylglycerol after 6 weeks compared with the control diet. In response to the 6%-SFA diet, subjects who were insulin resistant, who had a higher percentage of body fat, and/or who had a higher BMI - characteristics that describe most NAFLD patients - experienced smaller reductions in LDL, larger reductions in HDL, and increases in triacylglycerol compared with subjects who were insulin sensitive.

It is still unclear whether a minimum intake of SFAs in the diet is beneficial or even required for optimal health [38]. On the basis of the clinical evidence discussed above, SFA intakes < 7% and < 10% of energy may be suboptimal for NAFLD patients.

Supplementation with SFAs appears to reduce nutritional hepatic steatosis in adults; however, other histopathologic features of NAFLD remain to be studied [39].

**Monounsaturated fatty acids**

Monounsaturated fatty acids (MUFAs) are a class of fatty acids that are found in foods such as olive oil, nuts, and avocados. The beneficial effects of MUFAs on cardiovascular disease risk and blood lipid profiles have been extensively studied [36]. In particular, dietary MUFAs decrease oxidized LDL [40], LDL cholesterol [37], total cholesterol (TC), and triacylglycerol concentrations, without the concomitant decrease in HDL typically seen with low-fat diets [41, 42]. Additionally, the replacement of carbohydrate and saturated fat with MUFAs leads to reductions in glucose and blood pressure and to an increase in HDL in patients with diabetes [43]. A MUFA-rich diet (40% of energy as fat) also decreased VLDL-cholesterol and VLDL triacylglycerol and was more acceptable to patients with T2D than was a high-carbohydrate diet (28% of energy as fat) [44]. Therefore, an increase in the intake of MUFAs, particularly as a replacement for SFAs and as a higher proportion in the diet in lieu of carbohydrate, may be beneficial for NAFLD patients.
Further studies in humans are needed to ascertain whether the consumption of olive oil may be helpful in NAFLD patients.

**Polyunsaturated fatty acids**

Polyunsaturated fatty acids (PUFAs) are a class of fatty acids that include n-6 and n-3 fatty acids. The n-3 fatty acid α-linolenic acid is a precursor for the long-chain products docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). PUFAs have been shown to decrease the risk of heart disease when consumed in lieu of SFAs in both epidemiologic [45] and clinical [46] studies. The ratio of n-6 to n-3 fatty acids seems to be important in determining the effect of PUFAs on various lipid and non lipid indexes. Replacement of n-6 PUFAs with α-linolenic acid improved peripheral insulin sensitivity and lowered cholesterol concentrations in rats with fructose-induced insulin resistance [47]. An approximate dietary intake of 6% n-6 and 1% n-3 fatty acids as percentage of energy has been recommended to maximize the cardiovascular benefits of these essential fatty acids [48].

Several studies have shown a link between essential FA deficiency and the development of HS in animal models [49-51], a link that was first observed almost 30 years ago [52]. There is also an indication that essential FAs may be essential for VLDL secretion. In geese overfed with corn, HS is accompanied by a reduced essential FA content of membrane phospholipids despite an adequate dietary supply of both linoleic and α-linolenic acid [51].

**n-3 Fatty acids**

The effects of n-3 fatty acids on dislipidemia and insulin resistance have been extensively reviewed [53] and provide convincing evidence that n-3 FAs should be an important dietary component in patients with NAFLD and NASH. Specifically, DHA and EPA induce FA catabolism through the activation of peroxisome-proliferator activated receptor (PPAR–)–mediated pathways [54] and down-regulate DNL through sterol regulatory element binding protein (SREBP) pathways [55]. The effects of dietary fish oil, which is high in DHA and EPA, in animal models of insulin resistance are impressive. The beneficial effects include: 1) decreased plasma triacylglycerol, FFAs, glucose, and insulin; 2) prevention of peripheral insulin resistance; 3) decreased triacylglycerol concentrations, VLDL secretion, and lipogenesis in the liver; 4) decreased lipid concentrations and utilization and storage of glucose in skeletal muscle; and 5) decreased adipocyte cell size and visceral fat content and increased insulin-stimulated glucose transport in the adipose tissue [53].

Eicosapentaenoic acid treatment seems to be safe and efficacious for patients with NASH, largely due to its anti-inflammatory and antioxidative properties [56]. Another Tanaka N et al firstly have demonstrated detailed mechanisms
of steatosis-ameliorating effects of EPA without PPARα activation and ensuing augmentation of hepatic oxidative stress [57].

Walnuts, a good source of α-linolenic acid, may also be beneficial. When patients with type 2 diabetes (T2D) were placed on diets that included 30 g walnuts/day, plasma HDL and the ratio of HDL cholesterol to TC increased, and LDL decreased after 8 weeks [58].

In another study, hypercholesterolemic men and women who substituted 32% of their MUFA intake with walnuts had significant decreases in TC and LDL and improved endothelial function compared with controls [59].

