Diet, Weight Loss, and Liver Health in NAFLD: Pathophysiology, Evidence and Practice

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Abstract

Fatty liver accumulation results from an imbalance between lipid deposition and removal, driven by the hepatic synthesis of triglycerides and *de novo* lipogenesis. The habitual diet plays a relevant role in the pathogenesis of NAFLD, and both risky (e.g., fructose) and protective foods (Mediterranean diet) have been described, but the contribution of excess calories remains pivotal. Accordingly, weight loss is the most effective way to promote liver fat removal. Several controlled studies have confirmed that an intense approach to lifestyle changes, carried on along the lines of cognitive-behavior treatment, is able to attain the desired 7-10% weight loss, associated with reduced liver fat, NASH remission, and also reduction of fibrosis. Even larger effects are reported following bariatric surgery-induced weight loss in NAFLD, where 80% of subjects achieve NASH resolution at 1-year follow-up. These results provide solid data to evaluate the safety and effectiveness of the pharmacologic treatment of NASH. The battle against metabolic diseases, largely fuelled by increased liver fat, needs a comprehensive approach to be successful in an obesiogenic environment. In this review, we will discuss the role of hepatic lipid metabolism, genetic background, diet and physical activity on fatty liver. They are the basis for a lifestyle approach to NAFLD treatment.

Introduction

In the last 15 years the clinical importance of nonalcoholic fatty liver disease (NAFLD) has remarkably increased. Long considered an occasional finding of no clinical significance, it now ranks among the top three conditions for terminal liver failure and inclusion in the waiting list for liver transplantation.[1] However, the awareness of its importance and referral to specialist care from community physicians is suboptimal, as is the need for careful monitoring and intensive treatment among specialists.[2, 3] The reasons for inertia are probably multifactorial, and are rooted into the university curricula, lack of time and experience in addressing patients' needs to lifestyle changes, lack of adequate resources for a comprehensive team approach. This makes physicians exclusively rely on drug treatment, but the results have been so far rather poor. We will discuss the role of hepatic lipid metabolism, genetic background, diet and physical activity on fatty liver as background for a comprehensive lifestyle-based approach to NAFLD treatment.

Physiopathology of hepatic lipid accumulation

Fatty liver accumulation is the result of an imbalance between lipid deposition and removal (Figure 1), where the hepatic synthesis of triglycerides can be considered a partially protective mechanism, aimed at storing cytotoxic free fatty acids (FFA) as inertial components.

Hepatic FFAs arise from diet, lipolysis of visceral fat, and *de novo* lipogenesis; the last two components are mostly dependent on insulin resistance (IR) and are associated with obesity and type 2 diabetes (T2DM). The relative contributions of the three components to hepatic fat content in NAFLD was measured by a multiple stable-isotope approach.[4] FFA release from adipose tissue accounts for the greater proportion (60–80%) of triglycerides, whereas 15% are derived from dietary FFAs. Notably, the proportion of triglycerides coming from *de novo* lipogenesis (26%) is much larger than that measured in healthy individuals (5%). This component is strictly regulated by different nuclear receptor and cytoplasmic transcription factors: i) the liver X receptor (LXR), mediating hepatic fatty acid synthesis; [5] ii) the farnesoid X receptor (FXR), interfering with VLDL assembly and increasing triglyceride clearance; iii) the peroxisome proliferator activated receptors (PPARs) family. PPAR-α regulates FFA oxidation, PPAR-γ has an anti-inflammatory function, PPAR-δ suppresses hepatic lipogenesis also reducing the hepatic expression of pro-inflammatory and pro-fibrotic

genes. Several drugs acting on these receptors have been tested or are under investigation for the treatment of NAFLD, but no drugs have been approved by regulatory Agencies by 2015.

Another relevant aspect of steatosis is lipid removal mediated by both mitochondrial fatty acid oxidation and VLDL secretion. In NAFLD patients, a compensatory increase in VLDL-TG secretion has been reported, although not adequate to normalize intrahepatic fat content,[6] whereas the mitochondrial oxidative capacity is impaired, this issue contributing to fatty acid accumulation and oxidative stress.[7]

Interaction between genes and lipid metabolism

The genetic background provides the soil where environmental factors express their potential pathologic effect. A prospective twin study indicates that both hepatic steatosis and fibrosis are heritable traits,[8] and that discordancy in liver fat between the twins can be explained by epigenetic regulation by microRNAs.[9] Along this line two large epidemiological studies described an increasing gradient of steatosis in relation to ethnicity (African Americans < Caucasians < Hispanics < Asian-Indians) after adjusting for confounders.[10, 11] Variants in glucokinase regular protein receptor, neurocan, protein phosphatase 1 regulatory subunit 3B and lysophospholipase-like 1 have all been associated with fatty liver accumulation, but only patatin-like phosholipase domain-containing 3 (PNPLA3), and transmembrane 6 superfamily member 2 (TM6SF2) have been validated as risk factors for NASH severity and progression in genome-wide association studies (GWAS).[12, 13]

