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Metabolism and Target Organ Damage

Review

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What should we advise MAFLD patients to eat and drink?

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Abstract

In a time of food abundance and waste, and when sedentarism is the norm, metabolic-associated fatty liver disease (MAFLD) has become a major health threat in the Western world. While research is committed to finding a pharmacological treatment for MAFLD, it is time to go back to the basis and address the behavioral pathogenesis of MAFLD. All patients with MAFLD, irrespective of body weight, should be submitted to thorough dietary counseling. Diet is a learned behavior and should be addressed holistically and in a personalized fashion. The benefits of a suitable diet surpass an improvement of liver disease, having the potential to improve cardiovascular- and cancer-related mortality, in patients with MAFLD. This review summarizes the current state of the art of diet on MAFLD, presenting straightforward recommendations for everyday practice.

Keywords: MAFLD, diet, recommendations

INTRODUCTION

Throughout human evolution, dietary changes evolved at a rhythm that was not caught up by adaptations in human genome[1]. Dramatic changes in diet occurred in the past two centuries, after the industrial revolution allowed the introduction of prepackaged processed foods, hydrogenated vegetable oils and refined grains[1]. Indeed, humans are not adapted to the "western diet", which is hypercaloric, with surplus

fat and refined sugars, and deficient in vegetables and fibers. This disruptive shift in diet couples with the growing threat of sedentarism, creating the perfect conditions that have led to obesity being the pandemic of the 21st century.

The metabolic syndrome (MS) and metabolic-associated fatty liver disease (MAFLD) are manifestations of energy surplus, adiposopathy, and obesity. The prevalence of MAFLD increased more than 50% in the last 35 years, and it is already the number one cause of liver disease worldwide, afflicting one fourth of the overall population[2]. Furthermore, MAFLD is the most rapidly increasing etiology for end-stage liver disease[3], having recently reached the podium as the leading cause of chronic liver diseases in women on waitlist for liver transplantation and the second leading cause overall[4]. MAFLD is also associated with cardiovascular and all-cause mortality[5].

Recently, a panel of international experts defined as diagnostic criteria for MAFLD the presence of hepatic steatosis in overweight/obese or with type 2 diabetes mellitus (T2DM). In lean non-diabetic patients, besides liver steatosis, the diagnosis of MAFLD requires the presence of at least two metabolic disturbances, such as increased waist circumference, high blood pressure, dyslipidemia, insulin resistance (IR) and prediabetes, or high plasma C-reactive protein[6].

Despite intense research on the quest to find pharmacological treatment for MAFLD, currently no drug has yet been approved for it[7]. We do know, however, that weight loss is effective and can lead to reversal of the disease, with weight loss above 10% of body weight resulting in steatosis improvement in virtually all patients and fibrosis improvement in four out of five patients[8].

The famous quote from the 19th century by the German philosopher Ludwig Feuerbach "we are what we eat"[9] is echoing in the field of MAFLD. Indeed, awareness of the effects of our diet on the development and progression of MAFLD is increasing, and a dietary intervention must have a central position in the management of these patients.

This review critically summarizes the associations between diet and MAFLD, as well as the dietary recommendations clinicians should implement on their daily practice.

QUANTITY *VS.* QUALITY OF THE DIET AS A DRIVER FOR MAFLD

The first important question is whether diet composition is relevant to the development of MAFLD, or if, on the contrary, it all comes down to a mathematical equation of calories consumption. Table 1 summarizes the nine top epidemiological/observational studies regarding dietary behaviors of patients with MAFLD[10-18], and only two showed an increase in daily energy intake[14,15], even in the studies in which patients with MAFLD had clearly a higher body mass index as compared to controls. On the other hand, epidemiological studies presented very heterogeneous differences in the composition of diet in patients with MAFLD as compared to controls, the most consistent one being an increase in proteins intake[10,12,14-18].

The evidence of an association between excessive caloric intake and the development of MAFLD is stronger in interventional studies. Small short-term overfeeding studies on healthy subjects, in which excessive calories were presented either as fat[19] or carbohydrates[20], both were associated with increased body weight and liver fat[21]. In the reverse way, overweight or obese subjects submitted to hypocaloric diets restricting carbohydrates or fat presented similar reductions on body weight, liver fat content, and liver enzymes[22,23]. The effect of carbohydrates restriction may be faster than with fat restriction, with more pronounced effects after acute restriction (48 h), but similar after chronic restriction (from 11 weeks up to 2 years), when

Table 1. Summary of the main epidemiological studies evaluating an association between diet and MAFLD

