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Obesity and nonalcoholic fatty liver disease: From pathophysiology to therapeutics

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ABSTRACT

The obesity epidemic is closely associated with the rising prevalence and severity of nonalcoholic fatty liver disease (NAFLD): obesity has been linked not only with simple steatosis (SS), but also with advanced disease, i.e., nonalcoholic steatohepatitis (NASH), NASH-related cirrhosis and hepatocellular carcinoma. As a consequence, apart from increasing all-cause mortality, obesity seems to increase liver-specific mortality in NAFLD patients. Given the lack of approved pharmacological interventions for NAFLD, targeting obesity is a rational option for its management. As the first step, lifestyle modification (diet and exercise) is recommended, although it is difficult to achieve and sustain. When the first step fails, adding pharmacotherapy is recommended. Several anti-obesity medications have been investigated in NAFLD (e.g., orlistat, glucagon-like peptide-1 analogs), other anti-obesity medications have not been investigated (e.g., lorcaserin, phentermine hydrochloric, phentermine/topiramate and naltrexone/bupropion), whereas some medications with weight-lowering efficacy have not been approved for obesity (e.g., sodium-glucose cotransporter-2 inhibitors, farnesoid X receptor ligands). If the combination of lifestyle modification and pharmacotherapy also fails, then bariatric surgery should be considered in selected morbidly obese individuals. This review summarizes best evidence linking obesity with NAFLD and presents related therapeutic options.

Contents

Abbreviations: AASLP, American Association for the Study of Liver Diseases; AGB, adjustable gastric banding; AISF, Italian Association for the study of the Liver; ALT, alanine transaminase; APWP, Asia-Pacific working party; BMI, body mass index; CT, computed tomography; CVD, cardiovascular disease; DPP, dipeptidyl peptidase; EASD, European Association for the Study of Diabetes; EASL, European Association for the Study of the Liver; EASO, European Association for the Study of Obesity; F, fibrosis stage; FFAs, free fatty acids; FXR, farnesoid X receptor; GLP, glucagon-like peptide; HCC, hepatocellular carcinoma; HSCs, hepatic stellate cells; IL, interleukin; IR, insulin resistance; NHANES, National Health and Nutrition Examination Survey; LFTs, liver function tests; MetS, metabolic syndrome; MHO, metabolically healthy obese; MONW, metabolically obese normal weight; MUHO, metabolically unhealthy obese; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; NAFLD, nonalcoholic fatty liver disease; NAS, NAFLD activity score; NASH, nonalcoholic steatohepatitis; PPAR, peroxisome proliferator activated receptor; RBP, retinol-binding protein; RCT, randomized controlled trial; RYGB, Roux-en-Y gastric bypass; SGLT, sodium-glucose cotransporter; SPPARMs, selective PPAR-γ modulators; SS, simple steatosis; T2DM, type 2 diabetes mellitus; Th, T-helper lymphocytes; TNF, tumor necrosis factor; Treg, T-regulatory cells; TZDs, thiazolidinediones.

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1. Introduction

Obesity is a global health problem: it has been estimated that approximately 1.5 billion adults worldwide are overweight, among them about 200 million men and 300 million women are obese [1]. Even more alarming is the increasing trends in the prevalence of obesity in children and adolescents in developed and developing countries, leading to adverse effects in terms of both physical and mental health [2]. WHO reports an abrupt increase in global childhood obesity, from 32 million in 1990 to 41 million in 2016 (http://www.who.int/end-childhoodobesity/facts/en). However, there is a deficiency of longitudinal data introducing measured anthropometry to capture trends in USA adult obesity for the same people over time [3].

Obesity leads to the development of metabolic syndrome (MetS) and comorbidities, including type 2 diabetes mellitus (T2DM), nonalcoholic fatty liver disease (NAFLD), hypertension, hyperlipidemia, chronic kidney disease, cardiovascular disease (CVD), obstructive sleep apnea, osteoarthritis and malignancies (e.g., breast, colon and prostate), leading to increased mortality observed in obese individuals [4]. In this regard, weight loss interventions (diet and exercise) reduce all-cause mortality in obese adults [5].

Apart from the life expectancy, obesity essentially burdens the healthcare systems. It is estimated to account for 0.7–2.8% of the total health-care costs of a country and that obese have medical costs 30% higher than those of normal weight individuals [6]. Noteworthy, the total health-care costs are projected to double every decade [7].

The increase in the prevalence and severity of NAFLD has been linked with the rising trends in obesity [8]. NAFLD includes simple steatosis (SS) and nonalcoholic steatohepatitis (NASH), which may advance to cirrhosis and hepatocellular carcinoma (HCC) [9]. NAFLD has currently become one of the main causes of chronic liver diseases in the industrialized world, with an estimated global prevalence of 25–30% worldwide, rising up to 90% in morbidly obese patients [10]. Moreover, since the early stages of NAFLD usually disclose no obvious symptoms, the prevalence of obesity-driven NAFLD and following morbidity can be considered one of the main health crises of the next decade [11,12]. Likewise, NAFLD-related mortality continues to increase, in contrast to decreasing trends in viral hepatitis-related mortality [13]. Its mortality has been attributed to hepatic diseases (i.e., cirrhosis, its complications and HCC) and extra-hepatic diseases, including chronic kidney disease, CVD, and malignancies [14]. Nevertheless, the needs for the noninvasive diagnosis and specific treatment of NAFLD remain unmet [15,16].

In this review, evidence linking obesity with NAFLD is summarized, with a special focus on clinical data. A synopsis of the pathophysiology of NAFLD is initially provided, followed by selected epidemiological studies and, finally, clinical trials targeting NAFLD by treating obesity are reviewed.

2. Obesity-driven Pathophysiology of NAFLD

The pathophysiology of NAFLD and its progression is induced by multiple factors, in a "multiple parallel-hit" model [17,18]; in this regard, numerous genetic and environmental factors ("hits") interplay in an individual basis. Each NAFLD patient has been dynamically affected by a different pathogenetic combination lifelong, a consideration with diagnostic and therapeutic challenges. These factors include, but not limited to: specific genetic polymorphisms (e.g., of patatin-like phospholipase domain-containing protein 3 gene, transmembrane 6 superfamily member 2 gene) and epigenetic modifications [19], diet (e.g., excessive fat and fructose) and lack of physical activity [20], obesity and insulin resistance (IR) [21], dysregulation of adipokines [22], lipotoxicity [23], endoplasmic reticulum stress and oxidative stress [18], dysbiosis of the gut microbiota [24] and endocrine disruptors [25]. Under the combined effect of some of these factors, which also cross-talk each other in a dynamic manner, lipids are initially accumulated in the hepatocytes leading to SS. If SS is not timely managed, the liver is infiltrated by immune cells, thereby an inflammatory process is added, a condition characterized as NASH [26]. Again, if inflammation is not timely managed, the disease is complicated by hepatic fibrosis in a subset of patients [17].

Obesity seems to play a role in both the initial process leading to SS, but also to its progression to NASH [21] (Fig. 1). An adipocyte-like function has been attributed to hepatocyte, when the capacity of adipose tissue to store excess energy is diminished, e.g., in common obesity or conditions lacking adipose tissue such as lipodystrophies [27]. In these cases, hepatocytes store the extra lipids, mainly in the form of triglycerides, leading to SS. More specifically, excess circulating free fatty acids (FFAs) availability resulting from accelerated lipolysis and reduced fatty acid uptake in subcutaneous adipose tissue could lead to ectopic fat accumulation (e.g., in the liver, skeletal muscle) and, subsequently, to multi-organ IR [28]. Thus, the main substrate for intra-hepatic triglycerides FFAs is derived from the diet (approximately 15%) and adipose tissue lipolysis (approximately 60%), but also from *de novo* lipogenesis within the hepatocyte from other sources (approximately 25%), such as carbohydrates [29]. By this way, fat is redistributed from normotopic to ectopic stores.

Lipotoxicity and glucotoxicity, two processes starting with the exposure of hepatocytes to high lipid and carbohydrate levels, respectively, play central roles in both the development of SS and the subsequent progression to NASH. In this regard, high fat and carbohydrate diet, usually observed in obesity, predisposes to SS and NASH. Pathophysiological mechanisms connecting lipotoxicity and glucotoxicity with SS and NASH include mitochondrial defects, endoplasmic reticulum stress and oxidative stress [23,30]. More specifically, the release of FFAs from dysfunctional and insulin-resistant adipocytes lead to lipotoxicity, which is induced by the ectopic accumulation of triglyceride-derived toxic metabolites and the consequent activation of inflammatory pathways, cellular dysfunction, and lipoapoptosis; the lack of hepatocyte capacity to dispose excess FFAs results in lipoapoptosis, an essential feature of NASH [31].

