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Review

Diabetes as a risk factor for MASH progression

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ABSTRACT

Non-alcoholic (now: metabolic) steatohepatitis (MASH) is the progressive inflammatory form of metabolic dysfunction-associated steatotic liver disease (MASLD), which often coexists and mutually interacts with type 2 diabetes (T2D), resulting in worse hepatic and cardiovascular outcomes. Understanding the intricate mechanisms of diabetes-related MASH progression is crucial for effective therapeutic strategies. This review delineates the multifaceted pathways involved in this interplay and explores potential therapeutic implications.

The synergy between adipose tissue, gut microbiota, and hepatic alterations plays a pivotal role in disease progression. Adipose tissue dysfunction, particularly in the visceral depot, coupled with dysbiosis in the gut microbiota, exacerbates hepatic injury and insulin resistance. Hepatic lipid accumulation, oxidative stress, and endoplasmic reticulum stress further potentiate inflammation and fibrosis, contributing to disease severity. Dietary modification with weight reduction and exercise prove crucial in managing T2D-related MASH. Additionally, various well-known but also novel anti-hyperglycemic medications exhibit potential in reducing liver lipid content and, in some cases, improving MASH histology. Therapies targeting incretin receptors show promise in managing T2D-related MASH, while thyroid hormone receptor-β agonism has proven effective as a treatment of MASH and fibrosis.

1. Introduction

Nonalcoholic fatty liver disease (NAFLD), which has recently been renamed and redefined as metabolic dysfunction-associated steatotic liver disease (MASLD) [1], has become the most prevalent chronic liver disease globally [2]. Approximately one out of every three adults in the general population globally and one out of every four adolescents is affected by MASLD, rendering it one of the most common non-communicable diseases [3,4]. Its progressive form, nonalcoholic steatohepatitis, now metabolic dysfunction-associated steatohepatitis (MASH) [1], is the second-leading cause of end-stage liver disease and liver transplantation in Europe and USA [3]. Although the new definition of MASLD requires the presence of one out of five cardiometabolic risk factors, components of the metabolic syndrome, which might lead to different phenotypes [5], recent data indicate that the prevalence of NAFLD and MASLD is generally comparable [6–8]. Overall, its onset and progression are intricately linked with metabolic imbalances and insulin resistance [9]. Consequently, it is not surprising that its occurrence is even more pronounced in individuals with type 2 diabetes (T2D), where it reaches a prevalence rate of 60–75 % [10]. The presence of MASLD increases the risk of developing T2D in individuals, who are not initially affected and increases the risk of complications in individuals with pre-existing T2D. On the other hand, individuals with T2D tend to progress more rapidly to MASH, advanced liver fibrosis, cirrhosis and hepatocellular carcinoma [11–13]. Of paramount importance, the severity of liver fibrosis emerges as the most crucial histological predictor for the future development of liver-related complications, as validated by numerous cohort studies and meta-analyses [14–16]. The increased prevalence of MASLD and its accelerated progression contribute to a roughly threefold elevated risk of mortality from liver-related conditions in individuals with T2D compared to age- and gender-matched individuals without T2D [17,18]. Nevertheless, awareness regarding

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MASLD including MASH and its potential prognostic implications remains limited, both among affected individuals [19] and within the healthcare professional community [20]. The global burden of MASLD [10,21], the associated morbidity and mortality [18] as well as available non-invasive screening approaches [22–24] have been extensively reviewed before. Here we focus on T2D as a risk factor for MASH progression along with the underlying mechanisms of T2D-related MASH and the respective therapeutic implications for people with diabetes. While we appreciate that extensive knowledge on MASH progression mechanisms has been obtained in preclinical animal models, the present work is primarily focused on data from human studies.

2. Risk factors for MASH progression

The driving factors for MASLD progression are not completely understood. In the context of diabetes, the data shows some inconsistencies for several factors such as male sex, older age and Caucasian ethnicity, which have been established in non-exclusively diabetic cohorts [25]. More evidence is available for genetic variation, obesity, diet, hyperglycemia and dyslipidemia (Fig. 1).

2.1. Genetic factors

Genetic evidence points at several single nucleotide polymorphisms related to increased MASLD development risk. Among these, the most prevalent ones include PNPLA3 rs738409 I148M [26], which has been linked to hepatic steatosis due to PNPLA3 accumulation on lipid droplets [27], TM6SF2 rs58542926 E167K [28], known to diminish hepatic VLDL release, and MBOAT7 rs641738 [29], an enzyme responsible for the modification of phospholipid acyl-chains. These genetic variations have respective minor (risk) allele frequencies of 24 %, 7 %, and 43 %, as determined from data provided by the CARDIoGRAMplusC4D consortium [30]. They may also influence the development of hepatocellular carcinoma, irrespective of the activity level and extent of liver damage [31]. Although these variations were initially discovered in patients with hepatic steatosis detected by magnetic resonance spectroscopy (MRS), subsequent studies in biopsy-proven MASLD confirmed the impact of PNPLA3 and TM6SF2 variants for liver injury [32]. The role of rs641738C > T variant in MBOAT7 has also been demonstrated in a human biopsy MASLD cohort and deletion of MBOAT7 in hepatocytes in a mouse model of diet-induced MASH leads to increased fibrosis with no effect on inflammation [33]. In carriers of the PNPLA3 or the TM6SF2 polymorphisms with MASH the presence of T2D increases the risk of advanced fibrosis [34]. Still, the mechanism of the interplay between T2D and these gene variants for the progression of MASH remains unclear.

Of note, PNPLA3 stands out as a risk factor for the full histological spectrum of MASLD beyond a genome-wide critical threshold in the statistical testing [32]. However, it is important to note that, despite the prevailing understanding that steatosis in MASLD arises from increased flux of fatty acids derived from adipose tissue and higher lipogenesis, there is currently very limited data establishing a direct connection between these genetic variants and the above mentioned underlying biological pathways. In line, a recent case-control study showed some evidence that TM6SF2 rs58542926 dissociates hepatic lipid content from insulin resistance in T2D in the German Diabetes Study (GDS) [35], suggesting that the effect of this SNP is secondary to the diabetes-related metabolic alterations in MASLD [36]. Of note, in the same cohort of individuals with recent-onset T2D the PNPLA3 rs738409 has been linked to adipose tissue insulin resistance and excessive lipolysis, thereby demonstrating a possible contribution of this genetic variant to MASLD development in people with T2D and insulin resistance [37]. Decreased mitochondrial citrate synthase flux and increased ketogenesis has been recently implicated in the mechanism, by which steatosis induced by this variant, leads to progressive liver disease [38]. Hepatic activation of inflammatory pathways downstream from STAT3 via

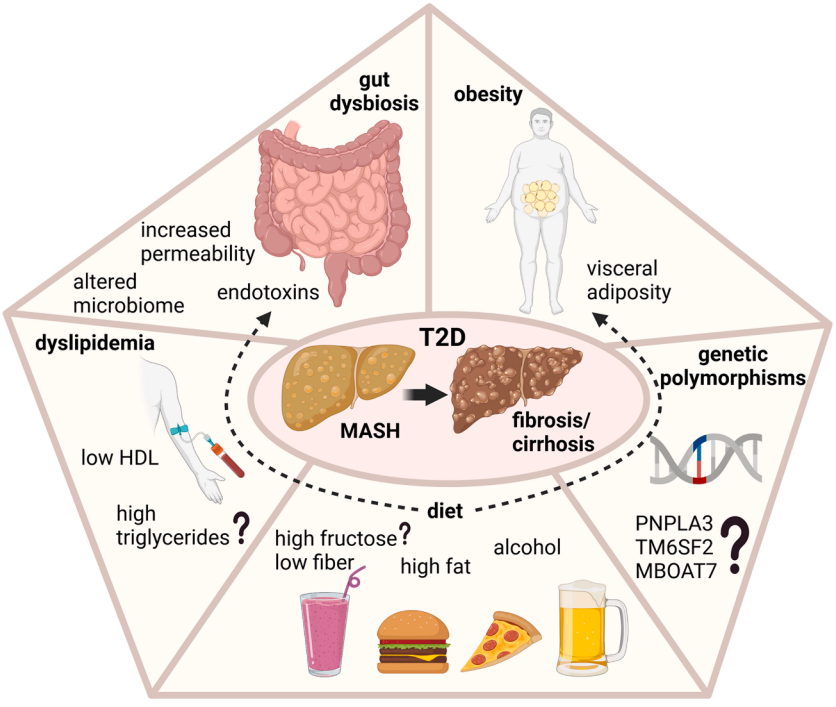

Fig. 1. Factors for metabolic dysfunction-associated steatohepatitis (MASH) progression in people with type 2 diabetes (T2D). Increase in the waist circumference and in the waist-to-hip ratio are risk factor for MASH and advanced fibrosis in people with T2D, while the role of genetic variants, known to accelerate MASH in non-exclusively diabetic populations, remains unclear in the context of T2D. On the other hand, dietary factors such as increased fat and alcohol intake as well as decreased fiber intake might trigger intestinal dysbiosis and contribute to diabetes-related MASH progression. Low HDL, but not increased LDL, has been described as a risk factor for advanced fibrosis in T2D. Figure created with biorender.com. MASH – metabolic dysfunction-associated steatohepatitis, T2D – type 2 diabetes, HDL – high-density lipoproteins, LDL – low-density lipoproteins.

ceramides has also been described as a potential mechanism in rodents [39]. Furthermore, an interaction between this SNP and visceral fat content has been suggested which increases the risk of hepatic fibrosis in histologically proven MASLD [40]. In summary, compelling evidence from multiethnic groups supports the notion that the PNPLA3 variant relates to progressive steatohepatitis, liver injury and higher risk of hepatocellular carcinoma in people with MASH [31,41,42], while with regard to T2D limited evidence suggests that it might further aggravate this link. Still, mechanistic studies linking common genetic variants in MASLD to the pathophysiological mechanisms of MASH progression in prospective human cohorts with and without T2D are missing.

2.2. Diet as a risk factor

The development of MASLD is closely linked to lifestyle factors, namely high calorie intake together with reduced physical activity. Excess calorie consumption has been particularly implicated in the progression of MASH through mechanisms of increased oxidative stress and endoplasmic reticulum stress (for details see Chapter 3.3.2). When energy intake surpasses the body's metabolic demands, substrate flux through the mitochondria increases, leading to higher reactive oxygen species (ROS) production. Oxidative stress can damage mitochondrial components, including proteins, lipids and DNA. As a response to this damage and oxidative stress, cells release proinflammatory cytokines, such as interleukin-1β (IL-1β) and tumor necrosis factor-alpha (TNF-α). The presence of proinflammatory cytokines triggers an inflammatory response, recruiting immune cells to the site of increased oxidative stress. As increased oxidative stress and inflammation are features of T2D *per se* [43], this might additionally favor MASH progression in the settings of overnutrition.