Ref.	Country	Study design	*n*	Differences in MAFLD *vs.* control group				
				BMI (kg/m^2)	Physical activity	E intake (kcal/day)	Alcohol intake	Macronutrients composition
Musso *et al.*[10] 2003	Italy	Case-control NASH by liver biopsy	25 NASH 25 controls	= 26 *vs.* 25	-	= 2638 *vs.* 2570	= 13.3 g/day *vs.* 13.5 g/day	*% kcal:* = **Fat** (35 *vs.* 32); [↑ SFA (14 *vs.* 10), = MUFA (18 *vs.* 17), ↓ PUFA (3 *vs.* 5), ↑ cholesterol (506 mg *vs.* 405 mg)] = **Carbohydrates** (45 *vs.* 49); ↓ fiber (13 *vs.* 23) ↑ **Proteins** (20 *vs.* 17)
Cortez-Pinto *et al.*[11] 2006	Portugal	Case-control NASH by liver biopsy	45 NASH 856 controls	↑ 31 *vs.* 27	-	= 2253 *vs.* 2218	-	*Intake in g:* ↑ **Fat** (80 *vs.* 73); [= SFA (23 *vs.* 23), ↑ MUFA (38 *vs.* 32), = PUFA (12 *vs.* 12), = cholesterol (307 mg *vs.* 330 mg)] ↓ **Carbohydrates** (244 *vs.* 261); = fiber (23 *vs.* 23) ↓ **Proteins** (100 *vs.* 105)
Zelber-Sagi *et al.*[12] 2007	Israel	Cohort MAFLD by ultrasound	349 (31% MAFLD)	↑ 30 *vs.* 26	-	= 2493 *vs.* 2382	-	*% kcal:* = **Fat** (37 *vs.* 38) = **Carbohydrates** (47 *vs.* 47) = **Proteins** (18 *vs.* 17), but ↑ in men (18 *vs.* 17)
Jia *et al.*[13] 2015	China	Cohort MAFLD by ultrasound	4206 (32% MAFLD)	↑ 27 *vs.* 24	= 12 MET/week *vs.* 12 MET/week	= 2218 *vs.* 2165	↓ Daily intake: 4.3% *vs.* 8.6%	↑ **Carbohydrates** intake in women: highest quartile of intake/sweet pattern score, OR 2.19 for MAFLD
Wehmeyer *et al.*[14] 2016	Germany	Case-control MAFLD by ultrasound	55 MAFLD 88 controls	↑ 30 *vs.* 24	-	↑ 2739 *vs.* 2173	-	*g/1000 kcal:* = **Fat** (43 *vs.* 45); [= SFA (18 *vs.* 18), = MUFA (16 *vs.* 18), = PUFA (7 *vs.* 8)] = **Carbohydrates** (104 *vs.* 102); ↓ fiber (9 *vs.* 10) ↑ **Proteins** (36 *vs.* 35)
Cheng *et al.*[15] 2016	China	Case-control MAFLD by ^{1}H-MRS	19 MAFLD 17 controls	↑ 36 *vs.* 27	= > 120 min/week: 23% *vs.* 21%	↑ 2901 *vs.* 2423	-	*Intake in g:* ↑ **Fat** (87 *vs.* 60); [↑ SFA 8 *vs.* 6), = MUFA (11 *vs.* 9), ↑ PUFA (16 *vs.* 11)] ↓ **Carbohydrates** (434 *vs.* 391); = fiber (21 *vs.* 20) ↑ **Proteins** (97 *vs.* 80)
Rietman *et al.*[16] 2017	Netherlands	Cohort MAFLD by FLI	1128 (21% MAFLD)	↑ 31 *vs.* 26	↓ > 30 min, moderate: 2 days *vs.* 3 days	= 1985 *vs.* 2048	↑ 9.8 g/day *vs.* 6.8 g/day	*% kcal:* = **Fat** (37 *vs.* 36); [= SFA (12 *vs.* 12), = MUFA (13 *vs.* 13), = PUFA (8 *vs.* 9)] ↓ **Carbohydrates** (42 *vs.* 44); ↓ Fiber (4 *vs.* 5) **Proteins** (14 *vs.* 14)
Alferink *et al.*[17] 2019	Netherlands	Cohort in elderly MAFLD by ultrasound	3882 (34% MAFLD)	↑ 29 *vs.* 26	↓ 35 MET/week *vs.* 44 MET/week	↓ 1996 *vs.* 2052	= 0.45 units/day *vs.* 0.45 units/day	*% kcal:* ↑ **Fat** (33 *vs.* 32); [↑ SFA (12 *vs.* 11), = MUFA (11 *vs.* 11), = PUFA (6 *vs.* 6)] = **Carbohydrates** (45 *vs.* 49); = fiber (3 *vs.* 3)

Noureddin *et al.*[18] 2020	USA	Case-control MAFLD by Medicare claims data	2974 NASH 29474 controls	↑ 27 *vs.* 26	↓ > 0.36 h/day: 20% *vs.* 23%	= 2122 *vs.* 2127	↓ 2.8 g/day *vs.* 6.7 g/day	↑ **Proteins** (16 *vs.* 15) *% kcal:* **= Fat**; [**=** SFA, = MUFA, **=** PUFA, ↑ cholesterol (OR = 1.16)] **= Carbohydrates**; ↓ fiber (OR = 0.84) ↑ **Red meat** (OR = 1.15) and **processed red meat** (OR = 1.18)

↑Increased intake in cases *vs.* controls. ↓Decreased intake in cases *vs.* controls. BMI: Body mass index; E: energy; MAFLD: metabolic dysfunction-associated fatty liver disease; MUFA: mono-unsaturated fatty acids; NASH: nonalcoholic steatohepatitis; PUFA: polyunsaturated fatty acids; SFA: saturated fatty acids.

achieving similar weight loss[24].

Besides how much we eat, when we eat seems to have an effect on the risk for developing MAFLD[25]. An overfeeding study provided excessive calories given as sugar at the main meals (hence increasing the size of the meal) or between meals as snacks (hence increasing the frequency of meals). Although the weight gain was not significantly different between groups, the group that increased the frequency of the meals had a dramatic increase in the liver fat content. This was associated with an increase in visceral fat and hepatic *de novo* lipogenesis (DNL).

More recently, how fast we eat might also have a role in MAFLD. Cross-sectional studies found that eating fast associated with a 4-fold increased risk for MAFLD[26], particularly in lean subjects[27].