When obesity is not successfully managed at the stage of SS, an intra-hepatic inflammatory process starts, possibly as an unsuccessful counterregulatory effort to limit SS [21]. This process resembles the low-grade inflammation occurring within the adipose tissue of obese individuals [32,33]. During this process, the hepatic innate immune cells, including Kupffer cells, dendritic cells and hepatic stellate cells (HSCs) are activated and the liver is progressively infiltrated by immune cells, including neutrophils, monocytes, T-lymphocytes and mainly macrophages [34]. Within the liver, the immune cells release cytokines that intensify the inflammatory process, but also contribute to fibrotic

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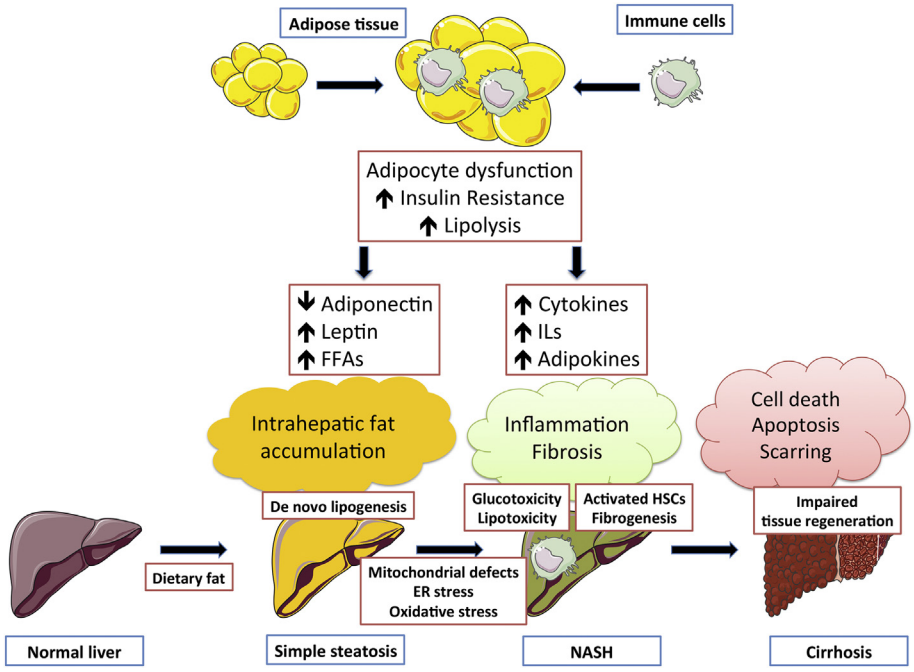

Fig. 1. Obesity-driven pathophysiology of NAFLD. The expansion of adipose tissue in obesity diminishes its ability to store excess energy. Adipocyte dysfunction and IR are increased, leading to lipolysis. Consequently, circulating FFAs and leptin increase, and adiponectin decreases, resulting in intrahepatic fat accumulation (SS), which is further amplified by the high dietary fat and carbohydrates (commonly observed in obesity), the latter increasing *de novo* lipogenesis. Upon the expansion of adipose tissue, it is also infiltrated by immune cells that produce cytokines and ILs. When obesity is not successfully managed at the stage of SS, immune cells also infiltrate the liver further contributing to a low-grade, but chronic intrahepatic inflammatory process. Lipotoxicity and glucotoxicity play central roles in both the development of SS and the subsequent progression to NASH. Mitochondrial defects, ER stress and oxidative stress link lipotoxicity and glucotoxicity with SS and NASH. When inflammation prolongs, fibrogenesis starts with HSCs as key players. Aggravation of fibrogenesis that may result in cirrhosis may represent an impaired mechanism of tissue regeneration, during which the replacement of hepatocytes subjected to cell death or apoptosis is unsuccessful. Abbreviations: ER, endoplasmic reticulum; FFAs, free fatty acids; ILs, interleukins; HSCs, hepatic stellate cells; IR, insulin resistance; NASH, nonalcoholic steatohepatitis; SS, simple steatosis.

process, which is usually appeared when the inflammation prolongs [22]. During fibrogenesis, the immune cells cross-talk with wound-healing cells, including activated endothelial cells, myofibroblasts and progenitor cells, within the liver.

Following liver injury, the aforementioned immune and wound healing cells are orchestrated targeting to tissue regeneration [35]. Under normal circumstances, this counterregulatory mechanism succeeds in the replacement of hepatocytes subjected to cell death or apoptosis. When this mechanism fails (e.g., in sustained obesity), fibrosis occurs, possibly as an unsuccessful effort against liver injury and tissue regeneration. Scar, i.e., cirrhosis, and neoplasia are the final results of persistent and exuberant responses of these processes. HSCs are the main cells responsible for liver fibrogenesis during chronic liver injury, by being activated and differentiated into myofibroblasts [36]. Myofibroblasts, in turn, express actin and diverse types of collagen, leading to extracellular matrix deposition and fibrosis. Likewise, activated HSCs induce granulocyte-macrophage colony-stimulating factor and interleukin (IL)-15 to prolong the survival of the neutrophils, which might further contribute to liver damage and fibrosis [37]. Moreover, transcriptomic profiling of obesity-associated NASH shows the existence of fibrosis-specific genes, a proportion of which are upregulated by activated HSCs [38].

Obesity also affects the liver through adipokines (e.g., leptin, adiponectin), hormones derived from the adipose tissue, which may contribute to SS, NASH, cirrhosis and carcinogenesis [22,39]. Adipokines are balanced in healthy normal weight individuals, but this balance is disrupted in obesity [21]. During the enlargement of adipose tissue, the secreted adipokines shift towards a more steatogenic, inflammatory and fibrogenic profile. Immune cells (macrophages, B-lymphocytes, T-lymphocytes and neutrophils), infiltrating adipose tissue during its enlargement, also produce ILs and classical cytokines (e.g., IL-1, IL-6, tumor necrosis factor [TNF]-α), which interplay with adipokines [22]. The balance between T-helper lymphocytes (Th)1/Th2-related cytokines is also essential, and lack or excess of pro-inflammatory cytokines in relation to deficiency of anti-inflammatory cytokines have been observed in the course of NASH in the liver and visceral adipose tissue [40]. Moreover, T regulatory cells (Treg) play an important role in regulating inflammatory processes in NASH, while Th17 may oppose Treg-mediated responses [41].

There is a continuous, dynamic antagonism between adipokines/cytokines with a favorable (e.g., adiponectin [42], obestatin [43]) and unfavorable (e.g., TNF-α, IL-6, chemerin, retinol-binding protein [RBP]-4, resistin) [22] effect on the liver; the former defending, whereas the latter promoting steatosis, inflammation and/or fibrosis [44]. However, the effect of adipokines is not always predictable, since it may be dual-faceted [45]. For example, leptin, the prototype adipokine, the circulating levels of which are positively associated with total fat mass, seems to have a different effect on the mice liver depending on the stage of NAFLD [46]. In this regard, leptin appears to exhibit an anti-steatotic action at the early disease stages, but it may also promote hepatic inflammation and fibrosis, when the disease progresses [47,48]. Although this hypothesis has not been as yet validated in humans, lower leptin levels were observed in controls, higher in SS patients and even higher in NASH patients [49], which may possibly imply an unfavorable effect of leptin on the disease progression.

Another example is adiponectin, which is paradoxically decreased, when visceral fat mass expands [42]. Noteworthy, hypoadiponectinemia is also associated with higher fat redistribution from normotopic to ectopic stores [50]. Adiponectin acts as an anti-steatotic, anti-inflammatory and anti-fibrotic adipokine [51,52]. In this respect, adiponectin inhibits pro-inflammatory cytokines (including TNF-α) and stimulates anti-inflammatory cytokines (e.g., IL-10), thereby resulting in inhibition of macrophage function and alleviates oxidative stress and fibrogenesis [53]. In humans, higher adiponectin levels were

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observed in controls, lower in SS patients and even lower in NASH patients [54], which are consistent with a favorable effect of adiponectin on NAFLD. Nonetheless, in NASH-related cirrhosis, adiponectin levels increase, which may be attributed to the decline in its hepatic clearance or a counterregulatory mechanism against the great increase of proinflammatory cytokines observed in cirrhosis [55]. However, owing to the aforementioned dual effect of adipokines, the effect of adiponectin may be inverted to unfavorable in NASH-related cirrhosis [45]. This unfavorable effect of adiponectin has been observed in other Mets-related diseases, including CVD, stroke and malignancies [56,57], although controversy still exists.

3. Epidemiological Studies Linking Obesity with NAFLD

Several studies have shown the close relationship of obesity with NAFLD, but also with advanced disease (NASH, NASH-related cirrhosis and HCC). There is a rise in the prevalence of NAFLD moving in parallel with the epidemics of obesity during the last two decades [10]: the prevalence of NAFLD has been increased globally from 15% in 2005 to 25% in 2010 [58], a trend paralleling the increasing prevalence of obesity [1]. Likewise, the prevalence of NASH has almost doubled within the same period [58]. This is also confirmed by more specific data from two cohort studies. A 6-year prospective study in China, showed that the age-standardized prevalence of obesity, overweight and NAFLD increased between 2007 and 2013 from 15.8% to 19.4%, 35.9% to 41.8% and 23.5% to 44.3%, respectively, in men, and from 13.2% to 18.8%, 31.1% to 37.5% and 17.6% to 43.1%, respectively, in women [59]. Importantly, a previous 12-year prospective Japanese study showed that BMI increase was associated with the onset of NAFLD, whereas BMI decrease with NAFLD resolution, notably, in both obese and non-obese individuals [60].

3.1. Obesity and NAFLD

Based on the aforementioned parallelisms in the epidemiology of obesity and NAFLD, it is not unexpected that the prevalence of NAFLD in obese individuals is higher than that of the general population (25–30% [61,62]), although it varies in different studies according to ethnicity, age, other predisposing factors, including T2DM, and, importantly, the method of diagnosis. In Asia-Pacific region, the prevalence of NAFLD in obese individuals ranges between 10% and 80%, with the lower prevalence in Korean (10–50%) and the higher in Japanese (50–80%) and Chinese (70–80%) [63]. In an Italian population the prevalence of NAFLD was 75.8% in obese and 16.4% in the normal weight, with a 4.6-fold higher relative risk in obese (Dionysos study) [64]. The prevalence of NAFLD was estimated to be 21.7% in overweight and 81.7% in obese Dutch [65] and 68% in US obese individuals [66]. The prevalence of NAFLD is even higher in morbidly obese patients, being over 90% in some studies [67–69].