High dietary sugar, particularly fructose, can stimulate hepatic *de novo* lipogenesis (DNL) and promote hepatic lipid accumulation. Furthermore, excessive fructose consumption can lead to insulin resistance and increased hepatic triglycerides synthesis, exacerbating MASH. Robust effects of fructose consumption on hepatic steatosis were reported in healthy male individuals [44,45]. In a nonrandomized crossover study, a 7-day hypercaloric fructose diet increased intrahepatic TAG content and augmented hepatic steatosis more than an isocaloric diet did, with more potent stimulation of hepatic DNL in 16 healthy males with a family history of T2D than in 8 humans without family history of T2D [46]. This finding indicates that fructose induces its detrimental effects especially under hypercaloric conditions, which are an important driver of T2D. Furthermore, the specific combination of fructose with trans fatty acids but not saturated fatty acids induces hepatic fibrosis in a long-term feeding experiment in rats [47]. The deleterious metabolic effects of fructose are likely mediated by the metabolism of fructose by fructokinase C, which results in ATP consumption, nucleotide turnover and uric acid generation that mediate lipid accumulation [48].The contribution of fructose to MASH progression in the settings of T2D in particular remains unclear.

Saturated fatty acids (SFA) accumulation, but not unsaturated fatty acids, promote ER stress and apoptosis in hepatocytes, likely favoring MASH progression [49,50]. In line, clinical trials in humans demonstrate, that while monounsaturated fat load does not alter hepatic steatosis [51], a single oral lipid challenge rich in SFA induces hepatic insulin resistance, augments hepatic lipid accumulation, gluconeogenesis and energy metabolism [52]. Complementing studies in rodents revealed upregulation of pathways such as LPS and NF-κB, possibly contributing to MASLD progression [52]. Whether these effects are augmented in T2D, however, remains unknown. Compelling evidence suggests that ER stress is of critical importance to SFA-induced cellular dysfunction, enhanced autophagy and lipoapoptosis [50]. Short-term overfeeding with SFA leads to hepatic steatosis and IR in overweight humans [53], but whether similar or more detrimental effects are present in people with T2D is unclear.

Inadequate fiber intake can alter the gut microbiota, promoting the growth of proinflammatory bacteria. Dysbiosis is tightly linked to T2D [54] and leads to the release of inflammatory mediators and gut-derived endotoxins, which can trigger hepatic inflammation [54]. Gut-derived endotoxins, such as lipopolysaccharides (LPS), activate Toll-like receptors (TLRs) in the liver [55]. TLR signaling promotes inflammation and might contribute to MASH pathogenesis [56].

Alcohol consumption can also exacerbate liver injury in MASH. Ethanol metabolism leads to ROS production causing oxidative stress and hepatocellular damage. In addition, alcohol can disrupt the gut barrier, leading to increased permeability and the translocation of gut-derived proinflammatory factors into the liver, contributing to inflammation and liver injury.

Metabolic toxins, especially alcohol abuse or high fat/low fiber diet in MASLD have been described to disrupt intestinal homeostasis by increasing intestinal permeability and altering microbiota [57] (also s. Chapter 4.2). Consequentially, the relative overgrowth of potentially pathogenic bacteria not only drives hepatic inflammatory immune responses and HSC activation due to portal delivery of pathogen-associated molecular patterns (PAMPs, as lipopolysaccharides, peptidoglycans, and flagellin), the altered microbiome also results in intestinal deconjugation of bile acids and therefore production of so-called secondary bile acids that suppress Farnesoid-X Receptor (FXR) signaling [58]. The contribution of these mechanisms in the context of T2D remains unclear.

2.3. Obesity as a risk factor

Of note, BMI and particularly central (visceral) adiposity have been suggested to play a key role. Higher waist circumference and waist-to-hip ratio have been described as risk factors for MASH and advanced fibrosis in people with T2D [59,60], while obesity *per se* has been associated with 2.5-fold increased risk of advanced fibrosis in a prospective T2D cohort after multivariable adjustment for age and sex [61]. On the other hand, the presence of T2D in the settings of obesity has been found particularly detrimental for the risk of MASH and fibrosis, as demonstrated by odds ratio of 9.7 in people with BMI > 50 kg/m^2 and metabolic disease such as T2D [62]. While this substantially compounded effect is of high clinical relevance, the contribution of the presence of T2D to advanced liver disease across the BMI spectrum also warrants investigation. Interestingly, MASLD is also seen in normal weight people and, as expected, T2D is less common in this population in comparison to non-lean humans with MASLD [63,64]. Still, T2D likely does not influence MASLD progression in lean individuals [65,66], suggesting BMI dependent effect of T2D.

2.4. Hyperglycemia as a risk factor

Hyperglycemia in T2D *per se* represents a risk factor which contributes to MASH progression via different mechanisms, including compromising intestinal barrier function (s. Chapter 4.2), modulation of hepatic lipid metabolism gene expression (s. Chapter 4.3.1) or generation of advanced glycation end-products (AGEs) (s. Chapter 4.3.2). Recent studies with paired liver biopsies revealed a tight link between diabetes-related hyperglycemia and advanced MASH. Fibrosis progression is not only accelerated in T2D compared to nondiabetic individuals [11], but HbA1c in particular is related to hepatic fibrosis progression independent of BMI [67]. Gene expression analyses in the latter study also demonstrated that the hyperglycemia effect on hepatic fibrosis might be mediated by hypoxia, oxidative stress and inflammation [67]. Further details on the relation between fibrosis prevalence and progression in T2D are outlined in Chapter 3.

2.5. Dyslipidemia as a risk factor

The production and/or clearance of all classes of lipoprotein particles involves the liver. Apart from its role in the metabolism of

lipoprotein particles, the liver participates in the metabolism of triglycerides and especially cholesterol. Hypertriglyceridemia, increased small dense low-density lipoprotein cholesterol (LDL) and decreased high-density lipoprotein cholesterol (HDL) are hallmarks of atherogenic dyslipidemia, which is not uniformly present in people with MASLD [68–72]. Still, only in combined MASLD and T2D dyslipidemia is an independent risk factor for liver fibrosis, but not in MASLD alone [73]. The link between altered lipid metabolism in MASLD and increased cardiovascular disease (CVD) risk has been substantiated by a large amount of evidence [74] and dyslipidemia has been suggested as a driver of MASLD-related liver events [75,76]. In T2D population with MASLD higher prevalence of CVD in multiple sites (coronary, cerebrovascular, and peripheral vascular disease) has been observed and LDL levels did not substantially contribute to the tight link between MASLD and CVD [77]. Furthermore, increased systemic LDL levels *per se* have not been explicitly related to MASH progression in humans, while low HDL has been identified as a factor related to advanced fibrosis in T2D [60]. Of note, statin-therapy might be able to reduce hepatic steatosis [78], but does not lead to MASH remission [79–81]. Proprotein convertase subtilisin/kexin type 9 (PCSK9), which is a key regulator of cholesterol homeostasis and intracellular lipogenesis, has been recognized to play a dual role for hepatic and systemic cholesterol levels by decreasing hepatic cholesterol uptake thereby preventing excess cholesterol accumulation in the liver while increasing plasma LDL [82]. Still, its relevance for MASH progression in humans remains unclear [83]. In contrast to systemic cholesterol, intracellular cholesterol content has been found to induce liver injury and drive MASH progression through several mechanisms. First, via direct modulation of gene transcription of SREBP2, a master regulator of sterol and fatty acid synthesis, as well as indirectly via activating liver and FXR by cholesterol-derived metabolites [84]. Second, through upregulation of TAZ (tafazzin), a transcriptional regulator promoting fibrosis [85], which increases hepatocyte Indian hedgehog transcription and secretion, leading to HSC activation. Furthermore, mitochondrial cholesterol accumulation from *in vitro* LDL loading in murine hepatocyte culture results in hepatocyte apoptosis by activating JNK1 [86]. Thereby intracellular cholesterol homeostasis remains of paramount importance for MASH progression and represents a possible future treatment target.

Hypertriglyceridemia is a common finding in MASLD and T2D because of the impaired dynamic balance between hepatic very low-density lipoproteins (VLDL) – triglyceride secretion and plasma clearance. In people with T2D hypertriglyceridemia has been related to increased MASH prevalence [60] and in nonobese MASLD hypertriglyceridemia is a key factor for advanced liver disease independent of T2D [65]. It has been suggested, that hepatic VLDL-TG secretion can compensate for increased intrahepatic triglyceride accumulation only to a certain level of 10 % liver fat content, after which VLDL production is not effective anymore and hypertriglyceridemia exacerbates further [87,88]. Still, the suggested association between hypertriglyceridemia and MASH progression [69] has not been substantiated with direct mechanistic evidence and Mendelian randomization points at no causal link between dyslipidemia and MASLD [89]. Circulating triglycerides seem far less important for MASH progression than the rates of hydrolysis of triglycerides in hepatocyte lipid droplets, non-esterified fatty acid (NEFA) flux, *de novo* lipogenesis (DNL) as well as intrahepatic fatty acid oxidation (see Chapter 4.3.1).

3. Prevalence and progression of liver fibrosis in MASH and T2D

People with T2D have been shown to have a higher prevalence of advanced fibrosis [90] and an exacerbated risk of developing MASH and advanced fibrosis or cirrhosis compared to the general population [12]. However, the real prevalence of advanced fibrosis in humans with T2D remains difficult to establish. Two recent meta-analyses in people with T2D and MASLD [10,90] suggested a prevalence of advanced fibrosis or cirrhosis between 14.9 % (11.0–19.9) and 17.0 % (7.2–34.8). It should be underlined that most studies included in these meta-analysis were based on the use non-invasive tests (NITs), such as vibration controlled-transient elastography (VCTE) or magnetic resonance-elastography (MRE), to assess liver fibrosis and not on liver biopsies (LB). Additionally, in the most recent review of the literature [91], prevalence of advanced fibrosis or cirrhosis ranged from 3 % to 38 %, according to the setting (primary care or diabetes clinics), and the diagnostic tools used (NITs or LB). For instance, using the same NIT (liver stiffness $>$ 9.7 kPa by VCTE), prevalence of advanced fibrosis was 15 % in 825 US individuals with T2D seen in primary care (NHANES cohort) [92] whereas it was 27 % in 1918 Chinese individuals with T2D seen in secondary/tertiary care diabetes clinics [93]. Finally, in the largest cohort to date (713 T2D French outpatients systematically screened for MASLD in diabetes clinics using a low ALT threshold ($>$30 IU/L in male and $>$ 20 IU/L in female) of whom 330 underwent a LB, we found a prevalence of advanced fibrosis and cirrhosis of 28 % and 10 %, respectively [60]. Interestingly, our findings are in keeping with those of another American study in 134 people with T2D who underwent a LB [61]. When looking at risk factors, liver lesions were independently associated with components of the metabolic syndrome but not with T2D complications. For instance, simple clinical predictors (waist circumference (M $>$ 102, F $>$ 88 cm), OR = 2.24; GGT (IU/L), OR = 1.008; HDL cholesterol (M $<$ 1.03, F $<$ 1.29 mmol/L) OR = 2.57; and FIB-4, OR = 3.01) had good performance (AUROC 0.77) for predicting advanced fibrosis.