The PNPLA3 gene encodes a transmembrane polypeptides chain with a triglyceride hydrolase activity, highly expressed in hepatocytes and adipose tissue. The I148M variant impairs phospholipase activity leading to defective lipid catabolism, increased synthesis of phosphatidic acid, and loss of retinyl-palmitate lipase activity in stellate cells. All these features can explain the association between the PNPLA3 variant and the full spectrum of liver damage, from steatosis to NASH, fibrosis and hepatocellular carcinoma,[14] as well as the extrahepatic metabolic comorbidities (carotid atherosclerosis and chronic kidney disease). TM6SF2 regulates hepatic triglycerides secretion, and the E167K aminoacidic substitution generates a functional impairment that promotes fatty liver accumulation, as well as disease progression.[15] Notably, probably due to the reduction in serum lipid levels, NAFLD patients carrying the variant, in spite of a higher risk of severe liver disease, are at lower risk of atherosclerosis.[15]

The role of PNPLA3 and TM6SF2 in NAFLD development, progression and outcome has been extensively validated at population level, but is not sufficient to accurately stratify the risk at individual level. Further studies are needed to fully clarify the role of these gene variants on interaction with environmental factors, on their prognostic value in subgroups of patients at different risk, and on response to lifestyle and pharmacological treatment.

Unhealthy diet and sedentariness as a risk factor for NAFLD

Excess calorie intake, unhealthy diet, and physical activity/sedentariness remain the main drivers of NAFLD, modulated by gene/behavior interaction.

Calorie intake

The close association between NAFLD and obesity highlights the role of excess dietary intake in NAFLD. The prevalence of NAFLD steeply increases with increased BMI and waist circumference throughout age, gender and ethnicity, in a manner largely resembling the prevalence of metabolic syndrome (MetSyn).[16] However, at any level of obesity a proportion of cases have normal biochemistry and no features of MetSyn (metabolically healthy obesity - MHO); the presence of liver fat has never been systematically ascertained in this subgroup. This issue is important, given the possible pathogenic role of liver fat in the development and progression from a metabolically-healthy condition to T2DM and cardiovascular risk,[17] and the evidence that transition from MHO to a diseased state is usually heralded by progressive weight gain.[18] Similarly, we need to know whether obesity *per se*, also during weight-stable periods, promotes and maintains liver fat *via* increased hepatic recirculation of FFAs or whether liver fat is only dependent on periods of weight gain/weight loss. In general, weight gain remarkably drives hepatic fat accumulation, and weight loss is the most effective way to promote fat removal.[19]

Normalweight subjects with NAFLD ("lean" NAFLD) constitute another area of great interest in NAFLD studies, and particularly challenging as to diagnosis and treatment. Their liver fat accumulation is expected to derive from a genetic background, prone to hepatic steatosis, prevailing over a healthy dietary intake, and associated with insulin resistance. Notably, these subjects are reported to have a poorer prognosis than overweight/obese NAFLD.[20]

Healthy vs. unhealthy diet

Among different nutrients, the relative proportion of fat and carbohydrates and the use of specific dietary sources have attracted a lot of attention.

A few studies have tested the association between fat intake and liver fat using food frequency questionnaires (FFQs), suffering from several limitations, from incomplete memory to incorrect estimate of portion size. In general, FFQs indicate that high dietary fat intake, particularly high habitual fat intake, increases the risk of NAFLD, but the confounding effect of increased calorie intake has never been ruled out.[21] Intervention studies, where fat intake was quantitatively or qualitatively modulated, also suffer from several limitations. In this case, the composition of the previous diet, the relative difference between the experimental and the habitual diet, and the length of dietary supplementation may make the difference. In a 4-week experiment, differences in liver fat content were observed in subjects fed either a diet with a high- or a low-total and saturated fatty acids (SFAs) content, without significant differences in insulin sensitivity,[22] whereas diets rich in monounsaturated fatty acids (MUFAs) fat or n-6 polyunsaturated fatty acids (n-6 PUFAs) tend to reduce liver fat. Notably, overfeeding with SFAs increases liver fat more than overfeeding with n-6 PUFA,[23] and the effect is further increased in the presence of dietary fructose.[24] The underlying hypothesis is that SFAs, MUFAs and PUFAs may differently regulate adipose tissue inflammation and *de novo* lipogenesis [22], but the effects of diets may also differ in lean vs. obese subjects, with obese subjects more prone to postprandial endotoxemia leading to chronic low-grade inflammation.[25]