The prevalence of NAFLD increases almost linearly with BMI, as shown in a Japanese population, being 10.5%, 37.9%, 58.4% and 84.2% in individuals with BMI <23, 23–25, 25–28 and ≥28 kg/m^2, respectively [70]. Likewise, in a large Korean cohort study, the incidence of NAFLD per 1000 person-years, after a 4.5-year follow-up of patients without NAFLD at baseline, showed an approximately linear relationship with BMI, being 4.9, 20.3, 52.9 and 85.9 for BMI categories of <18.5, 18.5–23, 23–25 and ≥25 kg/m^2, respectively [71].

Notably, obesity is independently linked with NAFLD, i.e., irrespective of other metabolic factors. In a large cohort study of approximately 77,500 metabolically healthy individuals without NAFLD at baseline, overweight (hazard ratio 2.2) and obese (hazard ratio 3.6) were at higher risk of NAFLD than normal weight individuals after a follow-up of 4.5 years [71]. The independent association between obesity and NAFLD has been validated by two meta-analyses, one consisting of 21 cohort studies [8] and another consisting of 21 observational studies, mostly case-control and cross-sectional [72]. In the former, obese had a 3.5-fold independently higher relative risk of NAFLD compared with lean individuals. Moreover, a dose-dependent association was shown, being 1.2 increase in relative risk of NAFLD per 1-unit rise in BMI [8]. The latter meta-analysis showed 2.9-fold and 2.3-fold higher odds ratios of NAFLD in persons with higher than lower BMI and waist circumference, respectively [72]. A dose-dependent association was also reported between BMI or waist circumference and NAFLD, being 1.3 and 1.1 increase in odds ratio of NAFLD per 1-unit rise in BMI and waist circumference, respectively [72].

By looking inversely, i.e., the rates of obesity within NAFLD and NASH, a meta-analysis has estimated that the pooled overall prevalence of obesity among NAFLD and NASH patient is 51.3% and 81.3%, respectively. Thus, it is verifying that obese constitute a high proportion of NAFLD patients [58]. This may also imply a potentially bi-directional association between NAFLD and obesity: obesity affects NAFLD, and NAFLD may also affect obesity via multiple mechanisms, including hepatic dysfunction, hepatic IR, oxidative stress, glucotoxicity and lipotoxicity [17].

Even more alarming is the prevalence of NAFLD in children and adolescents. A meta-analysis of 74 studies showed that the prevalence of NAFLD is 7.6% in children/adolescents in the general population, increasing to 34.2% in obese ones [73]. As in adults, NAFLD rates increase incrementally with BMI, being 2.3% in lean, 12.5% in overweight and 36.1% in obese children/adolescents. The odds ratio of NAFLD in overweight children compared with lean ones was 13.4 [73]. The incidence and prevalence of NAFLD seem to increase with greater rates in patients younger than 45 years vs. older patients, as shown in a study of US veterans [74]. These observations are alarming, because increasing rates of NAFLD in younger ages may be translated in higher rates of patients with advanced disease in the future [16]. A longitudinal study based on a large Danish registry, showed that BMI increases between 7 and 13 years was associated with NAFLD in adult life, even when adjusted for baseline BMI (hazard ratio 1.15 in men and 1.12 in women per 1-unit gain in BMI) [75]. The same group reported BMI at ages 7 and 13 years was associated with higher risk for liver malignancy overall (hazard ratio 1.20 and 1.30 per 1-unit BMI z-score, respectively) and HCC specifically (hazard ratio 1.18 and 1.33 per 1-unit BMI z-score, respectively) in adult life [76]. Data from the Cardiovascular Risk in Young Finns Study also showed that BMI in childhood/adolescence was an independent risk factor for adult NAFLD (odds ratio 1.3) [77]. Although it remains to be shown, the global rise in children obesity may result in a boost of NAFLD, including advanced disease in the near future.

A relevant issue deserving attention is the risk of NAFLD in the so-called metabolically "obese" normal weight (MONW), who are lean but metabolically unhealthy individuals [78]. This misconception is largely owing to the fact that the prominent classification of obesity is based on BMI. Current obesity guidelines fail to discriminate the management of metabolically healthy obese (MHO) or metabolically unhealthy obese (MUHO) or MONW, who have MetS risks, including NAFLD, despite being lean based on BMI classification [78]. Body composition may largely vary for a given BMI [79]. As a typical example, Asians have higher fat mass than Caucasians with the same BMI. This may implicate the comparative interpretation of NAFLD prevalence in Caucasians vs. Asians, thus different cut-offs should be properly used. This also highlights the established importance of waist circumference as a better than BMI index of central adiposity [21] and the need for re-classification of obesity based on waist circumference.

Given the above, a meta-analysis showed that lean patients with NAFLD had a worse metabolic profile than lean individuals without NAFLD, including larger waist circumference and higher IR, thus sharing common MetS risk factors with obese NAFLD patients [80]. However, the burden of MetS risk factors (e.g., IR, T2DM, hypertension) seems to be lower in MONW than obese NAFLD patients [80]. Importantly, the histological severity of hepatic lesions was shown to be significant in both obese and non-obese NAFLD patients, despite their phenotypic

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differences [81]. Furthermore, non-obese patients constitute a significant proportion of NAFLD patients in some pediatric series [82]. These issues are of clinical implication, since individuals with normal weight and BMI may have central obesity and NAFLD, whose risk may be misestimated. Noteworthy, treating NAFLD is equally important for MONW as for obese individuals, despite the lack of trials targeting specifically lean with NAFLD.

3.2. Obesity and NASH

NASH and hepatic fibrosis also increase with obesity. These associations are more crucial than those between obesity and NAFLD, given that NASH and significant fibrosis are associated with advanced disease and higher mortality rates [83]. More severe hepatic inflammation and fibrosis in obese than non-obese is a constant finding in the literature, validated by a recent study, in which obese vs. non-obese NAFLD patients had higher degree of NAFLD activity score (NAS), higher rates of hepatocellular ballooning, the hallmark of hepatic inflammation, and higher fibrosis stage [84]. These observations have been confirmed in a meta-analysis of 8 observational studies, in which overweight/obese NAFLD compared with lean NAFLD patients had more severe histological lesions, including NAS and fibrosis [85]. The risk of NASH was also lower in lean than overweight/obese individuals (odds ratio 0.6) [85].

In an early (late 1980s) autopsy study, NASH was reported in 18.5% of severely obese patients vs. 2.7% of lean ones [86]. Likewise, severe fibrosis was reported in 13.8% of the severely obese vs. 6.6% of lean individuals [86]. However, the rates of NASH seem to have been increased during the last three decades. In an Italian study, higher rates of NASH were observed in overweight/obese (40.9%) than normal weight (17.5%) individuals subjected to liver biopsy; the rates of significant fibrosis (fibrosis stage [F] ≥2) were also higher in the former (42.0%) than the latter group (17.5%) [87]. In the aforementioned US study, the rates of NASH was 80% among obese subjected to liver biopsy [66]. In morbidly obese, NASH has also been reported up to 65% of NAFLD patients [67–69]. Though this prevalence is much higher than the reported prevalence of NASH in the general population (3–5%) [88], it should be underlined that this may be partly attributed to selection bias, since liver biopsy is usually performed in NAFLD patients with high suspicion of advanced disease.

There are some good prospective studies strengthening the association between obesity and progression to NASH or significant fibrosis. Obesity was more prevalent in patients with than those without fibrosis progression (86% vs. 27%, respectively) in a 5-year prospective study with paired biopsies on untreated NAFLD patients [89]. It is noteworthy that the only factor independently associated with fibrosis progression was BMI in this study [89]. BMI (when patients with cirrhosis were excluded), as well as T2DM were independent prognostic factors of the progression of fibrosis in another prospective study of NAFLD patients subjected to serial liver biopsies (range of follow up 1–21 years) [90]. A third 13-year prospective study with paired liver biopsies on NAFLD patients showed that weight gain >5 kg, higher IR and more pronounced hepatic steatosis during follow-up were associated with the progression of fibrosis [91]. The last observation is noteworthy, since it validates the parallel trends of hepatic steatosis and fibrosis in NAFLD, at least until the disease progresses to NASH-related cirrhosis.

The relationship between obesity, NASH and hepatic fibrosis has already met clinical implication: weight or BMI have been included in some algorithms for the noninvasive prediction of NASH [92,93] or advanced fibrosis. [94–96].

3.3. Obesity and NASH-related Cirrhosis

The prevalence of cirrhosis owing to NAFLD has doubled between 2001 and 2013 (from 80 to 161 per 100,000 US veterans), accounting for 18% of overall cirrhosis incidence [97]. It has been estimated that the rates of the NASH progression to advanced fibrosis (F3) or cirrhosis (F4) is 10–25% over 8–14 years [98]. A meta-analysis of 11 cohort studies showed that the annual fibrosis progression rate in NASH patients is 0.14, corresponding to one stage of fibrosis progression over 7.1 years [99]. Importantly, patients with SS and F0 at baseline had also an annual fibrosis progression rate of 0.07, corresponding to one stage per 14.3 years [99]. This renders SS a potentially evolving rather than a reportedly benign phenotype. It should be also underlined that cachexia, sarcopenia, ascites and/or edema, which are closely related with cirrhosis, may methodologically implicate the estimation of the effect of obesity on cirrhosis, since BMI or waist circumference are not regarded as suitable indices of adiposity in this case.

Obesity increases the risk of liver cirrhosis. In an early cohort study, with obese NASH patients followed-up for 4.5 years, 7.1% had advanced fibrosis or cirrhosis at baseline [100]. During the follow-up, 7.7% of patients with fibrosis developed cirrhosis [100]. In a UK prospective cohort study (Million Women Study), the adjusted relative risk of cirrhosis increased by 1.3 for each 5-unit rise in BMI of women followed-up for 6.2 years; noticeably, about 17% of all hospital admissions and deaths related to cirrhosis were attributed to obesity [101]. In another 5-year cohort study, overweight or obese patients with compensated cirrhosis at baseline were at higher risk of clinical decompensation than normal weight ones. More specifically, the rates of clinical decompensation were 15%, 31% and 43% in lean, overweight and obese, respectively [102]. This risk was independent of liver function and portal pressure and seems to affect cirrhosis of all etiologies [102].