In a recent prospective multicenter US study in 447 people with MASLD and paired LB (median interval 3.3 years) from the NASH-CRN cohort, those with T2D had a significantly higher cumulative incidence of fibrosis progression ($\geq$1 stage increase) than those without T2D, at 4 years (24 % vs. 20 %), 8 years (60 % vs. 50 %), and 12 years (93 % vs. 76 %) (p = 0.005) [11]. Interestingly, after adjusting for potential influencing factors such as age, sex, BMI, ethnicity and baseline fibrosis stage, the presence of T2D was associated with a 69 % increase in the risk of fibrosis progression. Further studies in other settings and populations are needed. Altogether these results suggest that people with T2D should be systematically screened for MASLD and liver fibrosis as recommended recently by several guidelines [94–97]. Additionally, MASH should be considered as a complication of T2D.

In people with T1D, increased liver stiffness is found in ca. 5 % of the individuals [98] and surprisingly, longitudinal liver related outcomes are similar in T1D when compared with respective cohorts with T2D [99]. However, this classical diabetes classification has been recently challenged and new approaches for diabetes classification have been proposed, which help determine key features contributing to risk of complications in diabetes, including MASLD. Analyses of the GDS study validated the concept of 5 subtypes (clusters) of diabetes using comprehensive metabolic phenotyping in patients with recently diagnosed diabetes mellitus [100]. Interestingly, the subtypes of participants with severe insulin-resistant diabetes (SIRD) exhibited increased hepatic lipid content compared to all other subgroups in the settings of high BMI and adipose tissue insulin resistance. The prospective analysis of these participants with SIRD revealed increased hepatic fibrosis at 5 years follow-up [100], supporting the notion of a tight link between insulin resistance and hepatic fibrosis progression in MASLD. Also, carriers of the rs738409 polymorphism in the PNPAL3 gene were more often found in this particular subgroup and this SNP related to severe adipose tissue insulin resistance [37], suggesting that this genetic variant might contribute to the progression of liver disease in insulin resistant humans with diabetes (see Chapter 2.1). Still, the high prevalence of liver related outcomes in T1D does not seem to be reflected in the mainly corresponding to T1D severe autoimmune diabetes (SAID) cluster from the new classification, which is probably due to the short disease duration of 5 years at follow up.

4. Mechanisms of diabetes-related MASH progression

4.1. Timeline of diabetes-related MASH progression

Accumulating evidence suggests that early abnormalities in the development and progression of diabetes-related MASH entail diet-induced adipose tissue dysfunction and intestinal dysbiosis [101]. These early changes are followed by intrahepatic alterations including lipotoxicity and altered mitochondrial function [102]. Subsequently hepatic oxidative and ER stress as well as inflammation gain key roles as progressive drivers of hepatic injury. The mechanisms of MASH have extensively been studied in mouse models, even though a standard translationally relevant preclinical model which accurately reflects human physiology is currently missing [103]. While this review work focuses on data from human trials, the following mechanistic sections also include some key findings from mouse model studies. Of note, a rodent model of diabetes-related steatohepatitis has recently been proposed, which showed diabetes related inflammation activation in a single cell RNA sequencing analysis and might represent a suitable model for future studies on diabetes-related MASH [104].

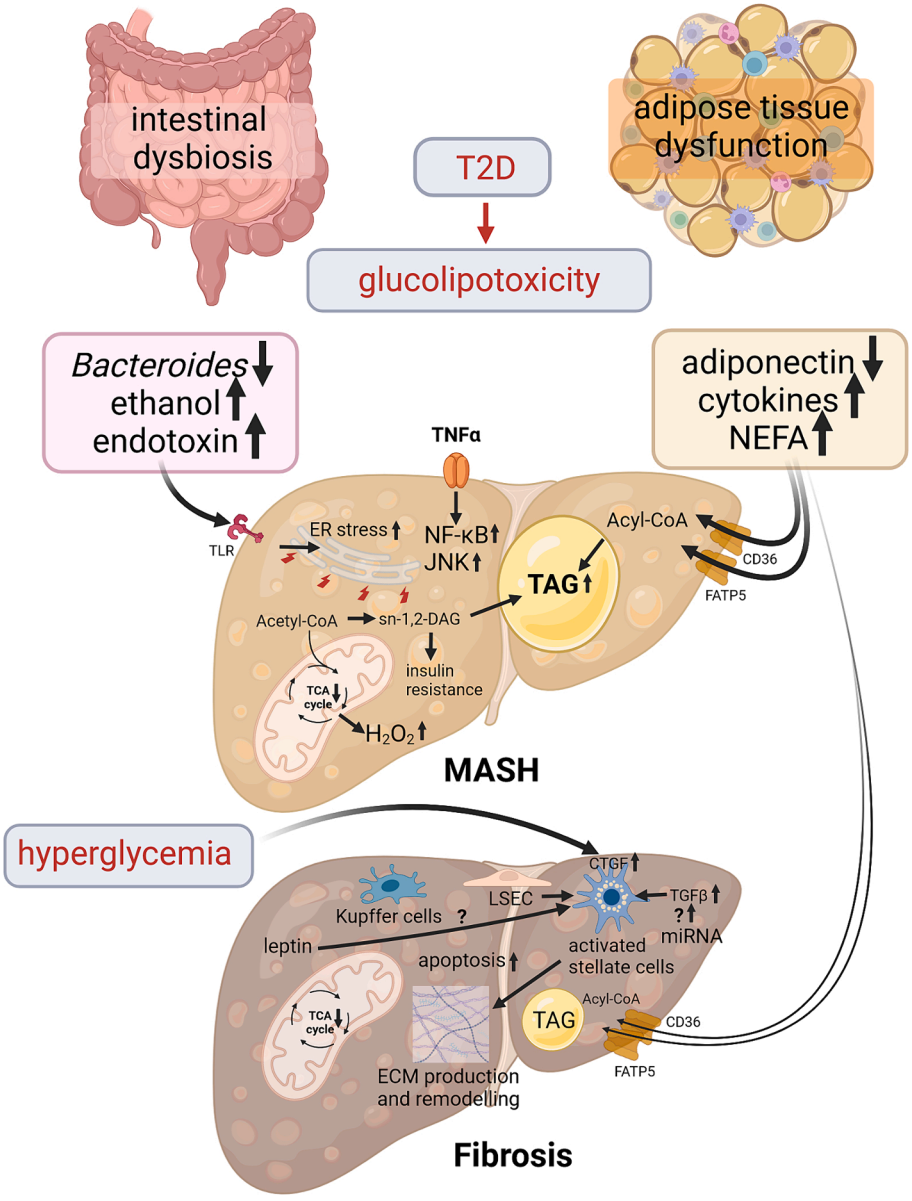

Fig. 2. Interplay between extrahepatic and intrahepatic factors driving diabetes-related metabolic dysfunction-associated steatohepatitis (MASH) progression. Energy-rich high-fat diets trigger intestinal dysbiosis and favor visceral fat expansion. Altered intestinal permeability facilitates translocation of inflammatory endotoxin (LPS) in the liver. Excessive fat accumulation in adipose tissue leads to altered secretion of adipokines, unrestrained lipolysis due to insulin resistance and inflammation, which accelerates hepatic lipid accumulation in MASH, while in advanced fibrosis lipid transport via FATP5 and accumulation are reduced. In the settings of decreased mitochondrial respiratory capacity in T2D lipotoxic mediators and oxidative stress increase. Lipid overload and LPS also lead to ER stress, which further enhances insulin resistance and inflammation via JNK and NF-kB pathways activation. Kupffer cells and liver sinusoidal endothelial cells (LSEC) are stimulated. They release proinflammatory cytokines and activate hepatic stellate cells, which are key in hepatic fibrogenesis as they regulate extracellular matrix production. Figure created with biorender.com. CTGF – connective tissue growth factor (also known as cellular communication network factor 2, CCN2), ECM – extracellular matrix, MASH – metabolic dysfunction-associated steatohepatitis, T2D – type 2 diabetes, FATP – fatty acid transporter 5, TAG – triacylglycerols, NEFA – non-esterified fatty acids, TCA – tricarboxylic acid cycle.

4.2. Extrahepatic mechanisms: overnutrition induced adipose tissue dysfunction and gut dysbiosis

Adipose tissue has been suggested as a key player both in T2D and MASLD development [43,87] (Fig. 2). In particular, the capacity of subcutaneous adipose tissue to expand is limited and once exceeded, visceral adipose tissue increases, mediating liver injury. In line, humans with newly diagnosed T2D and MASLD from the GDS exhibit an expansion in visceral adipose tissue in the early course of the disease which tightly relates to elevated liver lipid content [105]. Even though liver histology was not available in this study due to ethical considerations, the higher AST at follow up might point towards simultaneously developing liver injury in people with T2D. Furthermore, the PNPLA3 rs738409 variant has been shown to modulate the relationship between visceral adipose tissue and hepatic fibrosis as carriers with increased visceral fat had a higher risk of severe fibrosis [40].

Increased lipolysis and lower lipogenesis in visceral compared to subcutaneous adipose tissue facilitate hepatic delivery of lipid metabolites with detrimental effect on hepatic substrate utilization and lipotoxicity [106]. Serum metabolomics in MASLD reveal an increase in the levels of most triacylglycerol species with progression of steatosis and fibrosis, while levels of several phosphatidylcholine and sphingomyelin species decrease [107]. As >90 % of the here included European NAFLD Registry participants also exhibited T2D, the reported metabolic signature is likely valid for diabetes-related MASLD progression. The diacylglycerol-induced PKCε activation leading to inhibition of hepatic insulin signaling has been recognized as a major lipotoxic mechanism implicated in the development of hepatic insulin resistance [108,109], but hepatic diacylglycerols have not been directly related to diabetes-related MASH progression. Indeed, not liver but adipose tissue deletion of PKCε affects hepatic expression of genes involved in steatohepatitis development, indicating PKCε-dependent crosstalk between adipose tissue and the liver [110], that might contribute to MASH.

Of note, altered mitochondrial function in adipose tissue has been identified as an important player in the development of insulin resistance and progression of MASLD [106]. In particular, lower expression of proteins involved in mitochondrial function and lower availability of mitochondria–derived energy sources for lipogenesis in adipose tissue compromise adipose tissue's role as a principal sink of lipids. Moreover, mitochondrial function in visceral, but not subcutaneous adipose tissue is downregulated in humans with hepatic steatosis and MASH and is associated with decreased adipose tissue insulin sensitivity and elevated local inflammation, suggesting that impaired visceral adipose tissue energy metabolism might be implicated in MASLD progression [111]. This mechanism is likely diabetes-related, as VAT proteins related to key mitochondrial function features are also downregulated in T2D [112]. However, prospective data from biopsy-proven MASLD cohorts looking at the mechanistic link between adipose tissue dysfunction and diabetes-related MASH progression is lacking.