THE ROLE OF CARBOHYDRATES IN THE PATHOGENESIS OF MAFLD

Epidemiological studies do not favor an association between the proportion of energy intake as carbohydrates and the risk of having MAFLD or steatohepatitis [Table 1]. Similarly, interventional studies with high carbohydrates isoenergetic diets did not result in an increase on body weight or intrahepatic lipid content[28].

The type of carbohydrate ingested may modulate the risk of MAFLD, if not in hypercaloric[29-31] at least in isocaloric diets[32]. For example, a small crossover study provided two isocaloric diets with half of the energy from carbohydrates as fructose or almost all as complex carbohydrates (cereals, bread, pasta, rice, and potatoes). The high-fructose group developed an increase in DNL and a significant increase in liver steatosis[33].

Fructose and sugar-sweetened beverages

Preclinical and interventional human studies showed that, when compared to glucose, fructose supplementation was associated with higher adiposopathy and increased visceral fat, IR, and hypertriglyceridemia, at the expense of an increase in hepatic DNL, despite similar increase in body weight[29,34,35]. This is extremely relevant since, although the contribution of DNL for the intrahepatic lipid content is only 5% in patients without liver steatosis, it increases to 25% in

patients with MAFLD[36]. In addition, newly synthesized fatty acids are fully saturated, and hence DNL-derived fatty acids are potentially more lipotoxic[37]. Indeed, studies with rodents showed that fatty acids derived from fructose-driven DNL induced ER stress and cellular injury, which was not observed when the fatty acids overload came directly from the diet[38].

From a physiological point of view, fructose can promote liver steatosis both directly via DNL and indirectly via DNL feedback inhibition of fatty acids oxidation[39]. Indeed, unlike glucose metabolism, which is highly regulated, fructose phosphorylation is not regulated by the hepatic energy status. As such, ingested fructose suffers a first-pass metabolism, in which fructose is retained in the liver not reaching systemic circulation. Ingested glucose, on the other hand, is only partially retained in the liver and can be utilized by peripheral tissues as an energy source for exercising muscle and DNL/storage in the adipose tissue. This results that ingested fructose may act as unlimited substrate for hepatic DNL[40]. Additionally, fructose activates SREBP-1c independently of insulin, with activation of genes involved in DNL[41]. Furthermore, fructose inhibits PPAR-α activity and decreases FGF-21 expression, through a ChREBP-dependent manner[42].

Fructose also depletes ATP in hepatic cells, which promotes an increase in AMP-derived uric acid synthesis[43,44]. Uric acid may be a link between fructose consumption and the MS through a decrease in NO bioavailability, as NO is required for the insulin-stimulated glucose uptake. Accordingly, studies in rodents and randomized clinical trials in humans showed that fructose, but not dextrose, induced features of MS[45,46], which were prevented or reversed by allopurinol, an inhibitor of uric acid synthesis[45,47]. Fructose promotes small bowel bacterial overgrowth and increased gut permeability[48], increasing endotoxinemia, which also promotes IR[42]. Lastly, fructose inhibits leptin expression, blunting a satiety response to a meal[49].

Taking all into consideration, it comes with no surprise that different studies showed that, compared to controls, patients with MAFLD consume 2-3 times more fructose[50]. Patients with MAFLD with higher fructose consumption are also at increased risk of having steatohepatitis and advanced fibrosis[51]. Meta-analyses suggested a dose threshold for the deleterious effects of fructose, with fructose consumption lower than 10% of energy intake (< 50 g/day for a 2000 kcal diet) not inducing weight gain or dyslipidemia[52,53]. Animal models also corroborate a threshold effect for fructose-induced MAFLD and liver injury. Indeed, a study feeding rodents with 10%, 20%, and 30% energy from fructose showed a dose-response increase in liver steatosis. Furthermore, fibrosis only developed when fructose consumption was at least 20% of energy intake[54].

Fructose is a naturally occurring simple sugar present in fruit and honey, but it is mostly consumed as sucrose (a disaccharide that combines one molecule of glucose with one molecule of fructose) and the artificial sweetener high-fructose corn syrup (with a usual ratio of 55% glucose and 45% fructose)[55]. A major source of fructose in the western diet is sugar-sweetened beverages (SSBs) or soft drinks. The average sugar content of SSB is 10 g/100 mL (10 g for juices, 8.5 g for tea-based beverages, 5 g for sports drinks, and 7 g for energy drinks)[56]. Importantly, SSBs, besides fructose, contain other components such as caramel and aspartame, both with proinflammatory and diabetogenic properties. Furthermore, SSBs, unlike solid foods, induce lower satiety and hence promote an increase in caloric ingestion[57].

An interventional study on non-diabetic obese or overweight subjects delivered isocaloric diets with consumption of 1 L/day of SSB, low-fat milk, aspartame-sweetened drinks, or water for 6 months. At the end of the follow up, body weight was similar, but the sucrose group experienced an increase in visceral adipose tissue, liver and muscle steatosis, and dyslipidemia[58].

Epidemiological studies showed us that consumption of SSB is associated with an increased risk for central obesity and increased visceral fat[59-62], MS[59,63], dyslipidemia[64], T2DM[63,65-67], cardiovascular diseases[63,68], and mortality[69].

SSB consumption is also associated with MAFLD, as shown in different populations, independently of the presence of the MS[12,31,70-72]. Two studies from Israel showed that four out of five patients with MAFLD regularly drunk SSB, as opposed to only one out of five controls[70,71]. The effect can be seen with intakes ≥ 1 serving of SSB per week[72]. For intakes of ≥ 1 serving/day, the risk of having MAFLD increases by 50%[12], liver fibrosis by 250%[51], and hepatocellular carcinoma by up to 2-fold[73,74].