More data for the association of obesity with NASH-related cirrhosis are derived from studies with morbidly obese, whose best evidence is selectively presented hereby. In a systematic review, cirrhosis was diagnosed in 0–7% of morbidly obese undergoing bariatric surgery [69]. Advanced fibrosis (F3) and cirrhosis (F4) were reported in 6.1% and 6.1%, respectively, of morbidly obese NASH patients subjected to bariatric surgery; these rates corresponded to 1.6% and 1.6%, respectively, of the total cohort of morbidly obese of this study [103]. In another series, the rates of advanced fibrosis and cirrhosis were 8.3% and 5.6% within morbidly obese NASH patients, and 3.1% and 2.1%, respectively, within the total cohort [104]. In a third series, advanced fibrosis and cirrhosis was reported in 38.5% and 3.8% of morbidly obese NASH patients subjected to bariatric surgery, corresponding to 9.5% and 1.0% of the total cohort [105]. In a forth series, the rates of advanced fibrosis and cirrhosis were 29.4% and 3.9% within morbidly obese NASH patients, and 7.1% and 0.9%, respectively, within the total cohort [67]. Noteworthy, cirrhosis was unsuspected in all patients of the aforementioned studies with morbidly obese. This is rational, since a previous diagnosis of cirrhosis usually renders a patient not suitable for bariatric surgery.

Even more important is the estimation that NASH is the underlying disease in 30–70% of the cases of cryptogenic cirrhosis; however, the differential diagnosis of the underlying disease is usually difficult owing to the loss of hepatic steatosis, when NASH advances to cirrhosis [106], which occurs without significant weight loss [100]. Nevertheless, obesity and T2DM are more common (by about 2-fold) in patients with cryptogenic cirrhosis (cirrhosis of unknown origin) than cirrhosis of known etiology [107,108]. More recently, patients with NASH-related cirrhosis and cryptogenic cirrhosis were shown to share common characteristics, including similar BMI (34.8 and 33.6 kg/m^2, respectively), but cryptogenic was more aggressive than NASH-related cirrhosis [109]. Based on these findings, cryptogenic cirrhosis has been proposed as a different phenotype of NAFLD spectrum [109].

3.4. Obesity and NASH-related HCC

Obesity has been associated with cancer in general and HCC in particular [110,111]. It has been estimated that overweight and obesity account for 14% and 20% of all deaths from cancer in men and women, respectively, in the USA [111]. The rates of HCC are higher in obese than lean individuals, thus obesity was shown as a major contributor

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to HCC in patients with cryptogenic cirrhosis [112]. NAFLD has been estimated to account for 8–14% of HCC incidence in the US veterans, being relatively stable between 2011 and 2013 [97,113]. Similar contribution of NAFLD to HCC incidence was reported in a European population (12%), but its rates were increasing from 2.6% to 19.5% between 1995 and 2014, an increase following the temporal trend in metabolic risk factors, including overweight/obesity (from 34% to 52% in the same time frame) [114]. It is noteworthy that HCC could be developed in patients with NASH even in the absence of cirrhosis [113–115], thereby rendering NASH management of paramount importance.

It was early reported that obesity and T2DM were more common in patients with NASH-related HCC (41% and 50%, respectively) compared with HCC patients of other etiology (16% and 20%, respectively) [116]. In a meta-analysis of 11 cohort studies, higher relative risk of liver cancer was observed in both overweight (1.2) and obese (1.9) compared with lean individuals [117]. Specifically for HCC, higher adjusted relative risk of HCC (1.4) was shown in individuals with higher BMI in a 12-year prospective cohort study [118]. In another 9-year prospective cohort study, indices of obesity, including BMI, waist circumference, hip circumference and waist-to-hip ratio were positively associated with HCC [119]. Among all indices, waist-to-hip ratio showed the strongest association with HCC (relative risk between extreme tertiles 3.5) in this study. Besides, weight gain was associated with HCC (relative risk between extreme tertiles 2.5) [119].

It should be underlined that a higher percentage of patients with NASH-related HCC did not receive HCC surveillance in the 3 years before their HCC diagnosis and a lower percentage of them received HCC-specific treatment compared with patients with HCC of other causes [113]. This might be partly attributed to the notion that NAFLD is a generally benign disease, but should be taken into account by health care providers and policy makers.

3.5. Obesity, NAFLD and Mortality

NASH accompanied by obesity and MetS is more likely to progress to the development of end-stage liver disease leading to hepatic and extrahepatic mortality [120]. In this regard, obesity has been linked to higher mortality in NAFLD patients. In a 5-year prospective cohort study, higher rates of cirrhosis-related hospitalizations or deaths were observed in obese (adjusted hazard ratio 4.1) compared with lean nondrinkers without cirrhosis at baseline [121]. In an meta-analysis of 57 prospective studies, all-cause mortality (hazard ratio 1.3 per 5 kg/m^2 rise in BMI), liver-related mortality, owing mainly to cirrhosis (hazard ratio 2.2), as well as mortality from hepatic malignancies (hazard ratio 1.5) were shown to increase with increasing BMI [122]. Data from the third National Health and Nutrition Examination Survey (NHANES III) showed that obesity was independently associated with liver specific, but not overall mortality in NAFLD patients after about 14 years of follow-up [123]. The same group reported that BMI and waist circumference were independently associated with liver-specific mortality in NAFLD patient with and without elevated liver function tests, respectively, after 14 years of follow-up [124]. A more recent prospective study provided even more specific results for long-term major outcomes of obese NAFLD patients, showing that obese have more severe disease and a worst prognosis than nonobese NAFLD patients [84]. More specifically, during a 4-year follow-up, the rates of major events, including death, stroke, myocardial infarction, HCC and other malignancies, were overall higher in the obese than non-obese group (11.9% and 8.3%, respectively); notably, deaths (2.6%) and development of HCC (0.9%) observed only in the obese group [84]. Although the 20-year mortality of NAFLD-related HCC after liver resection in a European population was 36%, being similar to mortality of other major causes of HCC (i.e., alcoholic, hepatitis B and C) [114], the exact contribution of obesity to mortality of HCC remains to be shown. Likewise, despite increased comorbidities in patients transplanted for NASH-related cirrhosis, major morbidity, mortality and graft survival after 90 days were comparable to those of patients transplanted for other indications [125].

All the aforementioned considered, obesity is a major contributor and risk factor of NAFLD and it also increases the risk of advanced disease, including NASH-related cirrhosis and HCC. Except for increasing all-cause mortality, obesity increases liver-specific mortality. Based on these considerations, current guidelines suggest that follow-up for NAFLD is mandatory in obesity [126].

4. Targeting NAFLD by Treating Obesity

Despite the high prevalence of NAFLD worldwide and its associated morbidity and mortality, it is a seemingly paradox that there is no medication specifically approved for its treatment [15]. Given this lack of specific pharmacological interventions, targeting obesity through lifestyle modification remains the cornerstone of NAFLD management, as proposed by all guidelines [127].

The main target in the management of NAFLD is the resolution of NASH. Although it remains to be specifically shown, it is expected that successful NASH treatment may decrease the progression to advanced disease (i.e., cirrhosis and HCC) and decline NASH-related mortality [126]. Apart from the resolution of NASH, histological lesions defining NASH (i.e., steatosis and inflammation) and fibrosis are also endpoints of successful management. Specifically, fibrosis is a hard target, but also the main prognostic histological endpoint of advanced disease [83]. Weight loss results in the resolution of NASH and the surrogate histological lesions in a subset of patients. Resolution of NASH is achieved in 65–90% of patients achieving ≥7% weight loss [128]. It has been proposed that weight loss of ≥3% is needed to improve steatosis, ≥5% to improve inflammation and ≥10% to improve fibrosis [129].

Based on these observations and given that steatosis is a prerequisite for the subsequent hepatic inflammation and fibrosis [17], we have proposed that the prevention or resolution of SS might be a promising intervention to prevent from the subsequent development of NASH [130]. Thus, although it remains to be shown, SS seems to be an earlier and easier target in the management of NAFLD, which however requires the awareness of the physicians and the will of a preventive policy.

As for the management of obesity [131–133], a stepwise approach also seems to be appropriate for the weight management in NAFLD patients and is therefore suggested. Since there are not BMI cut-offs for the use of anti-obesity medications or bariatric surgery specifically in NAFLD, the same cut-offs recommended in common obesity could be adopted, until novel data guide us to tailor cut-offs specifically for NAFLD patients [131–133]. At the first step, the diet and exercise are recommended. When the first step fails to achieve the targets, the addition of pharmacotherapy is recommended in individuals with BMI ≥30 kg/m^2 or those with BMI ≥27 kg/m^2 and obesity-related comorbidities. If the combination of lifestyle modification and pharmacotherapy also fails, then bariatric surgery should be considered in selected individuals with BMI ≥40 kg/m^2 or those with BMI ≥35 kg/m^2 and obesity-related comorbidities [131–133]. Since NAFLD is an obesity-related comorbidity, the cut-offs of 27 kg/m^2 and 35 kg/m^2 may be considered for pharmacotherapy and bariatric surgery, respectively. Even lower BMI for Asian with NAFLD (32.5 kg/m^2) has been recommended as cut-off for bariatric surgery by the Asia-Pacific Working Party (APWP) [134]. Selected data on these three steps specifically in NAFLD patients are hereby summarized. Based on existing core evidence, an obesity-oriented algorithm for the management of NAFLD is presented in Fig. 2.