Well-known mediators of adipose tissue-liver crosstalk are the adipokines leptin and adiponectin, which regulate glucose production, lipogenesis and fatty acid oxidation in the liver. Substantial amount of mechanistic evidence from rodents points at leptin as activator of hepatic fibrosis via stimulation of hepatic stellate cells [113–115]. However, mechanistic studies in humans are scarce [116,117]. Leptin levels did not relate to fibrosis stage or fibrosis progression in human MASLD [118,119], while a correlation was found with the degree of steatosis [119,120]. On the contrary, adiponectin decreases with the progression from simple steatosis to MASH and later on increases with the development of cirrhosis and hepatic fat loss [117]. Whether these adipokines specifically contribute to MASH progression in T2D remains unclear. On the other hand, several microRNAs are released from adipocytes, which might serve as novel mediators of inter-organ crosstalk impacting T2D and may regulate hepatic fibrosis progression via transforming growth factor β [121] and NFκB-TNFα pathway [122].

Altered gut microbiota is found not only in T2D, but is also considered a major contributor to the progression of MASLD [54,58] (Fig. 2). It is known that both conditions are favored by metabolic endotoxemia, which is a low-grade inflammation state linked to intestinal dysbiosis and increased intestinal permeability. Disruption of the intestinal epithelial and gut vascular integrity occurs early on in the MASH evolution and prevention of this disruption can protect against the development of MASH [57]. Similarly, increased intestinal permeability is a characteristic of T2D and the resulting metabolic endotoxemia can trigger body weight gain and insulin resistance [123]. Of note, hyperglycemia *per se* enhances intestinal barrier permeability leading to systemic influx of microbial products and correcting hyperglycemia can restore the barrier function [124]. Also, both metabolic and inflammatory mechanisms are at play here, so that diabetes-related dysbiosis might modify the natural course of MASLD. Endotoxin, which is increased in serum of humans with T2D [125], binds to the CD14/TLR4 complex on the macrophage's surface and favors M1 macrophage proliferation with subsequent production of TNFα, IL-1β, and IL-6, which contributes to insulin resistance, but can also promote MASH progression [126]. Still, a direct effect of endotoxin in the development of MASH and/or fibrosis has not been clearly demonstrated and among humans with MASH serum endotoxin is not correlated with disease severity, suggesting that endotoxemia is not required in the pathogenesis [127].

Trimethylamine N-oxide (TMAO), which is another gut-derived bacterial factor, has been related to MASH mainly in the presence of T2D [128]. Intestinal interleukine 33 has recently been shown as the link between enhanced intestine-derived TMAO and aggravated MASLD inflammation and fibrosis [129]. Still, abundant preclinical data points at a the complex nonlinear relation between TMAO and MASLD, which is incompletely understood also in the context of T2D [130]. A recent multiomics approach revealed that gut permeability is key in the pathophysiology of MASLD with fibrosis, and that the gut-liver axis is partially independent of T2D in liver disease progression [131]. While it has been suggested that *Firmicutes* to *Bacteroidota* ratio may distinguish individuals with MASH fibrosis from healthy ones [132], recent evidence from this multiomics study suggests that *Firmicutes* abundance might be related to T2D and not to liver disease and that lower *Butyricicoccus* is specifically linked to MASLD with fibrosis. On the other hand, in a biopsy-proven human cohort *Bacteroides* abundance is independently associated with MASH, while *Ruminococcus* relates to advanced fibrosis [133]. Of note, the negative correlation between *Bacteroides/Prevotella* and MASH is independent of diet and BMI, suggesting liver disease-specific effect of these genera of intestinal bacteria [134]. Still, *Bacteroides* abundance also plays a role in T2D as it is reduced in humans with T2D. Furthermore, it positively modulates inflammation and gut permeability as well as increases adipose tissue fatty acid oxidation [135]. Thereby common alterations in the intestinal flora might contribute to the accelerated progression of MASH in T2D.

Additionally, individuals with MASH present with higher levels of blood ethanol concentrations due to increased abundance of alcohol-producing bacteria in the MASH microbiomes [136]. Once in the liver via the portal circulation, this endogenous alcohol likely aggravates hepatic oxidative stress and inflammation. Notably, obesity has also been associated with increased intestinally derived ethanol [137], which might represent a common pathogenic mechanism between T2D and MASH.

Gut microbiota is also involved in the production of secondary bile acids, which control inflammation, glucose and lipid metabolism via the nuclear FXR [84]. FXR activation has been shown to inhibit lipogenesis, decrease intracellular lipid accumulation, hepatic inflammation and fibrosis [58]. Tissue-specific differences in the FXR action on lipid metabolism have been described comprising hepatic FXR control of lipogenic genes and intestinal FXR control of lipid absorption [138]. While hepatic FXR action remains of critical importance for the progression of MASLD, intestinal FXR has mainly been implicated in the regulation of the glucose homeostasis during obesity and diabetes

development [139]. Despite these tissue-specific differences, modulation of FXR represents an important therapeutic target in both MASH and T2D.

4.3. Intrahepatic mechanisms

4.3.1. Lipotoxicity and mitochondrial function

Insulin resistance in both adipose tissue and skeletal muscle, which are hallmarks of T2D, favors hepatic lipid accumulation by providing precursors and substrates for *de novo* lipogenesis (DNL) and mitochondrial β-oxidation. Elevated NEFA and glycerol originating from insulin resistant adipose tissue serve as lipid sources for hepatic re-esterification in triglycerides and DNL, while hepatic triglycerides can be utilized through oxidation or export as VLDL particles. With the progression of MASH to fibrosis and cirrhosis hepatic lipid accumulation is usually lost, which relates to reduced hepatic fatty acid influx via fatty acid transport protein 5 (FATP5) [140]. FATP5 has also been implicated in body weight and energy homeostasis regulation [141], making it an important player in diabetes-related MASH development. On the other hand, DNL contribution to hepatic triglyceride accumulation is ~2-4fold higher in individuals with MASLD compared to obese and lean non-MASLD [142], while hepatic insulin resistance as seen in T2D [143] can further increase the relevance of DNL as a factor. Although modulation of DNL represents an interesting treatment target for MASLD, studies particularly looking at the role of DNL for diabetes-related MASH progression in humans are missing. It is known that DNL is regulated by several transcription factors among which are the sterol regulatory element-binding protein 1c (SREBP1c) and the carbohydrate regulatory element-binding protein (ChREBP) [143]. SREBP1c overexpression in the liver associates with hepatic insulin resistance, but unrestrained adipose tissue lipolysis and oxidative stress are what drive hepatic inflammation [144] and could possibly favor MASH progression. In line, in humans SREBP1c is upregulated in hepatic steatosis [145], but not in MASH [146]. In addition, hyperglycemia can activate ChREBP, which in turn stimulates the expression of glycolytic genes, augmenting substrate availability for DNL, and induces the expression of stearoyl-CoA desaturase 1 (SCD1), the enzyme responsible for the conversion of saturated to monounsaturated FA, increasing hepatic lipid accumulation [147]. Elevated expression levels of ChREBP were found in human MASH [147], so that its role as a diabetes-specific factor in MASH development cannot be excluded.

The specific lipid metabolites and cellular compartments that mediate lipid-induced hepatic insulin resistance have intensively been studied in the last two decades [148]. Evidence points at plasma membrane *sn*-1,2 DAGs that activate PKCε leading to inhibition of insulin receptor's tyrosine kinase activity as a main pathway in mediating lipid-induced hepatic insulin resistance [108,109]. Still, unlike ceramides, hepatic DAG have not been particularly implicated in MASH in humans. Specific ceramides and other sphingolipids are elevated in the liver of individuals with obesity and MASH [149,150] and the correlation with hepatic inflammation and oxidative stress suggests a distinct role in MASH progression [149]. A link to T2D is substantiated by the findings of increased specific ceramide species in humans with T2D relating to higher TNFα [151]. Still, mechanistic evidence in human prospective T2D and MASLD cohorts is lacking.

Changes in lipid availability induce alterations in lipid oxidation in hepatic mitochondria [152]. Hepatic oxidative capacity is up to 5fold higher in humans with obesity with and without hepatic steatosis [153]. Recent data confirmed the elevated hepatic maximal coupled respiration in humans with steatosis and obesity compared to lean individuals without steatosis [154]. The hepatic adaptation to increased lipid availability (mitochondrial flexibility) is lost with the progression to MASH, as people with MASH exhibit decreased hepatic mitochondrial respiratory rates in the settings of higher proton leak as well as upregulated oxidative stress and oxidative DNA damage [153]. Decreased hepatic mitochondrial respiratory chain complexes have also been described in MASH [155]. Of note, lower mitochondrial respiration and content were not confirmed in cohorts with T2D [156] and lean-to-overweight MASLD [157], suggesting metabolic condition-specific differences in mitochondrial changes. Recently we reported, that hepatic oxidative capacity is also not uniformly downregulated in human MASH as people with MASH and T2D but not non-diabetic individuals show reduced hepatic mitochondrial respiration, which relates to higher lipid peroxidation and hyperglycemia [158]. Surprisingly, oxidative capacity was also reduced in humans with MASH and hepatic fibrosis, pointing at mitochondrial function decline as a common feature of MASH with T2D or with fibrosis which likely accelerates metabolic liver disease progression [158].

In vivo hepatic energy metabolism measured using $^{1}H/^{31}P$ MRS in humans with MASH confirmed lower ATP flux and replenishing [159,160]. Of note, hepatic ATP content and ATP synthase flux are also reduced in T2D [161,162], pointing at disturbed hepatic energy homeostasis as a marker of metabolic liver disease, which could contribute to the accelerated progression of MASLD in T2D. In line, during the early time course of T2D impaired hepatic mitochondrial adaptation is paralleled by a substantial increase in liver lipid content [105], which likely sets the stage for the progression of liver injury.

4.3.2. Oxidative stress, endoplasmic reticulum (ER) stress and inflammation as drivers of progression

Decline of mitochondrial flexibility as seen in T2D might be paralleled by oxidative stress favoring the progression from hepatic steatosis to MASH and fibrosis. Mitochondria are a major source of ROS generation. Dysfunction in the electron transport chain (ETC) results in overproduction of ROS, predominantly superoxide anion radicals (O_2) and hydrogen peroxide (H_2O_2). Ineffective antioxidant defense mechanisms also contribute to ROS accumulation. Elevated ROS levels can cause oxidative stress, damaging cellular components and promoting inflammation in the liver. Of note, hepatic mitochondrial H_2O_2 emission is increased in MASH and in MASH with T2D while hepatic oxidative capacity correlates with hepatic lipid content and insulin resistance [153] as well as with lipid peroxidation and hyperglycemia [158]. Thereby mitochondrial alterations in MASH and T2D might upregulate oxidative stress and lipid peroxidation resulting in accelerated progression of liver disease.