Foods rich in fructose are the prototype of unhealthy diet. Fructose, contained in fruits and some vegetables, is structurally similar to glucose; it is mostly metabolized in the liver, and is fuel for *de novo* lipogenesis. The most abundant source of dietary fructose is the high fructose corn syrup (HFCS), used to enrich beverages and processed foods. The intake of HFCS-enriched foods has been linked to the obesity epidemics and to cardiometabolic-related diseases, including NAFLD. Soft drink consumption is associated with a higher risk for ultrasonography- or magnetic resonance imaging-assessed liver fat,[26, 27] and drinking more than six HFCS-enriched soft drinks/day increases the severity of steatosis and promotes fibrosis,[28] through mechanisms depicted in Figure 2. However, the deleterious effects of fructose on metabolic disturbances – obesity, hypertriglyceridemia, diabetes, uric acid, insulin resistance – are probably limited to subjects eating hyper-caloric diets.[29] High intake of fructose has been associated with the metabolic syndrome and NAFLD *via* insulin

resistance and increased *de novo* lipogenesis. There is also evidence that industrial fructose from processed foods and beverages may have a specific deleterious effect on the liver.[30] Consistent with these data, any reduction in industrial fructose intake improved metabolic syndrome in obese individuals, irrespective of dietary fruit consumption.[31] Differences between fructose sources may stem from the several healthy nutrients also present in fruit, having cytoprotective and antioxidant properties, compared to the unhealthy dietary styles associated with HFCS intake, including harmful SFAs and processed foods. The underlying biological mechanisms need further investigation, but they globally confirm the safe and healthy use of fruit in the Mediterranean diet, whereas HFCS should be excluded, also contributing to hypercaloric diet.

Physical activity and sedentariness

Physical activity regulates triglyceride turnover and, indirectly, liver fat, independent of weight loss. Both aerobic exercise and resistance training, without any calorie restriction, decrease intrahepatic triglycerides, possibly via enhanced whole-body and hepatic insulin sensitivity, increased whole-body lipid oxidation and decreased hepatic FFA uptake.[32] Notably, aerobic exercise elicits larger effects than resistance exercise, requiring larger volumes and intensities in NAFLD, although positive effects are also reported.[33] Certainly, any volume and intensity of physical activity, including leisure time and non-exercise activity is important to decrease the burden of triglycerides to and in the liver, compared with the time spent sedentary.

Diet and physical activity for NAFLD treatment *via* weight loss

The above pathophysiological considerations and the association of NAFLD with MetSyn, having abdominal obesity as the pivotal feature, point to weight loss and weight gain as the clinical features more strictly associated with NAFLD incidence and remission.[19] Accordingly, any recommendation on NAFLD treatment includes weight loss as background therapy, before or in addition to any pharmacologic intervention.[34, 35] However, achieving weight loss in the community is not easy; most patients report a long series of dieting and weight cycling, and the final effect on NAFLD outcome is uncertain.

Dietary restriction is the most effective way to reduce liver fat; a 5% reduction in BMI is accompanied by 25% reduction in liver fat on magnetic resonance imaging measurement,[36]

up to complete normalization of hepatic triglyceride content in a few weeks under a strictly hypocaloric diet. The optimal composition of the diet has been the subject of an intense search, and both low-fat and low-carbohydrate diets have been proposed. As demonstrated in obesity,[37] the macronutrient composition is scarcely important as long as calorie restriction is maintained.[38] Possibly, food choices based on the Mediterranean diet might be of additional help, considering the beneficial effect on cardiovascular outcomes.[39]

Physical activity is less important for weight loss; the daily amount of calories that may be burned by physical activity is limited compared with the calorie deficit achievable by dietary restriction. However, also physical activity *per se* may slowly reduce weight, as well as abdominal obesity[40] and hepatic fat,[41] and may be promoted in subjects non-compliant to dietary recommendations,[42] or may be combined with diet from the very beginning of behavior treatment, to improve outcome. Habitual exercise becomes mandatory during the weight loss maintenance phase. Unfortunately, the majority of individuals find it difficult to modify their diet, and even more difficult to attain the amount of exercise necessary for weight loss and long-term weight control. This problem is compounded by the fact that many physicians, despite their being well aware of the importance of exercise and healthy diet, have received no training on effective communication with patients in order to facilitate persistent lifestyle change.

Lifestyle modification intervention for NAFLD treatment

NAFLD patients can be encouraged to initiate and maintain lifestyle modifications aimed at weight loss using simple motivational and cognitive behavioral strategies and procedures. Lifestyle modification programs have three main components: (i) dietary recommendations, (ii) physical activity recommendations, and (iii) cognitive-behavioral therapy to address weight loss and weight maintenance obstacles.[43] Weight loss recommendations have been recently revised (Table 1);[44] while there is general agreement that the weight loss phase should last about six months, as after this period weight loss reaches a plateau, no definite data are available about the optimal duration and intensity of the weight maintenance phase,[37] but at least one-year follow-up is recommended.[44]

The strategies and the resources necessary to achieve patients' compliance are not available in most hepatological centers, and the possibility to address patients to metabolic units equipped with expert multidisciplinary teams has been previously suggested to increase

treatment outcomes.[45] Engaged patients should be referred to trained lifestyle modification counselors (e.g., dietitians, psychologists, physical activity supervisors, case managers),[46] working closely with the physicians to implement full lifestyle modifications, according to the principles of behavior therapy (Table 2).[47, 48] They are derived from the transtheoretical model and motivational interviewing,[49] and may be used for engaging NAFLD patients to start a weight loss lifestyle-based program,[47, 50] addressing both weight loss and weight maintenance obstacles (Table 3).[43, 48]