4.1. Step 1: Lifestyle Modifications

Clinical evidence for lifestyle modifications in NAFLD derives mainly from observational studies which only rarely have histological endpoints [20]. Characteristically, a relevant Cochrane database systematic review was not ended to a meta-analysis, because only one of the

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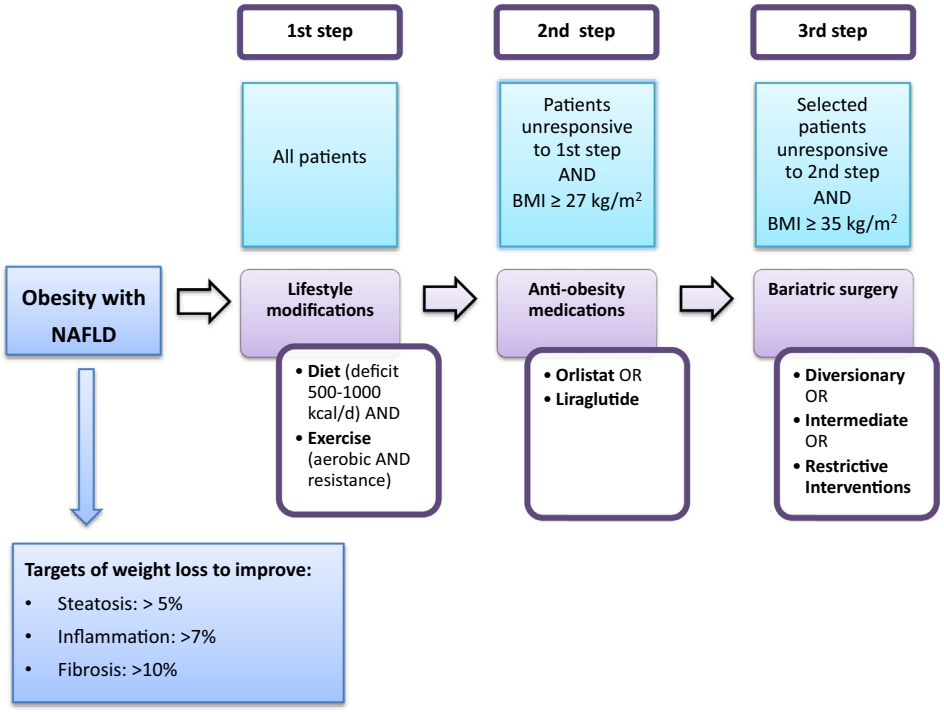

Fig. 2. An obesity-oriented algorithm for the management of NAFLD. At the first step, diet and exercise are recommended. When the first step fails to achieve the targets, the addition of pharmacotherapy is recommended in individuals with BMI ≥27 kg/m^2, since NAFLD is regarded as an obesity-related comorbidity. If the combination of lifestyle modification and pharmacotherapy also fails, then bariatric surgery should be considered in selected individuals with BMI ≥35 kg/m^2, again because NAFLD is considered to be an obesity-related comorbidity. Abbreviations: BMI, body mass index; NAFLD, nonalcoholic fatty liver disease.

included trials was considered to be of low risk of bias [135]. Another systematic review reported that the beneficial effect of diet and exercise on IR were evident only in overweight and obese individuals with NAFLD, thus indicating that weight loss is a major driver in improving IR and NAFLD indices [136]. An exercise oriented meta-analysis showed improvement in steatosis, even at an exercise level below that recommended for the management of obesity and even after achieving minimal or no weight loss [137]. Another meta-analysis of 21 trials also showed that exercise improved IR and steatosis, but not liver function tests (LFTs) [138], in contrast to other two meta-analyses showing exercise-related improvement of LFTs [139,140]. Importantly, one of them reported that the exercise was more beneficial in more obese individuals and its effect was not associated with the intensity of the interventions or the alterations in diet [140]. Regarding the type of exercise, current data are inconclusive for the superiority of aerobic or resistance training. One of the aforementioned meta-analyses reported a trend of aerobic exercise towards reducing steatosis more than resistance exercise [140]. Another meta-analysis reported similar efficacy of aerobic and resistance exercise to reduce steatosis [141]. However, intensity and energy consumption needed to achieve a similar result was lower for resistance than for aerobic exercise, thereby possibly rendering the former more suitable for NAFLD patients unwilling to participate in aerobic exercise or those with poor cardiorespiratory fitness [141]. Likewise, a meta-analysis of studies with children NAFLD indicated that exercise was effective to reduce abdominal and subcutaneous fat, and hepatic steatosis [142]. The effect of lifestyle interventions on NAFLD may be more effective in obese children than adults [140].

According to the: a) American Association for the Study of Liver Diseases (AASLD) [143], b) APWP [134], c) Italian Association for the study of the Liver (AISF) [144] and d) combined European Association for the Study of the Liver (EASL), European Association for the Study of Diabetes (EASD) and European Association for the Study of Obesity (EASO) [126] guidelines, structured programs are recommended combining a healthy diet and regular physical activity, targeting to a gradual weight loss of 7%–10% [126]. AASLD, AISF and EASL/EASD/EASO recommend a deficit of 500–1000 kcal/day, and the APWP a daily consumption of 1200–1600 kcal. The APWP do not favor any specific diet over the others [134], which is favored by two meta-analyses that did not show superiority of low carbohydrate or low fat diet on LFTs and hepatic fat content [139,145]. In line, it was supported that mainly calorie restriction and not the macronutrient composition drives the hepatic beneficial effect of a diet [146]. EASL/EASD/EASO [126] and AISF [144] favor the Mediterranean diet supporting that, apart from weight loss, it is beneficial for other MetS risk factors closely related with NAFLD (IR, T2DM, hypertension, CVD) [144].

A high-calorie diet, excess (saturated) fats, processed foods, refined carbohydrates, sugar-sweetened beverages, a high fructose intake and a Western diet should be avoided, whereas intake of fruits, vegetables, grains and omega-3 fatty acids are recommended [126]. Alcohol consumption >30 g/day for men and >20 g/day for women is discouraged, whereas coffee is not restricted [126]. Although the beneficial effect of low alcohol consumption remains debatable, some authors reported that modest alcohol consumption (0.5–1.4 drinks/day) was associated with lower, whereas alcohol consumption ≥1.5 drinks/day with increased all-cause mortality in NAFLD patients compared with abstinence from alcohol [147]. Other studies, however, reported than even modest alcohol consumption may be harmful in NAFLD patients [148]. Coffee and tea consumption may have a beneficial effect on NAFLD, including hepatic fibrosis [149], though more data are needed to reach safer conclusions. Both EASL/EASD/EASO [126] and APWP [134] recommend a gradual weight loss, because of a potential adverse effect of crash diets on NASH.

Regarding physical activity, all guidelines propose a combination of aerobic and resistance training [126,134,143,144], with minor differences, e.g., AASLD proposes at least 150 min/week of aerobic and resistance training [143] and EASL/EASD/EASO [126] propose 150–200 min/week in 3–5 sessions. It is recommended that the choice of diet and exercise should be tailored according to individual preferences, thus increasing the likelihood of long-term maintenance [126].

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4.2. Step 2: Addition of Pharmacological Interventions

Although lifestyle modifications are the cornerstone in the management of NAFLD, as mentioned before, they rarely accomplish and probably more rarely maintain considerable weight loss [126]. In this case, anti-obesity medications should be considered to add on diet and exercise. However, in most patients, anti-obesity medications result in weight loss <10% and then reach a plateau [150,151]. Therefore, they can rarely reach and retain the goal of 10% proposed for fibrosis resolution [129]. Another limitation of the pharmacological management of obesity is that most medications have not been approved for long-term use. However, since obesity is a chronic disease, like T2DM, long-term treatment is necessary to maintain the weight loss, otherwise, the discontinuation of medications leads to weight regain in the majority of patients [152]. Evidence on medications targeting obesity in NAFLD patients is summarized below and tabulated in Table 1.

4.2.1. Anti-obesity Medications Investigated in NAFLD

Approved anti-obesity medications having been investigated in NAFLD patients include orlistat and liraglutide, a glucagon-like peptide (GLP)-1 analog.

4.2.1.1. Orlistat. Orlistat has been approved as anti-obesity medication since 1998 and 1999 in the USA and Europe, respectively. It is the saturated derivative of lipostatin and acts by inhibiting gastrointestinal and pancreatic lipases, thus preventing the absorption of approximately one third of dietary triglycerides, thereby promoting weight loss. In a 6-month randomized controlled trial (RCT), orlistat (120 mg TID) decreased serum alanine transaminase (ALT) and ultrasonographic evidence of steatosis [153]. In a 6-month case series with obese NASH patients subjected to paired liver biopsies ($n = 14$), orlistat reduced weight, ALT and, noteworthy, steatosis in 10, inflammation in 11 and fibrosis in 10 of these patients [154]. Less encouraging were the results of another case series of obese NASH patients subjected to paired liver biopsy ($n = 10$): steatosis was reduced in 6, inflammation in 2 and fibrosis in 1 (whereas fibrosis worsened in another one) of these patients [155]. Finally, a 9-month RCT comparing vitamin E (800 IU daily) monotherapy with the combination of vitamin E and orlistat (120 mg TID) failed to show an additive effect of orlistat on NAFLD [156]. More specifically, LFTs, hepatic steatosis and inflammation, and NAS were similarly improved in both groups, possibly due to the fact that more weight loss was not achieved in the combination group compared to vitamin E monotherapy. When the patients were stratified according to weight loss instead of treatment group, IR and steatosis were improved in patients with weight loss >5%, and further improvement in inflammation, including ballooning, and NAS were observed in those achieving weight loss >9% [156]. This study implies that the improvement in hepatic histology is driven by weight loss and not orlistat. In a meta-analysis, orlistat was shown to improve BMI, LFTs and IR, but not liver fibrosis. Similar results were observed in patients with SS and NASH, thereby implying that orlistat might be used to improve LFTs and MetS parameters, but with limited efficacy on liver fibrosis [157].