Persistent hyperglycemia in T2D enhances the generation of AGEs, which can increase oxidative stress and initiate hepatocyte damage and liver fibrosis [163]. Receptors for AGEs are mainly present on Kupffer and hepatic stellate cells, which are key to MASH progression. AGE-induced oxidative stress can accelerate the glycation reaction and in turn lead to generation of further reactive oxygen species forming a positive loop [164]. Hyperinsulinemia and hyperglycemia in prediabetes and overt T2D might also drive fibrosis in MASH, as insulin and glucose might stimulate connective tissue growth factor upregulation in hepatic stellate cells in MASH [165].

Further support for this notion has been obtained from murine models of NASH and diabetes revealing operative hepatic mitochondrial plasticity in the development of diabetes with and without MASH, which is linked not only to systemic oxidative stress but also to hepatic unfolded protein response (UPR) dysfunction [166]. Abnormal mitochondrial function with depletion of ATP in the settings of hyperglycemia and high lipid influx might activate the UPR, which is an adaptive response to maintain the balance of protein folding in the ER and to restore ER homeostasis [167]. Lipid overload in hepatocytes leads to augmented ApoB synthesis and accumulation in the ER which eventually compromises ER function and induces ER stress [168]. ER stress in hepatic stellate cells is known to promote hepatic fibrosis [169] while induction of ER stress in the liver increases insulin resistance in relation to lipin-2 overexpression and DAG/PKCε-axis activation [170]. Hepatic UPR might be triggered to alleviate ER protein load and reduce liver injury. Still, sustained UPR can activate pathways related to inflammation such as JNK and NF-kB [167]. Thereby chronic ER stress likely plays

a role for MASLD progression in diabetes, which is also evidenced by the tight contact between ER and mitochondria as well as the relation between UPR and mitochondrial respiration in MASH and diabetes [166] suggesting a potential organelle cross-talk here.

Cellular cross-talk between hepatocytes, hepatic stellate cells (HSC), liver sinusoidal cells and macrophages promotes hepatic inflammation, which is key in the progression of metabolic liver disease. Hepatic stellate cells are crucial for hepatic fibrosis development, as they are the primary extracellular matrix-producing cells receiving signals from damaged hepatocytes or immune cells. The fibrogenic cytokine TGF-β has been shown to activate HSC upon exposure to high cholesterol levels [171] and further palmitate treatment of HSC leads to upregulation of several profibrogenic genes via inflammasome activation [172]. Hepatocyte cholesterol has been implicated in the development of "crown-like-structures" by activated Kupffer cells in the liver, which is a specific phenomenon in MASH and has been suggested as a mechanism of MASH progression [173]. Of note, increased hepatic "crown-like-structures" have also been described in an *ob/ob,* but not in a *db/db* mouse model [174], suggesting that this inflammatory feature might be linked to obesity- but not to diabetes-related MASH. The involvement of other immune cells in MASLD progression, such as B, T and natural killer cells has been demonstrated in mouse models, which lack these mature immune cells and at the same time exhibit decrease in liver fibrosis [175]. B cells, natural killer T cells, platelets and type 2 innate lymphoid cells favor the development of liver fibrosis, steatosis and liver injury, while natural killer cells might alleviate fibrosis by neutralizing activated HCS [175,176]. Activation of the IKKβ-NF-κB pathway by proinflammatory cytokines has been closely related with the inhibition of insulin signal transduction and the development of hepatic insulin resistance in MASLD and T2D [177]. Furthermore, activation of Toll-like receptor 4 by LPS due to gut dysbiosis and impaired intestinal permeability (see Chapter 4.2) also induces hepatic inflammation and insulin resistance [175]. In overall, inflammatory pathways promoting hepatic insulin resistance in T2D and MASLD might represent a driving force for accelerated metabolic liver disease in this population. This is supported by the notion that insulin resistant humans with diabetes are most likely to develop progressive metabolic liver disease and hepatic fibrosis [100], mechanistic evidence however is still lacking. Last, liver sinusoidal endothelial cells (LSEC) might represent an important link between hepatic insulin resistance and fibrosis. LSEC are fenestrated cells that represent the interface between hepatocytes and blood flow and communicate with hepatocytes, macrophages and HSCs. Under physiological conditions LSEC regulate lipid transport, maintain the quiescence of Kupffer cells, resident liver macrophages, and HSCs [178].

Table 1
Human randomized controlled clinical trials evaluating the effects of antihyperglycemic treatments on liver histology (MASH resolution and/or fibrosis improvement).

Study/Citation	Drug/Dose	Population	Design/ Duration	Effect on liver histology (placebo corrected resolution of MASH)	Fibrosis improvement (placebo corrected)	Metabolic effect	Side effects
Armstrong et al. Lancet 2016 [227]	Liraglutide 1.8 mg/ d	MASH±T2D n = 52	RCT 48 weeks	30 % MASH resolution without fibrosis worsening	↔	↓ Body weight 4,8 % ↓ HbA1c and glucose	GI 4 % trial discontinuation
Newsome et al. N Eng J Med 2021 [228]	Semaglutide 0.1/ 0.2/0.4 mg /d	MASH±T2D n = 320	RCT 72 weeks	19–42 % MASH resolution without fibrosis worsening	↔	↓ Body weight 4–12 % ↓ HbA1c and glucose	GI 2 % trial discontinuation
Loomba et al. N Eng J Med 2024 [233]	Tirzepatide 5/10/ 15 mg/d	MASH±T2D n = 157	RCT 52 weeks	34–53 % MASH resolution without fibrosis worsening	21–25 % with decrease of ≥ 1 fibrosis stage	↓ Body weight ↓ HbA1c	GItrial discontinuation equal to placebo (4 %)
Sanyal et al N Eng J Med 2024 [236]	Survodutide 2.4/ 4.8/6 mg	MASH±T2D n = 293	RCT 48 weeks	33–48 % MASH resolution without fibrosis worsening	12–14 % with decrease of ≥ 1 fibrosis stage	↓ Body weight ↓ HbA1c	GI 17 % trial discontinualtion
Joy TR et al. World J Gastroenterol 2017 [224]	Sitagliptin 100 mg/ d	MASH+T2D n = 12	RCT 24 weeks	No improvement in NAFLD activity score or fibrosis	↔	No effect on HbA1c or body weight	Well tolerated
Ratziu et al. Gastroenterology 2008 [195]	Rosiglitazone 8 mg/d	MASH±T2D n = 63	RCT 52 weeks	No change in NAFLD activity score ↓ Steatosis and inflammatory score	↔	↑ Body weight ↓ HbA1c and glucose	Weight gain, swollen legs
Belfort et al. Lancet 2006 [197]	Pioglitazone 45 mg/d and hypocaloric diet	MASH+T2D/IGT n = 55	RCT 24 weeks	↓ Steatosis and inflammatory score	↔	↑ Body weight ↓ HbA1c and glucose	Fatigue, swollen legs
Sanyal et al. N Eng J Med 2010 [198]	Pioglitazone 30 mg/d Vitamin E 800 IE/d	MASH±T2D n = 247	RCT 96 weeks	24 % MASH resolution with Vitamin E ↓ Steatosis and lobular inflammation with both Vitamin E and Pioglitazone	↔	↑ Body weight with Pioglitazone ↓ glucose with Pioglitazone No effect on body weight or glucose with Vitamin E	Weight gain
Cusi et al. Ann Intern Med 2016 [199]	Pioglitazone 45 mg/d and hypocaloric diet	MASH+T2D/ prediabetes n = 101	RCT 72 weeks	32 % MASH resolution	− 0.5 in fibrosis score	↑ Body weight ↓ glucose	Weight gain
Haukeland et al. Scand J Gastroent 2009 [246]	Metformin 2.5–3 g/ d	MASLD±T2D n = 48	RCT 24 weeks	No effect on NAFLD activity score No change in steatosis, inflammation or fibrosis	↔	Weight loss 4.3 kg ↓ HbA1c and glucose	GI

GI – gastrointestinal, IGT – impaired glucose tolerance, NAFLD – non-alcoholic fatty liver disease, NASH – non-alcoholic steatohepatitis, RCT – randomized placebo-controlled trial, T2D – type 2 diabetes.

During their interplay with immune cells LSEC lose their fenestrae and develop a basal membrane, which increases intrahepatic vascular resistance and could favor liver steatosis and initiate HSCs activation [178]. In the settings of MASH, LSEC display a pro-inflammatory phenotype that promotes steatohepatitis [178]. Insulin signaling in LSEC has been implicated in hepatic insulin resistance development indirectly through NO overproduction and tyrosine nitration of the insulin receptor [179], which might represent a hyperinsulinemia-driven mechanism perpetuating further liver injury in T2D and MASH.

5. Therapeutic implications

MASLD and T2D treatment strategies not only aim at reducing disease progression but eventually target T2D complications, reducing morbidity, and mortality [94]. In particular, several GLP-1 receptor agonists and SGLT-2 inhibitors exhibit not only cardiorenal but also hepatoprotective effects alongside improved glucose control, contributing to holistic diabetes care and improved patient outcomes (Table 1). Of note, the first metabolic drug targeting thyroid hormone receptor β (THRβ) has recently been approved for the treatment of MASH with fibrosis by the FDA [180].

5.1. General diabetes management through lifestyle

Adherence to a healthy lifestyle incorporating diet and regular physical activity is the first step in the management of both T2D and MASLD. Strategies to reduce body weight have proven successful as a non-pharmacological approach here, but are difficult to implement. Caloric restriction and exercise training not only improve glycemia, but can also reduce hepatic steatosis and even lead to MASH resolution [181]. A weight reduction of 10 % or more induces a resolution of MASLD [181] and improvement in hepatic steatosis is seen with weight loss of at least 5 % [182]. In a meta-analysis of 78 studies a weight loss of at least 7 % has been found to be necessary for MASLD activity score improvement [183]. Still, less than half of the patients are able to meet the goal of 7–10 % body weight reduction through intensive lifestyle modification and gain back the lost weight [181]. Long-term results of the DiRECT study also point at comparable weight loss with diet intervention and control at 5 years follow-up, suggesting that diet-induced weight loss is not a sustainable target on the long term in T2D [184].