Artificially sweetened beverages (ASBs) and 100% fruit juices seem to have similar dismal effects as SSB, regarding increasing the risk for obesity[75] and T2DM[76,77].

We should advise our patients that fruit should be eaten and not drunk. Consumption of 100% fruit juices increases by 15% the risk of developing T2DM, whereas whole fruit consumption decreases it. The effect of whole fruit consumption depends on the fruit ingested, with blueberries being associated with a 25% decrease in the risk of T2DM; grapes, raisins, and prunes by about 10%; and apples, pears, bananas, and grapefruit by about 5%. As an exception, cantaloupe has been associated with a 10% increased risk[78]. Unlike fruit juices, fruit intake, as a source of fructose, seems to be metabolically beneficial[79]. Low doses of fructose consumption paradoxically seem to have a beneficial effect on glucose metabolism, being associated with lower levels of glycated hemoglobin (HbA1c)[53]. Indeed, some authors found that a 7.5 g fructose intake per meal can improve long-term glycemic control in humans, through a decrease in the post-prandial glycemic response to high glycemic index carbohydrates[80]. This protective effect is mediated by an increase in the activity of glycogen synthase, shunting glucose for storage as glycogen[81].

ABSs seem to be diabetogenic and steatogenic mainly because their consumption increases appetite[82], but also through their effects on altering gut microbiota[83]. It could also be the case of reverse causation, in which patients at increased risk for obesity/T2DM and cardiovascular diseases would be more likely to switch from SSB to ASB in an attempt to control body weight.

Two studies also found that ingestion of ≥ 1 diet cola/soda per day increases by 40% the risk of having MAFLD[70,84]. Importantly, ASB, similar to SSB, also increases mortality, particularly cardiovascular mortality[85,86].

Fibers

Fibers can be classified in soluble fibers (present in barley, oats, beans, figs, prunes, and sweet potatoes) and insoluble fibers (present in cereals, whole-wheat bread, lentils, apples, avocado, and strawberries). The former delay gastric emptying, restricting caloric intake, whereas the latter promote satiety and act as prebiotics, for example increasing the abundance of *Bifidobacteria* and being metabolized by the microbiota to produce short-chain fatty acids[49]. Short-chain fatty acids have anti-diabetogenic and anti-inflammatory properties[87].

Interventional studies with fiber-rich diets consistently showed a beneficial effect, decreasing body weight, body fat, and waist circumference, as well as improving insulin sensitivity[88-91].

Epidemiological studies consistently found a protective association between fiber intake and the prevalence of MAFLD[11,14,15,92,93] and steatohepatitis[10]. A dietetic interventional study on MAFLD patients, with an

increase in fiber intake for 6 months was associated with an improvement in liver enzymes and intestinal permeability[94]. However, a shorter duration small clinical trial (12 weeks), on prediabetic subjects, failed to find a benefit on liver steatosis[95].

Higher fiber intake also seems to protect from hepatocellular carcinoma. A meta-analysis comprising more than one million participants showed an 8% decrease in the risk for hepatocellular carcinoma for each 100 g/day intake of vegetables[96].

THE ROLE OF FATS IN THE PATHOGENESIS OF MAFLD

Several epidemiological studies showed an association between higher percentage of energy intake as fat and the risk of having MAFLD[11,15,17], even though this association was not consistently observed[10,12,14,16,18]. Importantly, the type of fat ingested, particularly saturated fat and cholesterol, appears to have a dismal effect on the development and progression of MAFLD[10,15,17,18].

Saturated, polyunsaturated, and monounsaturated fatty acids and trans-fats

Saturated fatty acids (SFAs), such as palmitic acid, have all carbons in the hydrocarbon backbone connected by single bonds. As a result, the molecules in saturated fat are packed close together; the fat is solid at room temperature and very heat stable. SFAs are present mainly in animal products such as red meat, butter, and whole milk dairy products; some vegetable products such as coconut oil and palm oil; and prepared foods such as deserts and sausages[97]. SFAs have the potential to induce dysmetabolism and are toxic to hepatocytes. SFA can induce IR and inflammation, among other mechanisms, through direct binding to TLR-4 and indirectly through the synthesis of diacylglycerol and ceramides[98]. SFAs are highly hepatotoxic, inducing oxidative stress, ER stress, and apoptosis on hepatocytes[99-101]. SFAs also modulate gut microbiota to assume a more obesogenic and inflammatory phenotype[102,103].

Polyunsaturated fatty acids (PUFAs) have multiple double carbon bonds. PUFAs have anti-steatogenic actions, inhibiting the lipogenic transcription factor SREBP-1c while inducing PPAR-α, a regulator of fatty acids oxidation.

SFA intake seems to be associated with cardiovascular diseases[104], with a 10% decrease of coronary events for every 5% of energy intake conferred by PUFAs in substitution of SFAs[105]. Furthermore, intakes lower than 10% of energy as SFA decreases IR and dyslipidemia, whereas lower than 7% does not confer additional benefit and it may even be detrimental[49]. Recently, SFAs have also been associated with advanced fibrosis[106] and hepatocellular carcinoma, with an increase of 4% of liver cancer for each 1% energy intake from SFA[107].

Different dietary studies, with iso- or hypercaloric diets supplemented with SFAs or PUFAs, for as short as 3 weeks, consistently found SFAs supplementation, but not PUFAs, to induce an increase in liver fat content, circulating ceramides, markers of lipogenesis as well as IR, and increase in endotoxinemia, despite maintaining stable body fat and visceral adipose tissue depots[108-111].