Adverse effects of orlistat are usually mild-to-moderate gastrointestinal ones, including abdominal pain, oily spotting or stools, diarrhea, fecal urgency and incontinence, and flatus with discharge, owing to malabsorption of dietary lipids. Only rarely, cases of hepatic adverse effects (cholelithiasis, cholestatic hepatitis and subacute liver failure) and acute kidney injury have been reported [158], though the mechanism linking them with orlistat remains obscure. Orlistat may also interact with the absorption of fat-soluble drugs (e.g., warfarin, amiodarone, cyclosporine, thyroxine) and vitamins (A, D, E and K) [158].

4.2.1.2. Glucagon-like Peptide-1 Analogs. GLP-1 analogs, including exenatide, liraglutide, lixisenatide, dulaglutide, albiglutide and semaglutide, are mainly anti-diabetic medications [159]. Owing to their weight loss properties, liraglutide (3 mg subcutaneously QD) has been approved as anti-obesity medication since 2014 and 2015 in the USA and Europe, respectively. By activating the GLP receptors, GLP-1 analogs slow gastric emptying, decrease appetite, and increase postprandial satiety and fullness, beyond their insulin-stimulating and glucagon-inhibiting effects [159].

Liraglutide appears to decrease metabolic dysfunction, IR and lipotoxicity in the main organs contributing to the pathogenesis of NASH [160]. Liraglutide was initially administered in obese NAFLD patients with prediabetes at a lower dose (0.9 mg QD) than that later approved for obesity in a prospective uncontrolled study [161]. After a 5-month treatment, liraglutide reduced weight, LFTs, visceral fat and hepatic fat (evaluated by computed tomography [CT]). Notably, in a subgroup of patients ($n = 10$) that continued liraglutide treatment for about 2 years and were subjected to paired liver biopsy, NAS was improved in eight, remained stable in one and worsened in one patient, and fibrosis was improved in six, remained stable in three and worsened in one patient [161]. Later, in a 1-year phase 2 RCT in overweight/obese NASH patients with paired liver biopsies, definite NASH was resolved in 39% of patients in liraglutide group (1.8 mg QD) vs. 9% in placebo (relative risk 4.3). Moreover, higher rates of fibrosis progression were observed in placebo vs. liraglutide group (36% vs. 9%; relative risk 0.2) [162]. In another 6-month RCT, liraglutide (3 mg QD) was shown to be similarly effective with the combination of diet and aerobic exercise in reducing weight, hepatic fat (evaluated

Table 1
Potential effects of weight lowering medications on insulin resistance, ALT, NAS, and hepatic steatosis, inflammation and fibrosis in patients with NAFLD (data derived from clinical studies).

Medication	Insulin resistance	ALT	NAS	Hepatic steatosis	Hepatic inflammation	Hepatic fibrosis
Lipase inhibitors						
Orlistat	Decrease	Decrease	Unknown	Decrease	Decrease	No change
GLP-1 analogs						
Liraglutide	Decrease	Decrease	Decrease	Decrease	Possible decrease	Limited data
Exenatide	Decrease	Decrease	Limited data	Decrease	Limited data	Limited data
Lixisenatide	Limited data	Limited data	Unknown	Unknown	Unknown	Unknown
Dulaglutide	Decrease	Decrease	Unknown	Unknown	Unknown	Limited data
SGLT-2 inhibitors						
Dapagliflozin	Decrease	Decrease	Unknown	Decrease	Unknown	Limited data
Canagliflozin	Decrease	Decrease	Unknown	Unknown	Unknown	Unknown
Ipragliflozin	Decrease	Decrease	Unknown	Decrease	Unknown	Limited data
Empagliflozin	Decrease	Decrease	Unknown	Decrease	Unknown	Unknown
FXR ligands						
Obeticholic acid	Decrease	Decrease	Decrease	Decrease	Decrease	Decrease

Abbreviations: ALT, alanine transaminase; FXR, farnesoid X receptor; GLP, glucagon-like peptide; NAFLD, nonalcoholic fatty liver disease; NAS, nonalcoholic fatty liver disease activity score; SGLT, sodium-glucose cotransporter.

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by magnetic resonance imaging [MRI]) and ALT in obese NAFLD patients [163]. Similarly, liraglutide (1.2 mg QD) reduced weight, visceral fat, hepatic fat (evaluated by magnetic resonance spectroscopy [MRS]) and ALT levels in obese T2DM patients [164]. Data from a Canadian registry, showed that liraglutide reduced ALT levels in obese T2DM patients after a 5-month treatment, though did not remain robust after adjustment for weight loss [165]. When liraglutide was compared with metformin and gliclazide in NAFLD patients with T2DM in a 6-month RCT, all three medications reduced hepatic fat (evaluated by MRI), but the effect of liraglutide was greater with that of gliclazide [166]. As expected, when patients were stratified according to their weight loss, hepatic fat reduction was greater in those having lost ≥5% of weight. ALT and AST significantly decreased after liraglutide and metformin, but not gliclazide treatment, in this study [166]. On the contrary, another 4-month RCT did not show significant effect of liraglutide on hepatic fat (evaluated by MRS) and noninvasive indices of fibrosis in overweight/obese patients with T2DM [167]. The reasons for the conflicting results compared with the previous studies are unknown; however, it could be hypothesized that a 4-month treatment may be not sufficient for liraglutide to improve hepatic histology, especially fibrosis.

Apart from liraglutide, no other GLP-1 analog is currently approved for the treatment of obesity. However, there are few data regarding the hepatic effect of other GLP-1 analogs in obese with NAFLD. Based on a dynamic positron emission tomography study, exenatide was shown to decrease both hepatic and adipose tissue IR [168], which are regarded as key players in the pathogenesis of NAFLD [17]. In a prospective 7-month uncontrolled study with paired liver biopsies, exenatide (5–10 μg BID) provided variable results: NAS was improved in three of eight patients; fibrosis improved in four, remained stable in three and worsened in one patient [169]. In a 6-month RCT, exenatide reduced weight and hepatic fat (evaluated by MRS) more effectively than other standard anti-diabetic treatment [170]. Exenatide also appeared to be superior to metformin in reducing weight and LFTs after a 3-month treatment [171]. In a 1-year RCT, the combination of exenatide (10 μg BID) and pioglitazone (45 mg QD) reduced ALT and hepatic fat (evaluated by MRS) more effectively than pioglitazone alone, when added on metformin in obese T2DM patients [172]. Notably, the increase in weight observed in pioglitazone group was attenuated in the exenatide/pioglitazone group [172]. Furthermore, the combination of exenatide and insulin glargine was shown to decrease LFTs and reverse hepatic steatosis (evaluated by ultrasonography) more effectively than the intensive insulin therapy (insulin glargine and insulin aspart) in another 4-month RCT with obese with T2DM and NAFLD [173].

In a meta-analysis of 12 RCTs, lixisenatide improved ALT in patients with T2DM; importantly, this effect was shown to be limited only in overweight/obese patients [174]. In a 12-week uncontrolled study, dulaglutide decreased weight, ALT and, notably, liver stiffness (evaluated by transient elastography), a marker of hepatic fibrosis [175]. A large phase 2 RCT investigating the safety and efficacy of semaglutide specifically in NASH patients is currently running (NCT02970942).

The main adverse effects of GLP-1 analogs are gastrointestinal, including nausea, vomiting, diarrhea, constipation, dyspepsia, abdominal pain, flatulence and bloating. Despite the initial considerations, the risk of pancreatitis and pancreatic cancer does not seem to increase [176]. Contraindications for GLP-1 analogs include medullary thyroid carcinoma or type 2 multiple endocrine neoplasia, owing to a proliferative effect of liraglutide on thyroid C-cells shown in rodent studies [159].

4.2.2. Anti-obesity Medications Not Investigated in NAFLD

There are some more anti-obesity medications approved by FDA, which, however, have not as yet investigated in obese patients with NAFLD. They include lorcaserin, phentermine hydrochloric, diethylpropion, phendimetrazine, benzphetamine and the combinations phentermine/topiramate and naltrexone/bupropion. Their main effects and contraindications in obesity are summarized in Table 2. Given their weight loss effect, a beneficial effect on NAFLD is also expected and, therefore, starting clinical trials in obese patients with NASH is recommended.

4.2.3. Medications with a Weight-lowering Effect Not Approved for Obesity

There are also medications substantially reducing weight, such as the sodium-glucose cotransporter (SGLT)-2 inhibitors and the farnesoid X receptor (FXR) ligands, though they have not been approved as anti-obesity medications.

Table 2
Main mechanisms of action, weight loss effect, complications and contraindications of anti-obesity medications having not been investigated in patients with nonalcoholic fatty liver disease.