The exclusion of dietary factors such as ultra-processed foods, saturated fat and sugar-sweetened beverages represents a common dietary goal in both T2D and MASLD, while fructose has been recognized as a major mediator of MASLD [185]. Mediterranean diet has been suggested to be beneficial both in T2D [186] and MASLD [187], with its anti-inflammatory and antioxidant effects likely underlying this link. Still, interventional trials in humans have been limited to demonstrating reduction in liver lipid content along with insulin resistance [188,189], while no histological evaluation has been reported. In overall, although dietary composition does appear to influence hepatic fat deposition, no specific macronutrient diet has been shown to have a benefit for MASH in T2D.

Exercise has beneficial effect on glucose metabolism and hepatic lipid content independent of weight loss [190] and may modify *de novo* synthesis of non-esterified fatty acids. Vigorous exercise in particular appears to limit the progression of MASLD to MASH [191], but evidence in T2D populations is limited. Bariatric surgery has also been shown effectively to lead to MASH resolution, with T2D being the only baseline variable that negatively affects MASH resolution without progression of fibrosis [192]. On the other hand, recent evidence points at T2D remission induced by bariatric surgery in people with early stages of MASLD (simple steatosis), suggesting that liver injury plays an important role for the metabolic changes after operation [193].

5.2. Anti-hyperglycemic drugs as therapy of MASH

Given the tight link between MASH and T2D various anti-hyperglycemic agents have been assessed as possible MASH treatments (Table 1). Several clinical trials examining the effects of incretins and co-agonists, insulin-sensitizing thiazolidinediones, inhibitors of the sodium–glucose cotransporter 2 (SGLT2i) as well as one THRβ-agonist on NASH have provided promising results, which will be reviewed here. Metformin, which is the most widely used antihyperglycemig agent, has not shown efficacy in MASH [246], however, its anti-tumor effects might be relevant for advanced stages of liver disease. Emerging therapies for MASH targeting the FXR, PPARα, PPARδ and PPARγ, inhibitors of DNL (acetyl-CoA carboxylase inhibitors, fatty acid synthase inhibitors, stearoyl-CoA desaturase 1 inhibitors, diacylglycerol acyltransferase inhibitors, ketohexokinase inhibitors, mitochondrial pyruvate carrier inhibitors) as well as fibroblast growth factors 19 and 21 analogues have recently been extensively reviewed elsewhere [194] and are outside the scope of this work.

5.2.1. Thiazolidinediones

Pioglitazone and rosiglitazone are potent activators of the nuclear receptor PPARɣ, which plays a critical role for adipocyte function as well as glucose and lipid metabolism. As effective insulin sensitizers thiazolidinediones promote adipose tissue triglyceride storage, enhance insulin suppression of lipolysis and improve peripheral insulin sensitivity. Rosiglitazone has proven efficient in reducing liver lipid content in two RCTs [195,196], while treatment with pioglitazone effectively improves hepatic steatosis and inflammation [197–199] (Table 1). With regard to reduction of fibrosis, pioglitazone demonstrated efficacy in some [199] but not all trials [197,198]. The beneficial histological effects of thiazolidinediones have been confirmed in a meta-analysis including 8 RCTs [200] and a concentration-dependent as well as genetic-dependent response to pioglitazone has been suggested [201,202]. However, adverse effects of these PPARɣ agonists including weight gain, oedema and risk of bone fracture have rendered them obsolete in the antidiabetic treatment currently. Still, other molecular targets of thiazolidinediones such as the mitochondrial pyruvate carrier (MPC) have been identified [203], which has led to the development of MPC inhibitors as a possible future MASH treatment option. While preclinical trials revealed alleviation of liver injury and fibrosis via limiting HSC activation [204], a human clinical trial with the MPC inhibitor MSDC-0602K did not demonstrate effects on primary and secondary liver histology endpoints, but showed improved hepatic steatosis as well as insulin sensitivity [205]. Thereby these so called PPARɣ-sparing thiazolidinediones might hold promise as modulators of various metabolic risk factors while causing fewer adverse effects than traditional PPARɣ agonists.

5.2.2. SGLT2 inhibitors

SGLT2 inhibitors are approved antihyperglycemic agents in T2D which increase the urinary excretion of glucose. In addition to weight loss their positive effects also include the reduction of cardiovascular and renal events [206]. Mechanistic preclinical studies revealed protective effects of empagliflozin on insulin resistance and hepatic lipid accumulation in parallel to improved muscle mitochondrial function [207] as well as miRNA-34a-5p-mediated inactivation of HSCs resulting in reduction of fibrosis [208]. The metabolic effects of SGLT2 inhibitors likely are linked to the energy deficit due to enhanced glucosuria which might elevate ketogenesis, NEFA oxidation and autophagic flux as well as reduce inflammation and oxidative stress [209]. Human RCTs confirmed the lowering of liver lipid content with SGLT2 inhibitor treatment [210–213], which in the case of empagliflozin was paralleled by an increase in circulating adiponectin [212] and in the case of canagliflozin related tightly to weight loss [211]. Of note, dapagliflozin and empagliflozin have also been shown to decrease liver stiffness as measured using transient elastography [213,214]. However, studies involving histologically proven MASH have been limited to two small

uncontrolled open label trials [215,216] and no placebo-controlled RCTs have been reported so far. Ipragliflozin has shown benefits in terms of improved fibrosis and MASH resolution in a liver biopsy study in humans with MASLD and T2D [217]. Of note, a comparative study of the SGLT2 inhibitor tofogliflozin with glimepiride did not find differences in the histological features between the groups, but tofogliflozin treatment was related to changes in hepatic expression of genes involved in energy metabolism, inflammation and fibrosis [218]. In overall, SGLT2 inhibitors have proven useful in the management of glycemia, cardiorenal risk and lowering liver lipid content, but further RCTs involving histological analyses are necessary to determine their effectiveness in MASH.

5.2.3. Dipeptidyl peptidase-4 (DPP4) inhibitors (DPP4i)

DPP4i are antihyperglycemic agents which enhance glucagon like peptide 1 (GLP1) activity and are approved for T2D treatment, even though they do not induce weight loss or improve cardiovascular outcomes [219]. Levels of DPP4 are increased in MASLD, obesity and T2D, which relates to fibrosis and hepatocyte apoptosis [220]. Also, adipose tissue derived DPP4 has been linked to hepatic insulin resistance in a diet-induced obesity model [221]. Again in preclinical models DPP4i prevent the progression of hepatic steatosis to MASH and HCC and inhibit inflammatory responses [222,223]. However, placebo-controlled trials revealed no beneficial effects on hepatic histology [224] or liver stiffness, using MR-elastography [225]. Thereby this class might not represent an effective treatment option for MASH in T2D.

5.2.4. Incretin mimetics and co-agonists

Incretin mimetics such as GLP1 receptor agonists (GLP1RA) act through G-protein coupled receptor to stimulate the production and release of insulin and suppress glucagon secretion while also delaying gastric emptying, inhibiting appetite and reducing food intake. In addition to their potent glucose lowering effect GLP1RA reduce body weight and improve cardiorenal outcomes [226] In humans, MASH resolution without worsening of fibrosis was achieved with liraglutide [227] and semaglutide [228] treatment in randomized placebo-controlled trials, while exenatide did not lead to histological improvements in a case series study [229]. Liraglutide effects on MASH have been related to improvements in adipose tissue and hepatic insulin resistance as well as *de novo* lipogenesis, so that a disease modifying potential has been suggested [230]. However, in humans with MASH and compensated cirrhosis no effect of semaglutide on hepatic fibrosis has been observed [231]. Notably, the beneficial effects of GLP1RA in MASH are likely related to their substantial action on body weight among other extrahepatic metabolic effects, as GLP1 receptor is not expressed in the liver at appreciable levels [232].

Double or triple incretin-receptor agonists might hold promise as future treatment of MASH in T2D as they demonstrate superiority compared to GLP1RA regarding weight loss and glycemic control. The dual glucose dependent insulinotropic polypeptide (GIP)/GLP1 receptor agonist tirzepatide effectively induces MASH resolution in humans with MASH and fibrosis [233], while the triple GIP/GLP1/glucagon receptor agonist retatrutide substantially reduces liver lipid content in humans with MASLD [234]. The dual GLP1/glucagon receptor cotadutide demonstrated improvements in transaminases, propeptide of type III collagen level and fibrosis-4 (FIB-4) score in a 54 week RCT [235], while survodutide improved MASH without worsening of fibrosis in 43–62 % of the participants in a 48 week phase 2 trial [236]. The additive effect of glucagon receptor agonism in MASLD is incompletely understood and several aspects such as glucagon resistance and direct glucagon action on hepatic energy metabolism remain of high interest for further investigation [237]. Although these initial clinical trial results are promising, longer and larger trials are still missing currently.

5.2.5. Thyroid hormone receptor β agonists

Resmetirom, a THRβ agonist, has recently been approved as first agent for pharmacological treatment of MASH and MASH-related fibrosis by the FDA. In the MAESTRO-NASH trial both primary histological endpoints MASH resolution and fibrosis improvement were achieved after 52 weeks of treatment [180]. As more than 60 % of the participants presented with T2D it is likely that resmetirom is effective in T2D populations as well, while no effect was seen on body weight or glycemia. Recent systematic analysis demonstrated that it is well-tolerated and does not generally affect thyroid function [238]. Clinical trials with further two THRβ-selective agonists (VK2809 and ASC41) are currently ongoing.

5.2.6. Combination of antihyperglycemic drugs for the therapy of MASH

While monotherapy with antihyperglycemic agents induces 19–53 % MASH resolution (Table 1), combined antihyperglycemic treatment might hold promise as more effective therapeutic option. The combination of GLP1RA and SGLT2i is safe and highly effective in terms of improving glycated hemoglobin, body weight and blood pressure compared with each class alone in T2D [239]. In addition, reduced cardiovascular events with the addition of GLP1RA to SGL2i therapy has been suggested [240], increasing the interest in further combined treatment trials. In a MASH mouse model a distinct anti-inflammatory effect of a combination treatment of dulaglutide and empagliflozin has been observed [241]. A retrospective study in 6 humans with T2D and MASLD showed that a 5-year treatment with SGLT-2 inhibitors resulted in an improvement in liver steatosis and fibrosis, and that the addition of a GLP1RA was safe [242]. Furthermore, an improvement in FIB-4 was seen with the addition of ipragiflozin to current therapy with DPP4 inhibitor or GLP1RA in a retrospective study [243]. In RCTs in humans with T2D the combined treatment with exenatide and dapagliflozin resulted in comparable reduction of liver lipid content measured from MRS as with dapagliflozin alone [244] while FIB-4 reduction was seen only in the combination therapy [245]. Future clinical trials with histological follow up assessments will reveal whether the combined treatment with SGLT2i and GLP1RA represents an effective treatment option for MASH in T2D.