The crucial issue is motivation; most NAFLD patients do not perceive their condition as a disease, and their stage of change and motivation towards healthy diet and, particularly, towards habitual physical activity is low.[51] Multiprofessional teams trained in cognitive behavioral therapy are thus needed to support patients during the program and to tailor the program according to patients' specific needs. The most recent developments in weight loss lifestyle modification programs have made some steps to personalize treatment delivery by introducing individual sessions with a case manager,[52] and including procedures most likely to favor patients' motivation and adherence.[47]

Strategies to improve adherence

Adherence to the reduced caloric intake may be enhanced by increasing diet structure and limiting food choices, thereby reducing temptation and the potential mistakes in the assessment of energy intake.[43] A strategy to increase the diet structure is to provide patients with meal plans, grocery lists, menus, and recipes. This strategy is supported by a study showing that the provision of both low-calorie food (free of charge or subsidized) and structured meal plans – including liquid meal replacements or portion-controlled servings of conventional foods – results in greater weight loss than an unstructured diet.[53]

Unlike diet adherence, exercise adherence tends to increase the less structure is imposed, presumably *via* a reduction in the barriers to exercising (e.g., lack of time or financial resources).[47] Most patients practice larger amounts of physical activity if instructed to do so at home than if asked to attend on-site, supervised, group-based exercise sessions.[54] Also increasing daily activities (e.g., using stairs, walking, and reducing the use of labor-saving devices) can reduce weight similar to structured exercise programs, but provides greater weight maintenance over time.[55] It might be helpful to suggest multiple short sessions of

exercise, as opposed to long workouts,[56] and/or to engage patients in pleasant, leisure-time activities (e.g., dancing), to limit attrition.[57]

Clinical results

Several studies have tested the effectiveness of lifestyle modifications in NAFLD (Table 4);[58-73] only a few are based on solid behavioral strategies, not simply on intensive counseling for healthy diet and habitual physical activity. Overall, 7-10% weight loss is achieved in the majority of cases, accompanied by a remarkable normalization of liver enzymes and a systematic reduction of liver fat, measured by either surrogate algorithms or ultrasonography or magnetic resonance imaging. The clinical significance of hepatic fat clearance is however uncertain, considering that necroinflammation and fibrosis, not steatosis, regulate liver disease progression, and fibrosis dictates the final outcome.[74] The possibility that liver fat may drive cardiovascular mortality *via* T2DM development needs further investigation.

Following a series of controlled and uncontrolled studies, in an ancillary part of the Look AHEAD (Action for Health in Diabetes) Study,[64] the participants randomly assigned to an intensive lifestyle intervention lost significantly more weight, had a greater reduction in steatosis and a reduced likelihood of developing NAFLD than subjects receiving standard diabetes support and education. A proof-of-concept study in 31 biopsy-proven NASH tested the effectiveness of intensive behavior treatment *vs.* standard counseling for 48 weeks.[65] By the end of treatment, the participants lost on average 9.3% of initial body weight in the intensive arm vs. 0.2% in the control group and 72% vs. 30% of participants met the primary outcome (≥3-point improvement in NASH histological activity score (NAS) or post-treatment NAS ≤2). Notably, the participants who achieved the 7% weight loss goal, irrespective of treatment arm, had a significant improvement in steatosis, lobular inflammation, ballooning injury and NAS, with minimal changes in fibrosis.

More recently, the association between the magnitude of weight loss through lifestyle modifications and changes in histologic features of NASH was tested in a prospective study of 293 patients, at a tertiary medical center in Havana, Cuba.[73] Paired liver biopsies (baseline and 52-week follow-up) were available from 261 participants. Weight loss ≥5% was observed in 88 participants (30%). NASH resolved in 72 patients (25%), whereas NAS improved in 138 (47%), and 56 (19%) had regression of fibrosis. The probability to achieve NASH resolution was dependent on the amount of weight loss (58% in weight loss ≥5%;

90% in weight loss ≥10%); in this last subgroup 45% had regression of fibrosis. Therefore, lifestyle measures improve NASH provided that a substantial weight loss is achieved.

Notably, resolution of NASH may be similarly observed in subjects with massive weight loss after bariatric surgery. One year after surgery, 85% of morbid obese patients who lost on average 25% of their initial body weight had NASH resolution, with differences in relation to NASH severity (94% in mild NASH vs. 70 in severe NASH).[75] All necroinflammatory histological features were reduced, as was fibrosis in 34% of cases. Notably, the patients whose NASH did not regress at one-year had lost significantly less weight compared to subjects who had NASH resolution. Bariatric surgery is thus expected to become a standard treatment in morbid obese patients. It has been reported to produce beneficial effects on both the incidence of and the remission from high transaminase levels, proportional to the amount of weight loss,[76] curing NASH as well as T2DM by facilitating massive weight loss, and improving long-term survival.[77] More data are needed to define criteria for patients' selection, surgical treatment procedures, and clinical management to optimize the results and minimize risks.