Medication	Main mechanisms of action	Mean effect on weight loss (%)	Main adverse effects (>10%)	Main contraindications
Phentermine[a]	Sympathomimetic amine suppressing appetite by acting in CNS	3–5%	Dry mouth, insomnia, dizziness, palpitations, flushing, fatigue	CVD, severe hypertension, glaucoma, hyperthyroidism, drug abuse
Diethylpropion[a]	Sympathomimetic amine suppressing appetite by acting in CNS	Not well established	Dry mouth, insomnia, constipation	CVD, severe hypertension, glaucoma, hyperthyroidism, drug abuse
Phendimetrazine[a]	Sympathomimetic amine suppressing appetite by acting in CNS	Not well established	Similar to those of phentermine and diethylpropion	CVD, severe hypertension, glaucoma, hyperthyroidism, drug abuse
Benzphetamine[a]	Sympathomimetic amine suppressing appetite by acting in CNS	Not well established	Similar to those of phentermine and diethylpropion	CVD, severe hypertension, glaucoma, hyperthyroidism, drug abuse
Lorcaserin	Selective $5HT_{2C}$ receptor agonist suppressing appetite and promoting satiety by acting in CNS	3–5%	Headache, upper respiratory tract infection, nasopharyngitis	Valvulopathy, pulmonary hypertension, severe renal disease, psychosis, suicidal ideation
Phentermine/topiramate	Phentermine: as above Topiramate: GABA agonist and glutamate antagonist suppressing appetite and promoting satiety by acting in CNS	4–8%	Dry mouth, paresthesia, upper respiratory tract infection, nasopharyngitis, constipation, headache	CVD, severe hypertension, glaucoma, hyperthyroidism, drug abuse
Bupropion/naltrexone	Bupropion: norepinephrine and dopamine reuptake inhibitor, and nicotinic acetylcholine receptor antagonist suppressing appetite and increasing EE by acting in CNS Naltrexone: mu- and kappa-opioid receptor antagonist preventing any orexigenic effect of bupropion by acting in CNS	3–6%	Nausea, vomiting, constipation, headache	Severe hypertension, seizures, bulimia or anorexia nervosa, opioid abuse

Abbreviations: $5HT_{2C}$, 5-hydroxytryptamine 2C; CNS, central nervous system; CVD, cardiovascular disease; EE, energy expenditure; GABA, gamma-aminobutyric acid.
[a] Approved for short-term use (<12 weeks) due to side effects.

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4.2.3.1. SGLT-2 Inhibitors. SGLT-2 inhibitors, including canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, ipragliflozin and luseogliflozin, have been introduced for the treatment of T2DM [159]. SGLT-2 inhibitors prevent the reabsorption of glucose at the nephron, thus the resulting glycosuria improves the glycemic control and leads to weight loss, which is more marked in patients with worse glycemic control and decreases as it improves [177].

Dapagliflozin improved visceral fat, LFTs and hepatic steatosis, and showed a trend towards improvement of liver stiffness (evaluated by transient elastography) in T2DM patients with NAFLD (mean baseline BMI 27.6 kg/m^2) in a 6-month RCT [178]. In another 6-month uncontrolled study in obese NASH patients with T2DM, dapagliflozin also decreased weight, visceral fat and LFTs [179]. In a retrospective study, the combination of dapagliflozin and metformin reduced ALT and weight more effectively than the combination of metformin and dipeptidyl peptidase (DPP)-4 inhibitors; notably, this result remain robust after adjustment for weight loss [180]. Data from the aforementioned Canadian registry, also showed that both dapagliflozin and canagliflozin reduced ALT levels in obese T2DM patients after a 5-month treatment, which remained robust after adjustment for weight loss [165]; greater ALT reduction was observed in patients with higher baseline ALT levels [165].

Canagliflozin decreased ALT in T2DM with abnormal ALT levels (mean baseline BMI 27.7 kg/m^2), but not in those with normal ALT levels (mean baseline BMI 24.7 kg/m^2) in a *post-hoc* pooled analysis of two studies [181]. A pooled analysis of six studies showed a lowering effect of canagliflozin on LFTs in T2DM patients [182]. A meta-analysis also showed a beneficial effect of canagliflozin on LFTs in T2DM patients [183]. However, a subgroup analysis for obesity was not performed in either study [182,183]. In a retrospective study, canagliflozin or ipragliflozin treatment for 6 months in T2DM patients with NAFLD (mean baseline BMI 29.6 kg/m^2) reduced weight, ALT and AST [184]. In a 6-month uncontrolled prospective cohort study, canagliflozin reduced weight, LFTs and FIB-4, a noninvasive index of hepatic fibrosis [185].

Ipragliflozin reduced hepatic fat (evaluated by CT) and LFTs similarly to pioglitazone in T2DM patients with NAFLD (mean baseline BMI 30.7 and 29.9 kg/m^2, respectively) in a 6-month RCT; nonetheless, weight, visceral and subcutaneous fat decreased only after ipragliflozin treatment [186]. Likewise, in a 4-month uncontrolled study in T2DM patients (mean baseline BMI 29.7 kg/m^2), ipragliflozin reduced weight and fatty liver index, a noninvasive marker of steatosis [187]. In another uncontrolled retrospective study, ipragliflozin, added on GLP-1 analogs or DPP-4 inhibitors, in T2DM patients with NAFLD and abnormal ALT (mean baseline BMI 30.1 kg/m^2) resulted in weight loss, and reduction in ALT and FIB-4 after a median treatment of about 11 months [188].

Empagliflozin reduced weight, hepatic fat (evaluated by MRI) and ALT in T2DM patients with NAFLD (mean baseline BMI 30.0 kg/m^2) in a 5-month RCT [189]. Luseogliflozin reduced weight and hepatic fat (evaluated by CT) more effectively than metformin in T2DM patients with NAFLD (mean baseline BMI 27.9 kg/m^2) in another 6-month RCT [190]. In a *post-hoc* pooled analysis of two studies, empagliflozin reduced ALT independently from weight loss, especially in those with high baseline ALT levels [191].

All the aforementioned considered, a beneficial hepatic effect of SGLT-2 has been shown in patients with NAFLD and T2DM, obese to the most. Nevertheless, more studies with histological outcomes are required in obese patients with NAFLD.

The main adverse effects of SGLT-2 are mycotic genitourinary infections, which seem to be commoner in women than men [159]. Symptoms of osmotic diuresis (e.g., polyuria, nocturia, thirst, dry mouth) or owing to low blood volume (e.g., postural dizziness, hypotension) may also occur. Notably, there is consideration regarding ketoacidosis, even with mild hyperglycemia in T2DM, although the mechanism has not been elucidated [159].

4.2.3.2. FXR Ligands. Apart from its central role in bile acid metabolism, the activation of the FXR regulates the expression of various genes, crucial for lipid, glucose and lipoprotein metabolism, thus being possibly important for NAFLD [192]. In this regard, FXR ligands, such as obeticholic acid, have emerged as promising candidates for the treatment of NASH. FXR are nuclear receptors, whose activation result in reducing bile acids synthesis and their toxic accumulation, but also in decline of IR, hepatic gluconeogenesis and *de novo* lipogenesis [15]. In a 6-week phase 2 RCT, obeticholic acid (25 or 50 mg QD) decreased IR, LFTs and weight (in a dose-dependent manner) in patients with T2DM and NAFLD [193]. This led to a 17-month RCT (Farnesoid X nuclear receptor ligand obeticholic acid for non-cirrhotic NASH [FLINT]) in NASH patients receiving obeticholic acid (25 mg QD), which showed a favorable effect on hepatic histology (steatosis, inflammation and fibrosis) together with a decrease in LFTs and weight loss [194]. Nevertheless, pruritus was observed in 23% of patients as well as an adverse effect in lipid profile, which tempered the positive results of the study [194]. More conclusive results are expected by a phase 3 RCT evaluating the effect of obeticholic acid on NASH patients with fibrosis (REGENERATE), which is about to end in 2022 (NCT02548351). Despite the substantial number of patent applications claiming steroidal and non-steroidal FXR agonists, numerous questions on their therapeutic potential in NASH and cholestasis remain open leaving an area for the development of novel therapeutic agents [195].

4.3. Step 3: Surgical Interventions

Bariatric surgery may be considered in selected morbidly obese NAFLD patient unresponsive to lifestyle modifications and pharmacotherapy, as proposed by AASLD [143], EASL/EASD/EASO [126] and APWP [134] guidelines. The goal of 10%, which is considered to improve hepatic fibrosis [129], is usually achieved after bariatric interventions, which, however, are amputational with potential complications [196]. Nonetheless, progressive weight regain has been observed after some types of bariatric interventions, especially the restrictive ones [196]. A network meta-analysis reported that, although all bariatric interventions result in more effective weight loss compared with standard care, diversionary and intermediate (diversionary/restrictive) interventions, albeit more amputational, were superior than purely restrictive ones in weight loss [197]. By comparing two widespread interventions, Roux-en-Y gastric bypass (RYGB), being intermediate, and adjustable gastric banding (AGB), being restrictive, the former leads to greater weight loss, but also to more adverse effects compared to the latter [197]. A more recent meta-analysis of cohort studies with morbidly obese NAFLD patients, reported that bariatric surgery resulted in resolution of hepatic steatosis, ballooning and fibrosis in 66%, 50% and 40% of patients, respectively [198]. We would like to selectively present hereby the core evidence for bariatric surgery in NAFLD.

In a 3-year retrospective study, sleeve gastrectomy resulted in the remission of NAFLD in 89% of patients [199]. Improvement or resolution of steatosis, fibrosis and NASH were reported in 92%, 66% and 81% of patients, respectively, subjected to bariatric interventions in a meta-analysis of observational studies; notably, the rates of complete resolution of NASH was 66% [200]. Another meta-analysis, specific for intragastric balloons, showed decrease in LFTs, steatosis and NAS six months post-surgery [201]. Favorable effects on LFTs and histological outcomes were also shown in another systematic review of observational studies with pooled analysis: the weighted mean decrease in the incidence of steatosis, ballooning, lobular inflammation and fibrosis were 50%, 68%, 51% and 12%, respectively [202]. More moderate results were reported in another systematic review of cohort studies: reduction in LFTs following bariatric interventions was reported in almost half of the cohort studies (11 of 21) [203]. More importantly, improvement in hepatic steatosis, inflammation and fibrosis were shown in 18, 11 and six studies, respectively. Noteworthy, worsening in fibrosis was also reported in four studies [203].