6. Conclusions

Diabetes-related MASH progression is characterized by a multifaceted nature and the mutual interaction between MASH and T2D warrants further investigation of the common mechanisms and risk factors. Visceral adipose tissue expansion and altered gut microbiota are key factors in the progression of simple hepatic steatosis to MASH in individuals with T2D. Subsequently, MASH progression is accelerated by adipose tissue and muscle insulin resistance driving increased lipid influx and *de novo* lipogenesis in the liver, which favors lipotoxicity, altered mitochondrial function and oxidative stress. ER stress and inflammation further drive disease progression. In order to manage and treat diabetes-related MASH lifestyle modifications and weight loss remain of critical importance. Several anti-hyperglycemic agents show promise in improving liver histology, but their efficacy varies in treating different aspects of MASH and long-term large-scale trials are still missing.

CRediT authorship contribution statement

Sofiya Gancheva: Writing – review & editing, Writing – original draft, Visualization. **Michael Roden:** Writing – review & editing, Conceptualization. **Laurent Castera:** Writing – review & editing, Methodology, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: SG declares no competing interests. MR reports consulting fees and/or

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References

[1] Rinella ME, Lazarus JV, Ratziu V, Francque SM, Sanyal AJ, Kanwal F, et al. A multi-society Delphi consensus statement on new fatty liver disease nomenclature. J Hepatol 2023.
[2] Riazi K, Azhari H, Charette JH, Underwood FE, King JA, Afshar EE, et al. The prevalence and incidence of NAFLD worldwide: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol 2022;7(9):851–61.
[3] Devarbhavi H, Asrani SK, Arab JP, Nartey YA, Pose E, Kamath PS. Global burden of liver disease: 2023 update. J Hepatol 2023;79(2):516–37.
[4] Younossi ZM, Golabi P, Paik JM, Henry A, Van Dongen C, Henry L. The global epidemiology of nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH): a systematic review. Hepatol Baltim Md 2023;77(4):1335–47.
[5] Cusi K, Younossi Z, Roden M. From NAFLD to MASLD: Promise and pitfalls of a new definition. Hepatol Baltim Md 2024;79(2):E13–5.
[6] Song SJ, Lai JCT, Wong GLH, Wong VWS, Yip TCF. Can we use old NAFLD data under the new MASLD definition? J Hepatol 2023;S0168–8278(23):05000–6.
[7] Hagström H, Vessby J, Ekstedt M, Shang Y. 99% of patients with NAFLD meet MASLD criteria and natural history is therefore identical [cited 2023 Oct 2];0(0). Available from: J Hepatol [Internet] 2023. https://www.journal-of-hepatology.eu/article/S0168-8278(23)05080-8/fulltext.
[8] Ciardullo S, Carbone M, Invernizzi P, Perseghin G. Exploring the landscape of steatotic liver disease in the general US population. Liver Int Off J Int Assoc Study Liver 2023;43(11):2425–33.
[9] Targher G, Corey KE, Byrne CD, Roden M. The complex link between NAFLD and type 2 diabetes mellitus – mechanisms and treatments. Nat Rev Gastroenterol Hepatol 2021;18(9):599–612.
[10] En Li Cho E, Ang CZ, Quek J, Fu CE, Lim LKE, Heng ZEQ, et al. Global prevalence of non-alcoholic fatty liver disease in type 2 diabetes mellitus: an updated systematic review and meta-analysis. Gut 2023. gutjnl-2023-330110.
[11] Huang DQ, Wilson LA, Behling C, Kleiner DE, Kowdley KV, Dasarathy S, et al. Fibrosis progression rate in biopsy-proven nonalcoholic fatty liver disease among people with diabetes versus people without diabetes: A multicenter study. Gastroenterology 2023;165(2):463–472.e5.
[12] Jarvis H, Craig D, Barker R, Spiers G, Stow D, Anstee QM, et al. Metabolic risk factors and incident advanced liver disease in non-alcoholic fatty liver disease (NAFLD): A systematic review and meta-analysis of population-based observational studies. PLOS Med 2020;17(4):e1003100.
[13] El-Serag HB, Tran T, Everhart JE. Diabetes increases the risk of chronic liver disease and hepatocellular carcinoma. Gastroenterology 2004 Feb;126(2):460–8.
[14] Dulai PS, Singh S, Patel J, Soni M, Prokop LJ, Younossi Z, et al. Increased risk of mortality by fibrosis stage in nonalcoholic fatty liver disease: systematic review and meta-analysis. Hepatology 2017;65(5):1557–65.
[15] Taylor RS, Taylor RJ, Bayliss S, Hagström H, Nasr P, Schattenberg JM, et al. Association between fibrosis stage and outcomes of patients with nonalcoholic fatty liver disease: a systematic review and meta-analysis. Gastroenterology 2020;158(6):1611–1625.e12.
[16] Sanyal AJ, Van Natta ML, Clark J, Neuschwander-Tetri BA, Diehl A, Dasarathy S, et al. Prospective study of outcomes in adults with nonalcoholic fatty liver disease. N Engl J Med 2021;385(17):1559–69.
[17] Zoppini G, Fedeli U, Gennaro N, Saugo M, Targher G, Bonora E. Mortality from chronic liver diseases in diabetes. Am J Gastroenterol 2014;109(7):1020–5.
[18] Mantovani A, Scorletti E, Mosca A, Alisi A, Byrne CD, Targher G. Complications, morbidity and mortality of nonalcoholic fatty liver disease. Metabolism 2020;111S:154170.
[19] Ciardullo S, Monti T, Perseghin G. Lack of awareness of liver organ damage in patients with type 2 diabetes. Acta Diabetol 2021;58(5):651–5.
[20] Polanco-Briceno S, Glass D, Stuntz M, Caze A. Awareness of nonalcoholic steatohepatitis and associated practice patterns of primary care physicians and specialists. BMC Res Notes 2016;11(9):157.
[21] Younossi ZM, Tampi RP, Racila A, Qiu Y, Burns L, Younossi I, et al. Economic and clinical burden of nonalcoholic steatohepatitis in patients with type 2 diabetes in the U.S. Diabetes Care 2020;43(2):283–9.
[22] Castera L, Friedrich-Rust M, Loomba R. Noninvasive assessment of liver disease in patients with nonalcoholic fatty liver disease. Gastroenterology 2019;156(5):1264–1281.e4.
[23] Ciardullo S, Vergani M, Perseghin G. Nonalcoholic fatty liver disease in patients with type 2 diabetes: screening, diagnosis, and treatment. J Clin Med 2023;12(17):5597.
[24] Qi X, Li J, Caussy C, Teng GJ, Loomba R. Epidemiology, screening, and co-management of type 2 diabetes mellitus and metabolic dysfunction-associated steatotic liver disease. Hepatol Baltim Md 2024.
[25] Hossain N, Afendy A, Stepanova M, Nader F, Srishord M, Rafiq N, et al. Independent predictors of fibrosis in patients with nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol 2009;7(11):1224–9. 229.e1-2.
[26] Romeo S, Kozlitina J, Xing C, Pertsemlidis A, Cox D, Pennacchio LA, et al. Genetic variation in PNPLA3 confers susceptibility to nonalcoholic fatty liver disease. Nat Genet 2008;40(12):1461–5.
[27] BasuRay S, Wang Y, Smagris E, Cohen JC, Hobbs HH. Accumulation of PNPLA3 on lipid droplets is the basis of associated hepatic steatosis. Proc Natl Acad Sci U S A 2019;116(19):9521–6.
[28] Kozlitina J, Smagris E, Stender S, Nordestgaard BG, Zhou HH, Tybjærg-Hansen A, et al. Exome-wide association study identifies a TM6SF2 variant that confers susceptibility to nonalcoholic fatty liver disease. Nat Genet 2014;46(4):352–6.
[29] Mancina RM, Dongiovanni P, Petta S, Pingitore P, Meroni M, Rametta R, et al. The MBOAT7-TMC4 variant rs641738 increases risk of nonalcoholic fatty liver disease in individuals of European descent. Gastroenterology 2016;150(5):1219–1230.e6.
[30] Brouwers MCGJ, Simons N, Stehouwer CDA, Koek GH, Schaper NC, Isaacs A. Relationship between nonalcoholic fatty liver disease susceptibility genes and coronary artery disease. Hepatol Commun. 3(4):587.
[31] Liu YL, Patman GL, Leathart JBS, Piguet AC, Burt AD, Dufour JF, et al. Carriage of the PNPLA3 rs738409 C >G polymorphism confers an increased risk of non-alcoholic fatty liver disease associated hepatocellular carcinoma. J Hepatol 2014;61(1):75–81.
[32] Anstee QM, Darlay R, Cockell S, Meroni M, Govaere O, Tiniakos D, et al. Genome-wide association study of non-alcoholic fatty liver and steatohepatitis in a histologically characterised cohort☆. J Hepatol 2020;73(3):505–15.
[33] Thangapandi VR, Knittelfelder O, Brosch M, Patsenker E, Vvedenskaya O, Buch S, et al. Loss of hepatic Mboat7 leads to liver fibrosis. Gut 2021;70(5):940–50.
[34] Gabriel-Medina P, Ferrer-Costa R, Rodriguez-Frias F, Ciudin A, Augustin S, Rivera-Esteban J, et al. Influence of type 2 diabetes in the association of PNPLA3 rs738409 and TM6SF2 rs58542926 polymorphisms in NASH advanced liver fibrosis. Biomedicines 2022;10(5):1015.
[35] Szendroedi J, Saxena A, Weber KS, Strassburger K, Herder C, Burkart V, et al. Cohort profile: the German Diabetes Study (GDS). Cardiovasc Diabetol 2016;7(15):59.
[36] Bódis K, Bombrich M, Schön M, Knebel B, Zaharia OP, Bönhof G, et al. Effects of TM6SF2 rs58542926 polymorphism on hepatocellular lipids and insulin resistance in early type 2 diabetes. Nutr Metab Cardiovasc Dis NMCD 2023;33(9):1785–96.
[37] Zaharia OP, Strassburger K, Knebel B, Kupriyanova Y, Karusheva Y, Wolkersdorfer M, et al. Role of patatin-like phospholipase domain-containing 3 gene for hepatic lipid content and insulin resistance in diabetes. Diabetes Care 2020;43(9):2161–8.
[38] Luukkonen PK, Porthan K, Ahlholm N, Rosqvist F, Dufour S, Zhang XM, et al. The PNPLA3 I148M variant increases ketogenesis and decreases hepatic de novo lipogenesis and mitochondrial function in humans. Cell Metab 2023. S1550413123003777.
[39] Banini BA, Kumar DP, Cazanave S, Seneshaw M, Mirshahi F, Santhekadur PK, et al. Identification of a metabolic, transcriptomic, and molecular signature of patatin-like phospholipase domain containing 3-mediated acceleration of steatohepatitis. Hepatol Baltim Md 2021;73(4):1290–306.
[40] Li G, Tang LJ, Zhu PW, Huang OY, Rios RS, Zheng KI, et al. PNPLA3 rs738409 C>G variant influences the association between visceral fat and significant fibrosis in biopsy-proven nonalcoholic fatty liver disease. J Clin Transl Hepatol 2022;10(3):439–48.
[41] Singal AG, Manjunath H, Yopp AC, Beg MS, Marrero JA, Gopal P, et al. The effect of PNPLA3 on fibrosis progression and development of hepatocellular carcinoma: a meta-analysis. Am J Gastroenterol 2014;109(3):325–34.
[42] Kawaguchi T, Sumida Y, Umemura A, Matsuo K, Takahashi M, Takamura T, et al. Genetic polymorphisms of the human PNPLA3 gene are strongly associated with severity of non-alcoholic fatty liver disease in Japanese. PLoS One 2012;7(6):e38322.
[43] Xourafa G, Korbmacher M, Roden M. Inter-organ crosstalk during development and progression of type 2 diabetes mellitus. Nat Rev Endocrinol 2023.