Although most epidemiological studies did not find an association between dietary PUFA and MAFLD, patients with steatohepatitis seem to present lower PUFA intake[112,113].

PUFAs can be classified as omega-3 (Ω-3) or Ω-6 according to the position of the first double carbon bond (counting from the terminal methyl). Examples of Ω-6 PUFAs are linoleic acid and arachidonic acid. They derive from sunflower and meat/eggs and dairy, respectively, and have proinflammatory and prothrombotic

properties. Examples of Ω-3 PUFAs are eicosapentaenoic acid and docosahexaenoic acid (DHA), and they derive mainly from fatty fish. Ω-3 PUFAs tend to have anti-inflammatory, insulin-sensitizer, and anti-lipogenic properties[114]. Western diets typically contain higher amounts of Ω-6 compared to Ω-3 PUFAs[115]. Patients with MAFLD, compared to controls, tend to present lower hepatic levels of DHA, increased Ω-6/Ω-3 ratio, and negative correlation between hepatic Ω-3 PUFAs levels and SREPBP-1c (pro-lipogenic)/PPARα (pro-lipolytic) ratio[116,117]. Furthermore, compared to controls, patients with steatohepatitis seem to present a higher Ω-6/Ω-3 ratio in the diet[11]. Lastly, fish consumption appears to be associated with a 35% reduction and Ω-3 PUFA intake with a 50% reduction in the risk for hepatocellular carcinoma[118-121].

Supplementation with high doses of Ω-3 PUFAs seems to improve dyslipidemia[122] and cardiovascular morbidity/mortality[123]. However, effects on MAFLD were disappointing, with studies only demonstrating benefit in steatosis assessed by ultrasound, for doses of at least 0.83 g/day[124]. Supplementation with Ω-3 PUFAs did not seem to improve liver histology[125,126].

MUFAs, such as oleic acid, only have one double carbon bon and are mainly present in olive oil, avocado, nuts, and seeds. MUFAs are liquid at room temperature and less heat stable than SFAs. MUFAs are known to promote lipid oxidation while protecting from IR and seem to be protective from the MS and cardiovascular diseases[97].

Even though epidemiological studies failed to find an association between dietary MUFA intake and MAFLD, interventional studies in prediabetic and diabetic patients submitted to isocaloric diets with MUFA supplementation achieved a decrease in liver fat content and improvement in hepatic insulin sensitivity[95,127].

Olive oil is a major source of MUFAs. Extra-virgin olive oil contains 70%-80% MUFAs and 20% palmitic acid. It also contains α-tocopherol, polyphenols, and other anti-inflammatory and antioxidant phytochemicals[97,128]. When refined or heated, olive oil loses its natural compounds; hence, it should not be cooked at high temperature. The FDA recommends the intake of 20 g/day of extra-virgin olive oil to prevent cardiovascular disease, since it has been shown that each 10 g per 2000 kcal diet is associated with 7% decrease in overall and 13% cardiovascular mortality[129]. Regarding MAFLD, three small clinical trials also suggested benefit of dietary olive oil in serum lipid profile and improvement of hepatic steatosis[130-132].

Trans-fatty acids differ from unsaturated fatty acids by having a double bond in the *trans* instead of *cis* configuration, making them straighter and resembling the structure of SFA. Trans-fats are abundant in ultra-processed foods such as margarines and fast food. Trans-fatty acids probably have a role in the pathogenesis of MAFLD, since higher intakes of trans-fatty acids seem to be associated with increased risk of having MAFLD[17]. In addition, patients with MAFLD tend to present higher serum levels of trans-fatty acids[133]. Finally, preclinical studies in rodents suggest that trans-fats are associated with worse MAFLD and worse liver injury[134,135].

Importantly, high trans-fat-containing ultra-processed food intake has recently been shown to be associated with many chronic diseases such as obesity, MS, hypertension, T2DM, cardiovascular diseases, cancer, and mortality[136-140].

Cholesterol

Two large epidemiological studies found an association between high cholesterol intake and MAFLD, steatohepatitis, and advanced fibrosis[10,18,106]. Dietary cholesterol seems to have higher relevance in lean MAFLD[141]. Finally, dietary cholesterol seems to be associated with an increased risk for hepatocellular carcinoma, with a particularly aggressive phenotype, in rodent models[142].

Cholesterol has steatogenic effects, as its oxysterol metabolites are agonists of liver X-receptor-α, a transcription factor that increases SREBP-1c expression, and hence DNL[143]. Hepatic free cholesterol is also highly lipotoxic, inducing ER stress, mitochondrial dysfunction, and hepatocyte cell death. It also accumulates in Kupffer cells, inducing a proinflammatory response, as well as in hepatic stellate cells, promoting fibrogenesis[144].

THE ROLE OF PROTEINS IN THE PATHOGENESIS OF MAFLD

The association between higher protein intake and increased risk for MAFLD is the most consistent finding in dietary epidemiological studies[10,12,14-18]. Indeed, the risk of having MAFLD increased around 25% for each 1% of energy intake as proteins[16]. Data from epidemiological studies, however, conflict with those from interventional studie, suggesting that high-protein diets blunt the steatogenic effect of high-fat diets[145-147]. Importantly, those anti-steatogenic effects of high-protein diets were achieved for moderate intakes of proteins (25% of energy from protein), with no additional benefit for high intakes (40% energy from proteins)[148]. In addition, high-protein diets seem to improve body composition, increasing lean body mass and decreasing fat mass and waist circumference, as well as increasing muscle endurance[149-151]. However, it is also associated with an increase in inflammatory markers possibly through the promotion of gut microbiome dysbiosis[151,152]. Other potential negative impacts of high-protein diets are the potential to accelerate the progression or even induce chronic kidney disease in the long run[153]. Protein-derived nitrosamine and heterocyclic amines also increase the risk for colorectal cancer[154]. Furthermore, studies on rodent animal models suggest that high-protein diets may promote the development of MAFLD with a more inflammatory phenotype[155].