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Regarding the specific interventions, data from head-to-head comparisons are scarce, but RYGB may be superior to AGB, similarly to their aforementioned weight loss effects [197]. However, current data should be cautiously interpreted due to lack of randomization in most studies. Greater reduction in IR, NAS and steatosis were shown after RYGB than AGB in a large 5-year cohort study, which were evident at the first year and stable thereafter [204]. Nonetheless, similar rates of regression of bridging fibrosis were observed in those subjected to RYGB or AGB [204]. In another 1-year cohort study with morbidly obese NASH patients, the rates of NASH resolution was overall 85%, but higher rates were achieved after RYGB than AGB [205]. Specifically, patients subjected to AGB had higher rates of persistent NASH (30%) than those subjected to RYGB (8%) [205].

Regarding cirrhosis, limited data support that bariatric surgery decreases the risk of cirrhosis in NAFLD patients subjected to bariatric surgery. More specifically, in a US nationwide, retrospective study (2004–2012), the rate of subsequent cirrhosis was much lower in morbidly obese NAFLD patients subjected to bariatric surgery (1.5%) than those not subjected to bariatric surgery (11.1%) [206]. The same group, also reported lower rates of HCC in morbidly obese patients subjected to bariatric surgery than not (prevalence ratio 0.11), although this study did not include only NAFLD patients [207]. Nonetheless, there are considerations about patients with NASH-related cirrhosis subjected to bariatric surgery, which is diagnosed at the time of surgery in most cases. It has been proposed that the presence of cirrhosis at the time of bariatric surgery may be associated with higher peri-operative risks and mortality, especially in patients with decompensated cirrhosis [127]. There are cases of decompensation following bariatric surgery in patients with cirrhosis diagnosed at the time of surgery [208]. In a systematic review, higher than usual risk of complications and mortality were observed in patients with cirrhosis subjected to bariatric surgery (mostly diagnosed at the time of surgery) [209]. Collectively, complications were observed in 21% of patients, including liver decompensation (6.6%), early mortality (1.6%) and late mortality (2.5%) [209]. However, this systematic review included patients with cirrhosis of various diseases, i.e., not being specifically NASH-related. On the other hand, other authors did not observe higher post-surgery complications in NAFLD patients with F3/F4 compared with F1/F2 stages subjected to bariatric surgery [210]. However, it is underlined that the length of hospital stay was a little longer in the former group and, more importantly, only patients of the former group developed end-stage liver disease (4%) at one year post-surgery [210]. In another retrospective study, early complications occurred in 9 of 30 patients with NASH-related cirrhosis subjected to RYGB, most of them being minor, apart from one patient experiencing anastomotic leak [211]. Furthermore, one patient died within one year post-surgery owing to esophageal cancer [211]. Although more data are needed, in our opinion, there is need for careful pre-operative assessment, so as to exclude patients with cirrhosis, especially decompensated.

Considerations still exist about the potential worsening of hepatic histology following drastic weight loss after bariatric surgery. In the aforementioned meta-analysis, *de novo* or worsened NAFLD was shown in 12% of patients after bariatric surgery [198]. Specifically, in some morbidly obese patients, rapid weight loss preceded the onset of NASH [100]. Other authors reported that steatosis was reduced, but the incidence of lobular inflammation was increased after bariatric surgery [212]. There are also cases with advanced NASH occurring after rapid weight lost following bariatric surgery, who died or needed liver transplantation [213]. In our opinion, the close surveillance of patients may be the key to avoid the very rapid weight loss post-surgery, until more data clarify this issue.

Limited data have to-date assessed all-cause and liver-specific mortality in NAFLD patients subjected to bariatric surgery. In the aforementioned US nationwide study (2004–2012), the in-hospital mortality was lower in morbidly obese NAFLD patients subjected to bariatric surgery than in those who were not (incidence risk ratio = 0.08) [206]. In another retrospective study (Geneva cohort) with long-term follow-up (median 10 years), lower mortality was observed in morbidly obese subjected to bariatric surgery compared with propensity score–matched individuals of the NHANES III not subjected to bariatric surgery [214]. However, mortality was similar in NASH patients subjected to bariatric surgery compared with matched individuals [214]. Additionally, NASH was independently associated with all-cause mortality; patients with NAS ≥5 had higher mortality than patients with a NAS ≤2, and patients with F1 and F ≥ 2 had higher mortality than patients without fibrosis [214]. Although intriguing, this study did not prove that bariatric surgery *per se* is the cause of higher mortality, which may be attributed to the advanced disease itself. Further adequately powered, prospective cohort studies are required to clarify the effect of bariatric surgery on mortality in NAFLD patients, especially those with NASH.

Although more data are needed, individualized bariatric surgery may be suitable for selected morbidly obese NAFLD patients unresponsive to previous lifestyle modifications and pharmacological treatment. Recent data do not favor bariatric surgery in morbidly obese patients with NASH-related cirrhosis. In line, EASL/EASD/EASO guidelines suggest that the possible benefits of bariatric surgery in severely obese NAFLD patients should be balanced against its possible peri- and post-operative complication risks [126].

5. Treating NAFLD by Targeting Fat Redistribution

The concept of MHO vs. MUHO vs. MONW, primarily based on body fat distribution and the presence or absence of ectopically deposited fat in the liver and elsewhere when storage space in subcutaneous adipose tissue is limited, becomes clinically relevant in the case of the potential use of thiazolidinediones (TZDs; pioglitazone and rosiglitazone), which are peroxisome proliferator activated receptor (PPAR)-γ ligands, in NAFLD patients. There is a seemingly paradox for PPAR-γ agonists, in the treatment of NAFLD, as elsewhere summarized [215]. In brief, PPAR-γ agonists, including TZDs, have provided promising results for the treatment of NAFLD, improving steatosis and inflammation, although their effect on fibrosis is marginal, possibly owing to the lack of long-term trials [215]. On the other hand, weight gain (mean increase 2.0–3.5 kg) is a main adverse effect of PPAR-γ agonists. The prevailing explanation to this seemingly paradox is that PPAR-γ agonists, including TZDs, beyond any fluid retention, result in adipose tissue redistribution, i.e., fat is redistributed from the abdominal (including the liver) stores to the subcutaneous ones, i.e., from ectopic to normotopic distribution, thus decreasing IR and consequently NAFLD severity. Furthermore, despite weight gain that usually results in adiponectin decrease, PPAR-γ agonists, lead to substantial increase in adiponectin, by inducing adiponectin production and secretion apparently due to fat redistribution from intra-abdominal to subcutaneous fat; this by far supersede any effect of the medications on body weight [215]. Despite weight gain, most NAFLD patients in RCTs with TZDs were overweight/obese [215], which renders PPAR-γ agonists, including TZDs and non-TZD selective modulators, such as INT 131 (see below), promising medications for the treatment of NAFLD patients, regardless of their weight. PPAR-γ agonists may be more suitable in MONW than obese with NAFLD, since the normal BMI of the former limits concerns about the weight gaining effect of PPAR-γ agonists; in this regard, head-to-head comparative studies investigating the effect of PPAR-γ agonists on obese vs. MONW with NAFLD may be enlightening.

To overcome weight gain and other adverse effects of PPAR-γ agonists, including TZDs (e.g., edema, fluid retention, negative impact on bone metabolism), selective PPAR-γ modulators (SPPARMs), including INT131, have been developed [215]. INT131 was well-tolerated, increased adiponectin and improved glycemic control in T2DM patients at least as full dose pioglitazone did. Importantly INT131 resulted in much less edema in relation to pioglitazone [215]. Based on these properties, INT131 and other SPPARMs are regarded as promising candidates for NASH treatment.

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6. Closing Remarks

This review supports the association of obesity with NAFLD and its severity, based on pathophysiological and epidemiological data. Therefore, targeting obesity or fat redistribution may play a central role for NAFLD management. However, there are many issues that remain to be elucidated.

First, it is largely unknown whether the combination of obesity and NAFLD synergistically affect morbidity (e.g., T2DM, hypertension, CVD) and mortality, beyond the separate effect of obesity and NAFLD on them. If this is the case, then treatment of both obesity and NAFLD is expected to improve the outcome more than separately treating obesity or NAFLD.

Second, other treatments have been also investigated in NASH patients and much more are under investigation, as elsewhere summarized [15,216]. Most of them (including vitamin E, statins, pentoxifylline, ursodeoxycholic acid, omega-3 and probiotics) are weight neutral, though no definite conclusion could be made for those currently under investigation.

Moreover, NAFLD is a multifactorial disease, so a multiple-targeted treatment may be more appropriate for it [83,217]. Apart from obesity, when other MetS risk factors, including T2DM and dyslipidemia, coexist, there is higher risk of NAFLD and advanced disease [10,218]. By targeting obesity, more than one target is usually achieved, which may be: decrease in adipose tissue mass; improvement in adipokine profile; decrease in IR; and decrease in adipose tissue, hepatic and systematic inflammation. Some medications may have additive benefits, as they were described above. Nevertheless, in most cases anti-obesity medications cannot achieve the cut-off of 10% weight loss, set for the improvement of fibrosis [129]. In these cases, combination treatment with other agents targeting different pathogenetic “hits” in a personalized basis may be more useful [83,217], though remains to be shown. Concomitant management of MetS-related co-morbidities, including hypertension, T2DM and dyslipidemia, is also important [126], possibly following a diabetes-like approach [83,217]. In the near future, deeper knowledge of the disease pathogenesis and the decoding of individual genetic footprint may allow a more focused and personalized therapeutic approach [15,83].

Last but not least, prevention rather than treatment of obesity should be the main goal of policymakers and healthcare systems. Although it remains to be definitely shown, the earlier the disease appears and the longer it lasts, possibly the higher the burden of advanced disease in the future. Considering the increasing prevalence of NAFLD in children and adolescents, skills towards a healthier lifestyle should be taught since infancy, aiming at avoiding obesity and its comorbidities, including NAFLD, before their appearance render treatment of advanced disease unavoidable.

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