Conclusion

Weight loss is a strategy of paramount importance in NAFLD management, but is rarely systematically pursued in individual patients using the most effective behavioral techniques and thus remains ineffective in a proportion of cases. The LookAHEAD study has been recently stopped because of failure to reach the desired targets of weight loss-induced reduction of cardiovascular mortality. This negative result has cast doubts on the behavioral treatment of overweight/obesity in the community,[78] where the long-term results of weight loss have never been systematically analyzed.

Several new drugs are under investigation to reach the same targets (agreed by regulatory Agencies) tested in weight loss studies (reduction of NAS score, no worsening of fibrosis). They might be particularly important in the non-negligible proportion of cases of "lean" NAFLD, where weight loss cannot be systematically pursued. The results of non-pharmacologic intervention provide solid data to compare drug safety and effectiveness, and for cost-effectiveness analyses.[79] The battle against metabolic diseases, largely fuelled by increased liver fat needs a comprehensive approach; healthcare professional must be ready to

change their mind and behavior, if they wish to be successful in modifying the behavior of their patients in an obesiogenic environment.

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Figure 1
Pathophysiology of liver fat accumulation in NAFLD

Legend for Figure 1
Dietary lipids, lipolysis of visceral fat and *de novo* lipogenesis differently contribute to the pool of lipids stored in the liver; lipolysis and *de novo* lipogenesis, strictly regulated by a number of hepatocellular nuclear receptors, account for the largest proportion of hepatic free fatty acids (FFA) pool. Hepatic FFAs are partly oxidized as energy sources, partly are stored as triglycerides and finally excreted as components of VLDL. The whole process is however unable to dispose of the excess fat, and triglycerides accumulate in the liver.

Abbreviations: FFA, free fatty acid; RXR, retinoid X receptor; LXR, liver X receptor; FXR, farnesoid X receptor; PPAR-α, peroxisome proliferator activated receptor α; PPAR-δ, peroxisome proliferator activated receptor δ; PPAR-γ, peroxisome proliferator activated receptor γ.

Figure 2
Mechanisms of fructose-induced liver damage

Legend for figure 2
Fructose is converted by fructokinase and. Fructose induces sterol regulatory element-binding protein 1c expression in the liver and prompts hepatic and extrahepatic insulin-resistance *via* fatty liver and visceral fat accumulation, but also amplifying insulin release and exhaustion of pancreatic β-cells *via* activation of the sweet taste receptors. Fructose metabolism by fructokinase to fructose-1-phosphate is rapid, not controlled by feedback regulation; its down-stream products become substrate for *de novo* lipogenesis and lead to massive ATP depletion and consequent increase in AMP levels. AMP is converted to uric acid a factor involved in the pathogenesis of metabolic disturbances including NAFLD/NASH, whereas ATP depletion is responsible for reduced triglyceride synthesis and increased toxic free fatty acids, exacerbating lipotoxicity. In addition, fructose enhances the generation of tissue advanced glycation end-products, prompting ROS production and hepatic stellate cell activation, and favors intestinal bacterial overgrowth and intestinal permeability, features leading to liver endotoxemia, toll like receptor activation and finally hepatic inflammation and fibrogenesis. Other mechanisms potentially linking fructose intake to NAFLD and liver damage are fructose-induced copper deficiency, fructose-related increase in lipocalin - a protein involved in acute phase response, immune response and apoptosis -, and impairment of liver autophagy. Fructose can also indirectly affect the risk of NAFLD and liver damage by modulating central appetite signaling, through changes in both peripheral (ghrelin and leptin) and hypotalamic (cannabinoid 1 receptor) appetite peptide levels, as well as an effect on brain satiety centers.

Abbreviations: HFCS: high fructose corn syrup.

Table 1
Dietary and physical activity recommendations for weight loss

Dietary recommendations [44]

1. restrict the overall calorie intake to 1200- 1500 kcal/d for women and 1500-1800 kcal/d for men;
2. produce a 500 kcal/d or 750 kcal/d energy deficit;
3. comply to one of the evidence-based diet that restricts certain foods (particularly, high-carbohydrate foods, low-fiber foods, or high-fat foods) in order to create an energy deficit by reduced food intake.
4. individualize the choice of calorie-restricted diet to the patients' preferences and health status.

Physical activity recommendations

1. help patients gradually achieve a level of physical activity sufficient to produce a calorie deficit of at least 400 kcal/day;
2. encourage patients to check their baseline number of steps using a pedometer and then to add 500 steps at 3-day intervals up to a target value of 10,000–12,000 steps/day;
3. Jogging (20–40 min/day), cycling, or swimming (45–60 min/day) may replace walking;
4. Resistance training may be superimposed or serve as an alternative for subjects who have physical limitations preventing aerobic training.