Importantly, not all proteins have the same effect on health, with animal protein, as opposed to plant protein, having a detrimental effect. Indeed, ingestion of animal proteins seems to be associated with obesity, MS, and T2DM, while plant protein tends to be protective[156,157]. Plant protein intake is also associated with a decrease in all-cause and cardiovascular-related mortality[158-160]. Similarly, regarding MAFLD, epidemiological studies found animal proteins to increase its risk, while plant proteins to decrease it[16,17]. The difference between plant and animal proteins may relate to the nutritional characteristics of foods containing those proteins. For example, animal proteins usually come from foods that have high index of SFA, whereas plant proteins come from foods that contain fibers and phenolic compounds[161,162]. Plant and animal proteins also have different amino acid compositions, with plant proteins being enriched in arginine, glycine, and glutamate/glutamine while animal proteins in branched-chain amino acids (BCAAs). Arginine provides substrate for NO, which has vasodilator properties and beneficial effects on endothelial function and other cardiometabolic functions. Glycine and glutamine potentiate the action of insulin and lower blood pressure. On the other hand, BCAAs are associated with obesity, IR, and cardiovascular diseases[161].

Recently, it has become clear that the type of animal protein has a role in cardiometabolic health, with red meat being the most deleterious one. Indeed, large epidemiological studies showed a positive association between red meat ingestion, and a negative one between white meat (e.g., poultry and fish), and all-cause and cancer-, cardiovascular-, and liver-related mortality[163]. Similar associations were found for chronic

liver disease and hepatocellular carcinoma[120,121,164]. Epidemiological studies unraveled an association between meat and processed meat consumption and MAFLD[12,17,165,166], with intakes higher that 36 g/day of meat protein (equivalent to 110 g of red meat) being associated with more than 3.5-fold increased risk[12]. Importantly, unhealthy cooking of red meat, such as fried or grilled and broiled to well-done level, are also associated with further increase in IR and the risk of having MAFLD. Unhealthy cooking increases the generation of heterocyclic amines, which promote inflammation and oxidative stress, having diabetogenic and steatogenic properties by itself[166]. Heterocyclic amines are also mutagenic compounds and can be associated with some types of cancer such as breast and colorectal cancer[167]. Additionally, unhealthy cooking of red meat increases the generation of advanced glycation end products[168], which have also been associated with MAFLD[169].

Regarding plant proteins, interventional studies with high-soy diets have suggested a beneficial effect in patients with MAFLD, resulting in a decrease in liver enzymes and the oxidative stress marker malondialdehyde[170]. However, those effects on liver enzymes were not supported by a recent meta-analysis[171]. Importantly, research on the cardiometabolic effects of soy protein only found benefit for intakes higher than 25 g/day, which are extremely difficult to achieve[172]. For example, a community with particularly high soy consumption, the Adventist vegans in the United States on average only consume 13 g/day[173].

ALCOHOL AND MAFLD - MORE THAN THE SUM

There is consensus that more than 2 drinks/day (20 g of alcohol) in women and 3 drinks/day (30 g of alcohol) in men are potentially hepatotoxic. There is still no consensus on the effect of lower amounts of alcohol intake (i.e., moderate alcohol consumption) in patients with MAFLD. Several epidemiological studies and meta-analyses suggested that moderate alcohol consumption could be protective for the development of MAFLD, steatohepatitis, and advanced fibrosis[174-181]. Such studies, however, have been criticized for having methodological flaws, not taking into consideration alcohol patterns, with potential underestimation of alcohol consumption, and incomplete adjustment for confounders[182]. Furthermore, that protective effect was observed for wine but not for beer and was lost with binge drinking (defined as drinking more than four drinks for women or five drinks for men on one occasion)[177,183]. Indeed, binge drinking at least monthly is associated with progression of liver fibrosis in MAFLD patients[184], and binge drinking weekly increased more than 3-fold the risk for decompensated liver disease[185]. Importantly, several recent cross-sectional[186,187] and longitudinal studies were in disagreement with previous studies and did find a positive association between moderate drinking and progression of steatohepatitis and liver fibrosis in MAFLD patients[188-190].

Before we recommend moderate alcohol intake for patients with MAFLD, we must keep in mind that there is a synergistic effect for the development of liver disease among alcohol consumption, obesity, MS, and T2DM[191]. Indeed, whereas in subjects with normal weight there is no association between moderate alcohol intake and elevated liver enzymes, overweight who drink > 2 drinks/day and obese who drink ≥ 1 drink/day have an increased risk for altered liver enzymes[192-194]. In addition, in overweight, drinking > 1 drink/week was associated with a 2-fold increased risk for chronic liver disease[195]. Moderate alcohol consumption and T2DM synergistically increase the risk for advanced fibrosis in MAFLD[187]. Obesity and any alcohol use have a synergistic effect not only in the risk for liver cirrhosis but also for hepatocellular carcinoma[196,197]. Furthermore, for patients with MAFLD-associated cirrhosis, any alcohol intake seems to be associated with a 3.5-fold increased risk of hepatocellular carcinoma[198] and should be highly discouraged.