The first studies to have examined the effects of n-3 fatty acid supplementation in NAFLD patients were published. One such study found that 1 g fish oil/day for 12 months decreased blood triacylglycerol concentrations, liver enzymes, fasting glucose, and steatosis in NAFLD patients [60].

These preliminary results, along with the evidence reviewed above, suggest that the consumption of n-3 fatty acids found in fish oils and walnuts is likely to improve blood lipid profiles and to reduce inflammation, steatosis, and liver damage in NAFLD patients.

**trans Fatty acids**

**trans** Fatty acids occur naturally in foods such as dairy products as a result of bacterial metabolism and in foods such as margarine as a result of hydrogenation. **trans** Fatty acids consist of multiple isomers that have differential effects on human metabolism [61]. The bacterially derived cis-9, **trans**-11 conjugated linoleic acid and **trans**-11 oleic acid typically found in dairy products do not have adverse effects on lipoprotein profiles [62]. Conversely, intake of **trans**-10, **cis**-12 conjugated linoleic acid from hydrogenated oils has been found to increase inflammatory markers [63], induce endothelial dysfunction, and unfavourably alter the blood lipid profile by increasing the LDL:HDLC and TC: HDL ratios [64].

The association between **trans** fatty acids and increased risk of developing insulin resistance and coronary heart disease by raising LDL cholesterol levels, lowering HDL cholesterol levels, raising triglyceride levels, and increasing CRP [65] suggest that they may be involved in NAFLD pathogenesis.

Although the specific mechanisms of action are not yet clear, the recommendation to avoid the intake of **trans** fatty acids from hydrogenated oils seems well founded for those at risk of dyslipidemia.

Therefore, the role of **trans** fatty acids in human NAFLD needs to be evaluated, which presents a challenge to nutritional epidemiologists, as information on **trans** fatty acids content in food is unknown in many cases.

**Glycemic index and fiber**

Several trials have shown decreases in TC in response to intake of soluble fiber from sources such as oats [66]. This type of evidence has led the Food and Drug Administration to approve a claim of cardiovascular disease risk reduction for the labelling of oat products and foods containing soluble fiber [67]. The so-called “second-meal effect” of low-glycemic index (GI) foods or slow-release carbohydrates improves the glycemic response to a subsequent meal and was first described in the early 1980s [68]. The effects of high-fiber, low-GI carbohydrates on glycemic response and cholesterol concentrations were reviewed recently in a meta-analysis [69] and provide evidence that these dietary components may be beneficial to individuals with impaired insulin response.

A breakfast containing a high-fiber indigestible and fermentable starch compared with a low-GI starch reduced FFAs in the blood after a subsequent meal [70]. Whereas both breakfasts lowered glucose concentrations, only the breakfast containing the low-GI starch decreased insulin concentrations. Although the results of this study cannot be generalized for long-term effects on glycemic control or lipid profiles, it seems reasonable to conclude that the inclusion of carbohydrates that are high in indigestible and fermentable fiber and low in GI can be helpful in maintaining glucose, insulin, and FFA concentrations in individuals with insulin resistance and NASH.

**Sucrose and fructose**

Several studies have shown that high intakes of fructose increase DNL in animal models and in humans [71, 72]. One study of lean and obese women found that 4 days of overfeeding with either a glucose or sucrose drink increased DNL 2–3-fold [73]. The higher the woman’s baseline lipogenesis rate, the higher the increase in DNL in response to the 4 days of overfeeding, with a trend toward a higher increase with sucrose than with glucose. These data suggest that some individuals may be more sensitive to fructose-induced stimulation of DNL.

Sweetened drinks, such as sodas, are typically consumed as additional calories and lead to excess intake of as much as 150–300 kcal/d [74]. It is recommended that intakes of refined sugars and high-fructose or high-glucose foods and beverages should be reduced in the NAFLD population. High intakes of fructose and glucose as simple sugars stimulate the de novo synthesis of fatty acids, especially in individuals with insulin resistance and in those who are overweight [20, 73, 75, 76].

**Protein**

There is little information on the effect of protein quantity, quality, and composition on the pathophysiology of NAFLD. It is known that protein deficiency or malnutrition can cause steatosis [77]. Considering that the total protein content and quality are typically high in the average American diet, protein deficiency is highly unlikely in NAFLD patients. Conversely, an excessive intake of protein may cause glomerular sclerosis, intrarenal capillary hypertension, and eventually renal malfunction in certain vulnerable individuals who have underlying renal insufficiency [78–80]. Studies of high protein intake and their possible effects on NAFLD are lacking.
NAFLD and diet

Specific recommendations and future directions

Taking into account the evidence discussed in this article, the authors recommend a highly individualized approach for the dietary treatment of NAFLD based on a thorough assessment of individual metabolic, physiologic, and nutritional status and personal goals and preferences. The composition and the relative macronutrient content of diet are shown in Table I. Most NAFLD patients would benefit from the guidelines given below.