Strategies such as frequent self-weighing (at least weekly), consumption of a reduced-calorie diet, and high levels of physical activity (>200 min/week) are associated with better weight maintenance over time.

Table 2

General principles for enhancing motivation to lifestyle modification

a)	*Conceptualization of motivation*. Motivation is a dynamic entity, waxing and waning as a function of shifting personal, cognitive, behavioral, and environmental factors. Thus, a patient's motivation may require continuous attention to these factors throughout the course of treatment, not only during the engagement process.
b)	*Collaborative therapeutic style*. Clinicians should adopt a collaborative rather than a confrontational approach. Being kind and friendly, and showing interest and concern for the patient as a person, are appreciated by all patients, but are especially important when dealing with those suffering from NAFLD associated with obesity, as they frequently suffer from negative judgment by clinicians for their excess body weight and unhealthy behavior.
c)	*Functional analysis*. Clinicians should empower patients by eliciting, rather than providing, a functional analysis of the pros and cons of lifestyle changes, as change is facilitated by a sense of personal investment.[50]
d)	*Roll with resistance*. For similar reasons, and to avoid alienating the patient, clinicians should not address resistance with confrontation, but with a collaborative evaluation of the variables involved in maintaining the unhealthy lifestyle.[50]
e)	*Support self-efficacy*. In the evaluation interview, clinicians should promote self-efficacy by raising the hope that lifestyle changes can be attained. During the program, self-efficacy should be encouraged by designing an individualized diet and physical activity regime that patients are confident they will be able to achieve and stick to.
f)	*Educate patients*. Clinicians should educate patients about the benefits of weight loss and lifestyle modification on NAFLD management. Another strategy of promoting patients' engagement in treatment is also to give detailed written information about aims, duration, organizational procedures and the results of lifestyle modification.[47] In reluctant patients, it might be helpful to propose treatment as a sort of experiment of limited duration, leaving the door to old habits open should they fail to perceive a benefit after an agreed period of time.[47]

Table 3

Procedures for addressing weight loss and weight maintenance obstacles in a lifestyle modification program.

Procedures for addressing weight loss obstacles
– Self-monitoring
– Goal setting
– Stimulus control
– Practicing alternative behaviors
– Proactive problem solving
– Cognitive restructuring
– Involving significant others
Procedures for addressing weight maintenance obstacles
– Providing continuous care
– Encouraging patients to work on weight maintenance instead of weight loss
– Establishing weight maintenance range and long-term self-monitoring
– Building a long-term weight control mindset
– Devising a contingency plan
– Building a weight maintenance plan

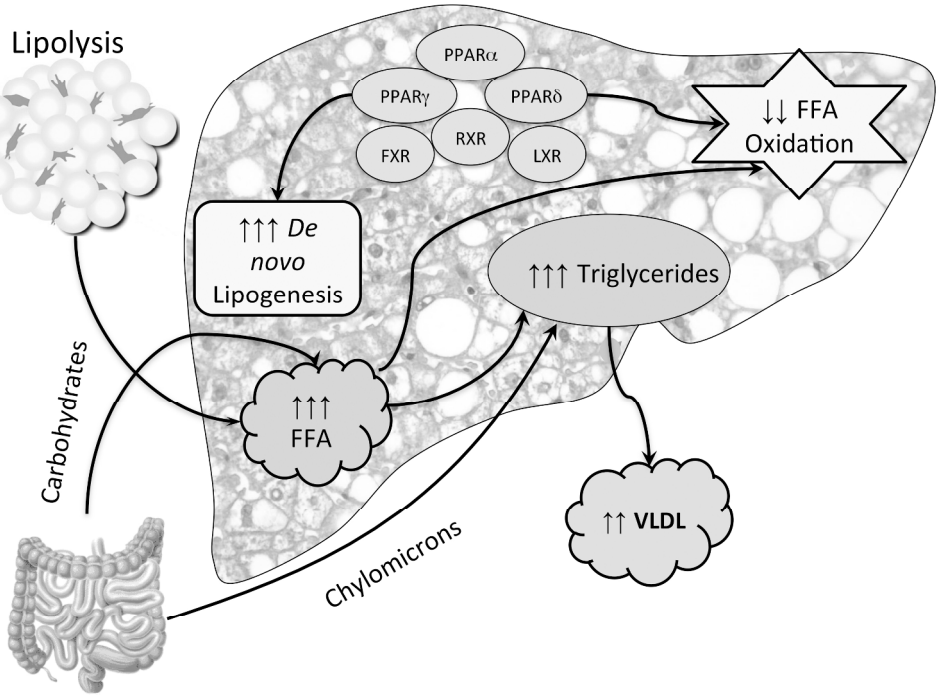
Table 4
Studies of lifestyle intervention in NAFLD