Regarding mortality, a recent study suggested that regular drinking less than 1.5 drinks/day was associated with a 40% decreased mortality in patients with MAFLD, but drinking higher than that with a 45% increased mortality[199]. Of note, the beneficial effect on mortality was only verified in men and patients without fibrosis (assessed by FIB-4 < 1.79)[199]. Importantly, obese patients who drink > 1 drink/week presented a 5-fold increased liver-related mortality[195].

Lastly, recently the J-shape effect of alcohol intake on mortality, in the general population, has been challenged. In fact, despite that the J-shape may occur for cardiovascular- and T2DM-associated mortality, overall, because alcohol intake is linearly associated with other causes of mortality such as cancer and infections, any alcohol intake is linearly associated with progressively increased mortality[200]. Of note, the beneficial arm in the J-curve for cardiovascular mortality was lost in smokers.

COFFEE SEEMS PROTECTIVE FOR MAFLD

Unlike alcohol, data on coffee seem more consensual in decreasing around 30% the risk of developing MAFLD and progressive fibrosis[201,202]. There seems to be a non-linear dose-response for coffee intake, with decreased risk for MAFLD and liver fibrosis when drinking at least three coffees/day[203,204].

Coffee contains different biologically active compounds such as antioxidant chlorogenic acids, kahweol, cafestol, and caffeine. The protective effect of coffee on liver health appears to be specific for coffee and not shared with other caffeinated drinks such as tea, soft drinks, and energetic drinks[205].

Not all coffee seems to have the same protective effect, with protection from MAFLD described for filtrated/regular coffee (which better preserves its chlorogenic acids) but not for espresso coffee (obtained from high-pressure boiling water through a column of coffee, which can modify several of its components[206])[207]. Decaffeinated coffee has shown the same beneficial effect on MAFLD as compared to regular coffee[208].

Finally, a similar non-linear response was found for hepatocellular carcinoma, with a decreased risk for subjects who drank at least two coffees/day (or decaffeinated coffees)[209].

EATING PATTERNS AND MAFLD

Different diets have been proposed for the management of MAFLD, the most studied ones being the Mediterranean diet (MD), the Dietary Approaches to Stop Hypertension (DASH) diet, and the intermittent fasting diet.

MD has its origins in the traditional diet from Mediterranean countries and is characterized by a high consumption of plant-based foods such as vegetables (up to 6 servings/day), fruits (up to 3 servings/day), whole grains, seeds, nuts, and legumes. It is relatively low in carbohydrates (40% of the calories), particularly sugars and refined carbohydrates[210]. It allows moderate consumption of protein-source foods such as fish and poultry, but it is scarce in red meat. MD is rich in MUFAs, primarily from olive oil (which is the main added lipid) and olives, and restricts fatty dairy products. MD is particularly enriched in fibers and provides a high Ω-3/Ω-6 ratio. It also allows for moderate drinking, particularly red wine[211,212].

Epidemiological studies found that higher adherence to MD was associated with lower severity of hepatic steatosis and lower likelihood of steatohepatitis, liver fibrosis, and hepatocellular carcinoma[213-217]. Interventional studies showed that consuming MD was associated with an improvement in liver enzymes,

steatosis, liver stiffness, and lipid profile, even without weight loss[218-227]. We still need long-term trials to understand the role of MD on liver histopathology. Importantly, high adherence to MD has also been associated with decreased all-cause and cardiovascular mortality[228].

The DASH diet was developed in the early 1990s as an intervention to manage arterial hypertension, emphasizing a low sodium intake and the consumption of minimal processed fresh foods[229]. Two epidemiological studies found that high adherence to the DASH diet was associated with lower risk of having MAFLD[230,231]. A small randomized controlled trial on MAFLD also suggested that engaging a DASH diet for 8 weeks resulted in improvement in liver enzymes[232].

The newest diet is time-restricted feeding as a form of intermittent fasting, which restricts the eating window, without emphasizing calorie restriction. This diet seems effective in decreasing body weight[233], whereas many authors disclaimed that the effect is resultant of an actual calorie restriction. A recent meta-analysis, in patients with MAFLD, found intermittent fasting to be beneficial in weight loss and liver enzymes[234], even though it failed to demonstrate additional metabolic benefit compared to calorie-restriction diets[235]. Long-term feasibility and stronger endpoints require further research. For the time being, it is wise to advise against this diet for patients with MAFLD-associated cirrhosis, due to the effect of fasting on sarcopenia development in those patients.

RECOMMENDATIONS

The recommendations from the international guidelines[236-240] are summarized in Table 2.

Patients should be clearly informed regarding the severity of their illness and its prognostic consequences, but also the reversibility that could be expected when engaging weight loss-directed lifestyle behaviors[241]. Exercise recommendations should always be a part of the lifestyle changes advised, keeping in mind that the benefits of exercise occur even without weight loss[242].

Simple recommendations should be given [Table 3], particularly the advice to eat less[14], tailoring the weight loss according to the severity of liver disease: 3%-5% if isolated steatosis, 7% if steatohepatitis, and 10% when fibrosis is present[8].