Evidence of beneficial effects from weight loss through surgical methods in obese patients with NAFLD [36, 38] suggests that weight reduction through dietary means would also have positive effects. Specifically, weight loss resulted in a significant decrease in the prevalence of the metabolic syndrome and marked improvements in liver steatosis, inflammation, and fibrosis [35]. However, very few studies examining the effects of different dietary and lifestyle approaches in achieving weight loss in NAFLD have been done, and further studies are urgently needed [37].

Decreased total fat consumption could lead to a decrease in postprandial lipemia and the associated disruptions in lipid metabolism. Further studies are required to ascertain whether the consumption of smaller meals that are lower in total fat may be helpful in NAFLD patients.

Regular, moderate exercise is independently associated with a 25–35% decrease in CHD risk over a 20-year period [81], regardless of diet and other risk factors. An exercise strategy of walking a distance of 2 miles, 3 days/week, at a target heart rate of 60% of heart rate reserve (as measured by peak oxygen uptake) resulted in increases in HDL and fitness equivalent to a more rigorous exercise program of walking 3 miles, 3 days/week, at 80% of heart rate reserve [82]. Further studies are needed to elucidate the effects of specific exercise strategies in the NAFLD populations.

The intake of diets that are lower in carbohydrate, lower in saturated fat, but higher in protein than the average American diet - which consists of ~47% carbohydrate, 38% fat (20% SFA), and 15% protein - tend to be beneficial for ameliorating features of the metabolic syndrome, including effects on insulin sensitivity and blood lipids [77]. Certain individuals may be susceptible to renal malfunction associated with high protein intakes [78]; therefore, an increase in total protein intake may not be appropriate in these patients. Studies are needed to examine the effects of modifying the protein content in NAFLD patients.

An emphasis on MUFA s from foods such as olive oil, in favour of high-SFA foods such as fatty meats and full-fat dairy products, is advisable because SFAs have deleterious effects on liver function and raise blood LDL concentrations [93–95], whereas MUFA s are beneficial in reducing the risk of CHD and T2D through effects on blood lipids, endothelial function, and insulin sensitivity [43, 44, 93, 96].

The recommendation to avoid the intake of sodas and other sweetened drinks is substantiated by observations that high fructose intakes, high sucrose intakes, or both can induce DNL, which leads to higher blood triacylglycerol concentrations and lower insulin sensitivity [69–71, 76]. Soda consumption contributes to a substantial proportion of the calorie intake in many overweight and obese individuals [74]. A reduction in the consumption of simple sugars, especially in the form of sweetened beverages, which provide sugar in a very accessible and easily absorbable form, would help to reduce the exaggerated glucose and insulin excursions that are associated with insulin resistance. In addition, a reduction in the consumption of sweetened beverages would lead to a reduction in total calories consumed, which would facilitate weight loss.

Poor adherence in weight loss and lifestyle modification

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SFA, saturated fatty acids; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids.

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<th>Relative amounts of selected nutrients typical of diet</th>
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is a crucial issue in overweight and obese individuals [97, 98]. Weight loss through diet and exercise tends to be successful in the first 6 months, but in the long-term, most individuals are unable to maintain this weight loss [81]. Strategies to improve adherence and long-term behavioral modification are therefore imperative for the successful treatment of NAFLD through dietary approaches.

**Conclusive remarks**

There is no consensus as to what diet or lifestyle approach is the right one for NAFLD patients, largely because of a lack of scientific evidence. It is likely that there will not be solely one correct approach for all NAFLD patients, and diets will therefore need to be tailored to individual needs. The inclusion of n-3 fatty acids, high-MUFA foods, fruit, vegetables, and low-GI, high fiber foods and reduced intakes of saturated fats, simple carbohydrates, and sweetened drinks may be universally recommended to NAFLD patients. More studies are needed to clarify the specific effects of different diets and dietary components on the health of NAFLD patients.

Anyway, all NAFLD patients, whether obese or of normal weight, should be informed that a healthy diet has benefits beyond weight reduction. They should be advised to reduce saturated/trans fat and increase polyunsaturated fat with special emphasis on n-3 fatty acids. They should reduce added sugar to its minimum, try to avoid soft drinks containing sugar (including fruit juices that contain a lot of fructose) and increase fiber intake [99]. For the heavy meat eaters, especially those of red and processed meats, less meat and increased fish intake should be recommended. Minimizing fast food intake will also help maintain a healthy diet. Physical activity should be integrated into behavioral therapy in NAFLD, as even small gains in physical activity and fitness may have significant health benefits. A combination of educational, behavioral, and motivational strategies is required to help patients achieve lifestyle change [100].

However, whether any type of diet including weight loss diets can prevent HS or fibrosis is uncertain because data on histology before and after dietary intervention are lacking. It is important to establish the effects of diet composition on the natural course of NAFLD. Such data are not available at present. The general recommendations described in this review may be a useful guide for determining the appropriate diet for individual patients now, while evidence based recommendations from future clinical trials are assembled.

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