Author, year	Type of study	Patients	Experimental treatment (time)	Outcome measures	Results
Ueno, 1997 [58]	Controlled cohort study	25 obese NAFLD; 15 treated, 10 un-treated	Diet & exercise; (3-mo)	Weight loss, liver enzymes, histology	WL equal to 3 BMI units; improved liver enzymes and steatosis in the treated group
Hickman, 2004 [59]	Cohort study	10 NAFLD (3 with FUP biopsies)	Behavior therapy (3-mo treatment, 12-mo FUP)	Weight loss, liver enzymes, HRQL, histology	Reduced steatosis, HRQL, liver enzymes; WL maintenance associated with physical activity
Kantartzis, 2009 [60]	Cohort study	50 NAFLD + 120 controls	Intensive lifestyle intervention (9-mo)	Total, subcutaneous and visceral fat by MRI; liver fat by MRS; Cardiorespiratory fitness	Body and hepatic fat significantly decreased at FUP. Cardiorespiratory fitness (baseline and FUP) determines hepatic fat content
Oza, 2009 [61]	Cohort study	67 NAFLD (22 at FUP)	Home-base behavior therapy (6-mo)	Weight loss, biochemistry, abdominal CT scan	5-kg WL in completers; WL associated with reduced visceral fat and improved liver enzymes
St George, 2009 [62]	Randomized controlled study	152 NAFLD (3 groups of graded intensity and duration treatment, 1 control)	Low intensity (3 sessions, 1-mo); Moderate intensity (6 sessions, 10-wk)	Biochemistry, normalization of liver enzymes	Graded improvement in metabolic factors and liver enzymes according to duration and intensity of treatment. Likelihood of elevated ALT reduced by 70% in treated cases
Albu, 2010 [63]	Cohort LookAHEAD study	48 obese T2DM	Intensive lifestyle intervention (1-yr)	Biochemistry, insulin resistance; total, subcutaneous, visceral and hepatic fat by CT scan	10% WL and decrease in adipose tissue and hepatic fat at FUP. Metabolic improvements driven by changes in weight and hepatic fat
Lazo, 2010 [64]	RCT within the LookAHEAD study	96 T2DM (46 assigned to ILI; 50 to DSE)	Intensive lifestyle intervention (1-yr)	Biochemistry; intra-abdominal fat (steatosis = ≥5.5% IHTG at MRS)	WL and % decrease in IHTG significantly larger in ILI; reduced risk of NAFLD development in ILI (3% vs. 26% in DSE)

Promrat, 2010 [65]	Randomized controlled study	31 biopsy proven NASH (21 LS-treated, 10 CON)	Intensive lifestyle intervention (48-wk)	WL ≥ 7%, biochemistry; reduced NAS (≥3 points) or post-treatment NAS ≤ 2; NASH remission at histology	WL, 9-3% in LS vs. 0.2 in CON; NAS outcome reached in 72% vs. 30%; improved steatosis, ballooning and lobular inflammation in WL ≥7%, irrespective of treatment arm.
Moscatiello, 2011 [66]	Controlled cohort study	150 NAFLD (68 CBT-treated; 82 Diet)	Intensive lifestyle intervention (3-mo); 2-yr FUP	WL ≥7%, normalization of liver enzymes, insulin resistance, parameters of MetSyn. Data analyzed at 6-mo and 2-yr, adjusted for propensity score	Higher probability of WL target and normal liver enzymes in CBT, after adjustment for propensity and weight changes. Similar trend in the outcome goals of IR and MetSyn score. Effects are largely maintained at 2-yr FUP
Sun, 2012 [67]	Randomized controlled study	1087 US-diagnosed NAFLD (LS, 724; CON, 363)	Intensive lifestyle intervention; 6- and 12-mo FUP	WL and liver enzymes; energy intake ≤ 25-30 kcal/kg BW; PA ≥23 METs/h/wk + 4 METs of exercise. Visceral fat by CT	WL larger in LS (11.6% vs. 0.4% in CON); liver enzymes, IR and parameters of MetSyn better in LS vs. CON at 6- and 12-mo. Reduced VFA in LS at 12-mo.
Eckard, 2013 [68]	Randomized controlled study	56 biopsy-proven NAFLD (4 groups with variable diet and exercise intensity)	Low-fat diet (20% fat) + exercise; moderate fat/low-CHO (30% fat) + exercise, and exercise only vs. standard care (6-mo FUP)	WL, biochemistry, body composition (DXA) and histology (NAS score)	Only 41 cases at FUP. No subgroup achieved a WL ≥5% and no systematic differences between groups were observed. High risk of type-2 error. NAS decreased in all subgroups over the 6-month period and there was a significant decrease in pre to post NAS and in the patients as a whole ($p < 0.001$). No changes in DXA.
Scaglioni, 2013 [69]	Cohort study	12 NAFLD patients	Intensive lifestyle intervention (3-mo)	WL, biochemistry, IR, PA (ArmBand ®), liver fat content (scores and DPI)	WL, 8% at FUP; modest increase in daily PA; significantly reduced liver enzymes and decreased total hepatic fat content
Hickman, 2013 [70]	Randomized controlled study	21 NAFLD (18 with NASH at baseline)	8 treated with diet (DT), 13 treated by circuit exercise (CE) (6-mo)	WL, IR (tracer methodology), adiposity (CT scan), histology	WL, 10% in DT vs. unchanged in CE. Steatosis and NAS were reduced in DT, unchanged in CE. Steatosis reduction associated with WL
Yoshimura, 2014 [71]	Randomized controlled study	33 subjects with visceral adiposity	Calorie restriction (CR, 18), calorie restriction +	WL, body composition (DXA), visceral adiposity (CT scan), biochemistry, physical	WL and reduction of fat mass, visceral adiposity and hepatic fat not different between groups; physical fitness improved in EX