Regarding the macronutrient composition, daily intake of energy should be 45%-65% from carbohydrates, 20%-35% from fat, and 10%-35% from proteins[243]. Not all carbohydrates are the same. Added sugar should be restricted to no more than 5%-10% of daily calories[244], while fibers ingestion should be at least 25 g/day in women and 38 g/day in men, particularly promoting a high intake of vegetables and legumes. A practical tip is to suggest vegetable soup as a starter in every meal. Regarding fruit intake, it should be no more than 2-3 portions per day and should be eaten as whole fruit rather than drunk as fruit juice. Patients should abstain from drinking SSB, including ASB. Patients should also be advised on the type of fat they should consume, avoiding processed food, desserts, and fast food (high in saturated and trans-fats), while electing MUFA-rich olive oil as the preferred oil. Recommended olive oil intake is 20 g/day, avoiding cooking it at high temperatures. To achieve a good Ω-3/Ω-6 PUFA ratio (minimum Ω-3 PUFA intake of 0.35-0.40 g/day), prefer fish to meat, eating 2-3 portions of fatty fish per week. Red meat meals should not surpass three meals per week and may be substituted for plant proteins (e.g., soy).

Coffee, including decaffeinated coffee, should not be restricted, and two coffees/day seem to help prevent hepatocellular carcinoma, while three coffees/day prevent steatohepatitis and fibrosis.

Table 2. International Guidelines on diet for patients with MAFLD

	AGA 2021[236]	AASLD 2018[237]	EASL, EASD, EASO 2016[238]	NICE 2016[239]	WGO 2014[240]
Energy restriction	Hypocaloric: 1200-1500 kcal/day or ↓ from baseline 500-1000 kcal/day	Hypocaloric: ↓ from baseline 500-1000 kcal/day	Hypocaloric: ↓ from baseline 500-1000 kcal/day	Hypocaloric: ↓ from baseline 600 kcal/day	Hypocaloric: ↓ calories intake 25%
Weight loss target	≥ 5% if steatosis ≥ 7% if NASH ≥ 10% if fibrosis	3%-5% if steatosis 7%-10% if NASH ± fibrosis	7%-10%	-	5%-10%
Macronutrient composition	Minimize SFA, ↓ red and processed meat	Less relevant	Low to moderate fat and moderate to high carbohydrates	Low fat diets	Avoid trans-fats ↑ Ω-3/Ω-6 PUFA
Fructose intake	Avoid fructose commercially produced	-	Avoid fructose-containing foods and beverages	-	Avoid fructose and soft drinks
Dietary pattern	Mediterranean diet	Mediterranean diet?	Mediterranean diet	-	-
Alcohol intake	Restrict. Abolish in smokers (current or former)	Insufficient data	< 30 g/day in men and < 20 g/day in women. Abolish if cirrhosis	< 14 drinks/week	-
Coffee intake	-	-	No liver limitations	-	-

↑Increase. ↓Decrease. MAFLD: metabolic dysfunction-associated fatty liver disease; AGA: American Gastroenterological Association; AASLD: American Association for the Study of the Liver; EASL: European Association for the Study of the Liver; EASD: European Association for the Study of Diabetes; EASO: European Association for the Study of Obesity; NASH: nonalcoholic steatohepatitis; NICE: National Institute for Health and Care Excellence; PUFA: polyunsaturated fatty acids; SFA: saturated fatty acids; WGO: World Gastroenterology Organization.

Table 3. Simple dietary recommendations for patients with MAFLD

Avoid/do not or drink or eat	May/should drink or eat
• Soft drinks • Fruit juices • Alcohol (no more than 1-2 drinks/day and total abstinence if smoker, obese or with liver cirrhosis)	• Coffee (2-3 servings/day)
• Processed fruits • Sugar-added fruits (no more than 1-2 servings/week) • Red meat (no more than 2-3 servings/week) • Animal-origin fat/butter	• Fresh fruits (3 servings/day); nuts weekly • Vegetables and legumes (6 servings/day) • Unrefined cereals (8 servings/day) • Fish (4-6 servings/week); poultry/egg (2-4 servings/week) • Olive oil (20 g/day) • Low-fat milk, cheese or yogurt (2-3 servings/day)

MAFLD: metabolic dysfunction-associated fatty liver disease.

While there are still not enough data to advise regarding moderate alcohol consumption in patients with MAFLD, it should be strongly advised against in patients with liver cirrhosis, obese, and smokers (current or former).

Two dietary patterns that seem to promote improvement of MAFLD and that incorporate the above recommendations are the Mediterranean and the DASH diet, and they should be considered when advising patients.

CONCLUSIONS

MAFLD is associated with adiposopathy and energy surplus, conditions that are the result of an imbalance between the energy intake and the energy expenditure. As such, what one eats and how much one eats, in harmony with individual metabolism and physical activity, are clearly the basis of the pathophysiology of MAFLD. Despite this intuitive aphorism, it is difficult to scrutinize the role of diet and individualize diet components in the development and progression of MAFLD. This relation is even more intricate, as we know today that our genetics and gut microbiota modulate the way diet programs our metabolism.

Having all that in mind, we can still safely advise MAFLD patients to "eat less" to promote a tailored weight loss according to the severity of their overweight and liver disease. Dietary recommendations should be provided by a specialized multidisciplinary team, with dedicated dietitians, and psychological cognitive-behavioral support as needed. Secondly, we should advise patients to "eat better", advertising a Mediterranean-like diet, favoring unprocessed fresh foods and fish, in detriment to fast foods, sugar-added foods, and trans-fat-rich foods including red meat. Water is the best drink to promote, and there should be no place for sugary or artificially sweetened drinks. If no other contraindication, coffee might be beneficial in preventing progression of liver disease and hepatocellular carcinoma. While the effects of moderate alcohol intake are still controversial, it should be strongly discouraged for patients with liver cirrhosis, obesity, or smokers.

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