			exercise (EX, 300 min/wk, 15)(12-wk)	fitness (VO2max), PA (accelerometer)	
Wong, 2013 [72]	Randomized controlled study	154 NAFLD identified during a screening program	Intensive lifestyle intervention (LS, 77; standard care (SC, 77)(12-mo)	NAFLD remission (IHTG <5.5% at MRS), WL, biochemistry, changes in liver stiffness (Fibroscan)	NAFLD remission, 64% in LS vs. 20% SC; WL much larger in LS. NAFLD remission + ALT normalization, 39% in LS and 7% in SC. Changes in liver stiffness larger in LS
Vilar-Gomez, 2015 [73]	Cohort study	293 biopsy-proven NASH (261 with FUP biopsies)	Intensive lifestyle intervention (12-mo)	NASH resolution without fibrosis worsening; NAS improvement (≥2 points); improved histological lesions (≥1 point)	NASH remission, 25%; NAS reduction in 47%, regression of fibrosis in 19%. WL ≥5% in 30%. NASH remission dependent on WL and disease severity (presence of risk factors.

Abbreviations: ALT, alanine transaminases; BMI, body mass index; BW, body weight; CBT, cognitive-behavior therapy; CE, circuit exercise; CHO, carbohydrates; CON, controls; CR, calorie restriction; CT, computed tomography; DPI, Doppler power index; DSE, diabetes support & education; DT, diet treatment; DXA, dual-energy X-ray absorptiometry; EX, exercise; FUP, follow-up; HRQL, health-related quality of life; IHTG, intra-hepatic triglyceride; ILI, intensive lifestyle intervention; IR, insulin resistance; LS, lifestyle; MET, metabolic equivalent; MetSyn, metabolic syndrome; MRS, magnetic resonance spectroscopy; MRI, magnetic resonance imaging; NAS, NAFLD activity score; PA, physical activity; RCT, randomized controlled study; SC, standard care; T2DM, type 2 diabetes mellitus; VFA, visceral fat adiposity; WL, weight loss.



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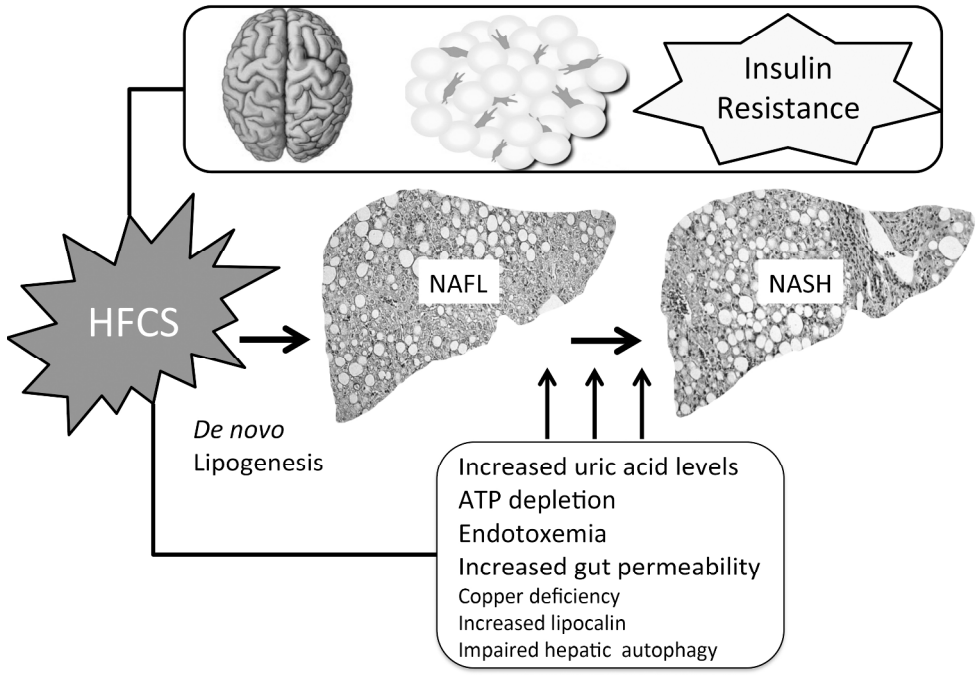

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