[44] Ngo Sock ET, Lê KA, Ith M, Kreis R, Boesch C, Tappy L. Effects of a short-term overfeeding with fructose or glucose in healthy young males. Br J Nutr 2010;103(7):939–43.

[45] Theytaz F, Noguchi Y, Egli L, Campos V, Buehler T, Hodson L, et al. Effects of supplementation with essential amino acids on intrahepatic lipid concentrations during fructose overfeeding in humans. Am J Clin Nutr 2012;96(5):1008–16.

[46] Lê KA, Ith M, Kreis R, Faeh D, Bortolotti M, Tran C, et al. Fructose overconsumption causes dyslipidemia and ectopic lipid deposition in healthy subjects with and without a family history of type 2 diabetes. Am J Clin Nutr 2009;89(6):1760–5.

[47] Jeyapal S, Putcha UK, Mullapudi VS, Ghosh S, Sakamuri A, Kona SR, et al. Chronic consumption of fructose in combination with trans fatty acids but not with saturated fatty acids induces nonalcoholic steatohepatitis with fibrosis in rats. Eur J Nutr 2018;57(6):2171–87.

[48] Jensen T, Abdelmalek MF, Sullivan S, Nadeau KJ, Green M, Roncal C, et al. Fructose and sugar: A major mediator of non-alcoholic fatty liver disease. J Hepatol 2018;68(5):1063–75.

[49] Wei Y, Wang D, Topczewski F, Pagliassotti MJ. Saturated fatty acids induce endoplasmic reticulum stress and apoptosis independently of ceramide in liver cells. Am J Physiol Endocrinol Metab 2006;291(2):E275–81.

[50] Han J, Kaufman RJ. The role of ER stress in lipid metabolism and lipotoxicity. J Lipid Res 2016;57(8):1329–38.

[51] Sarabhai T, Kahl S, Szendroedi J, Markgraf DF, Zaharia OP, Barosa C, et al. Monounsaturated fat rapidly induces hepatic gluconeogenesis and whole-body insulin resistance. JCI Insight 5(10):e134520.

[52] Hernández E, Kahl S, Seelig A, Begovatz P, Irmler M, Kupriyanova Y, et al. Acute dietary fat intake initiates alterations in energy metabolism and insulin resistance. J Clin Invest 2017;127(2):695–708.

[53] Luukkonen PK, Sädevirta S, Zhou Y, Kayser B, Ali A, Ahonen L, et al. Saturated fat is more metabolically harmful for the human liver than unsaturated fat or simple sugars. Diabetes Care 2018;41(8):1732–9.

[54] Manilla V, Santopaolo F, Gasbarrini A, Ponziani FR. Type 2 diabetes mellitus and liver disease: across the gut-liver axis from fibrosis to cancer. Nutrients 2023;15(11):2521.

[55] Chen SN, Tan Y, Xiao XC, Li Q, Wu Q, Peng YY, et al. Deletion of TLR4 attenuates lipopolysaccharide-induced acute liver injury by inhibiting inflammation and apoptosis. Acta Pharmacol Sin 2021;42(10):1610–9.

[56] Rivera CA, Adegboyega P, van Rooijen N, Tagalicud A, Allman M, Wallace M. Toll-like receptor-4 signaling and Kupffer cells play pivotal roles in the pathogenesis of non-alcoholic steatohepatitis. J Hepatol 2007;47(4):571–9.

[57] Mouries J, Brescia P, Silvestri A, Spadoni I, Sorribas M, Wiest R, et al. Microbiota-driven gut vascular barrier disruption is a prerequisite for non-alcoholic steatohepatitis development. J Hepatol 2019;71(6):1216–28.

[58] Albillos A, de Gottardi A, Rescigno M. The gut-liver axis in liver disease: Pathophysiological basis for therapy. J Hepatol 2020;72(3):558–77.

[59] Bazick J, Donithan M, Neuschwander-Tetri BA, Kleiner D, Brunt EM, Wilson L, et al. Clinical model for NASH and advanced fibrosis in adult patients with diabetes and NAFLD: guidelines for referral in NAFLD. Diabetes Care 2015;38(7):1347–55.

[60] Castera L, Laouenan C, Vallet-Pichard A, Vidal-Trécan T, Manchon P, Paradis V, et al. High Prevalence of NASH and advanced fibrosis in type 2 diabetes: A prospective study of 330 outpatients undergoing liver biopsies for elevated ALT, using a low threshold. Diabetes Care 2023;46(7):1354–62.

[61] Ajmera V, Cepin S, Tesfai K, Hofflich H, Cadman K, Lopez S, et al. A prospective study on the prevalence of NAFLD, advanced fibrosis, cirrhosis and hepatocellular carcinoma in people with type 2 diabetes. J Hepatol 2023;78(3):471–8.

[62] Ooi GJ, Burton PR, Bayliss J, Raajendiran A, Earnest A, Laurie C, et al. Effect of body mass index, metabolic health and adipose tissue inflammation on the severity of non-alcoholic fatty liver disease in bariatric surgical patients: a prospective study. Obes Surg 2019;29(1):99–108.

[63] Chen F, Esmaili S, Rogers GB, Bugianesi E, Petta S, Marchesini G, et al. Lean NAFLD: a distinct entity shaped by differential metabolic adaptation. Hepatol Baltim Md 2020;71(4):1213–27.

[64] Weinberg EM, Trinh HN, Firpi RJ, Bhamidimarri KR, Klein S, Durlam J, et al. Lean Americans with nonalcoholic fatty liver disease have lower rates of cirrhosis and comorbid diseases. Clin Gastroenterol Hepatol 2021;19(5):996–1008.e6.

[65] Leung JCF, Loong TCW, Wei JL, Wong GLH, Chan AWH, Choi PCL, et al. Histological severity and clinical outcomes of nonalcoholic fatty liver disease in nonobese patients. Hepatology 2017;65(1):54–64.

[66] Wang Q, You H, Ou X, Zhao X, Sun Y, Wang M, et al. Non-obese histologically confirmed NASH patients with abnormal liver biochemistry have more advanced fibrosis. Hepatol Int 2019;13(6):766–76.

[67] Sako S, Takeshita Y, Takayama H, Goto H, Nakano Y, Ando H, et al. Trajectories of liver fibrosis and gene expression profiles in nonalcoholic fatty liver disease associated with diabetes. Diabetes 2023;72(9):1297–306.

[68] Chen Z, Qin H, Qiu S, Chen G, Chen Y. Correlation of triglyceride to high-density lipoprotein cholesterol ratio with nonalcoholic fatty liver disease among the non-obese Chinese population with normal blood lipid levels: a retrospective cohort research. Lipids Health Dis 2019;18(1):162.

[69] Méndez-Sánchez N, Cerda-Reyes E, Higuera-de-la-Tijera F, Salas-García AK, Cabrera-Palma S, Cabrera-Álvarez G, et al. Dyslipidemia as a risk factor for liver fibrosis progression in a multicentric population with non-alcoholic steatohepatitis. F1000Research 2020;9:56.

[70] Yang MH, Sung J, Gwak GY. The associations between apolipoprotein B, A1, and the B/A1 ratio and nonalcoholic fatty liver disease in both normal-weight and overweight Korean population. J Clin Lipidol 2016;10(2):289–98.

[71] Bril F, Sninsky JJ, Baca AM, Superko HR, Portillo Sanchez P, Biernacki D, et al. Hepatic steatosis and insulin resistance, but not steatohepatitis, promote atherogenic dyslipidemia in NAFLD. J Clin Endocrinol Metab 2016;101(2):644–52.

[72] Peng K, Mo Z, Tian G. Serum lipid abnormalities and nonalcoholic fatty liver disease in adult males. Am J Med Sci 2017;353(3):236–41.

[73] Julián MT, Pera G, Soldevila B, Caballería L, Julve J, Puig-Jové C, et al. Atherogenic dyslipidemia, but not hyperglycemia, is an independent factor associated with liver fibrosis in subjects with type 2 diabetes and NAFLD: a population-based study. Eur J Endocrinol 2021;184(4):587–96.

[74] Deprince A, Haas JT, Staels B. Dysregulated lipid metabolism links NAFLD to cardiovascular disease. Mol Metab 2020;1(42):101092.

[75] Nderitu P, Bosco C, Garmo H, Holmberg L, Malmström H, Hammar N, et al. The association between individual metabolic syndrome components, primary liver cancer and cirrhosis: A study in the Swedish AMORIS cohort. Int J Cancer 2017;141(6):1148–60.

[76] Kanwal F, Kramer JR, Li L, Dai J, Natarajan Y, Yu X, et al. Effect of metabolic traits on the risk of cirrhosis and hepatocellular cancer in nonalcoholic fatty liver disease. Hepatol Baltim Md 2020;71(3):808–19.

[77] Targher G, Bertolini L, Padovani R, Rodella S, Tessari R, Zenari L, et al. Prevalence of nonalcoholic fatty liver disease and its association with cardiovascular disease among type 2 diabetic patients. Diabetes Care 2007;30(5):1212–8.

[78] Tziomalos K, Athyros VG, Paschos P, Karagiannis A. Nonalcoholic fatty liver disease and statins. Metabolism 2015;64(10):1215–23.

[79] Nelson A, Torres DM, Morgan AE, Fincke C, Harrison SA. A pilot study using simvastatin in the treatment of nonalcoholic steatohepatitis: A randomized placebo-controlled trial. J Clin Gastroenterol 2009;43(10):990–4.

[80] Barb D, Cusi K. Reply to “statins and non-alcoholic steatohepatitis”. Metabolism 2017;1(66):e3–5.

[81] Bril F, Portillo Sanchez P, Lomonaco R, Orsak B, Hecht J, Tio F, et al. Liver safety of statins in prediabetes or T2DM and nonalcoholic steatohepatitis: post hoc analysis of a randomized trial. J Clin Endocrinol Metab 2017;102(8):2950–61.

[82] Lebeau PF, Byun JH, Platko K, MacDonald ME, Poon SV, Faiyaz M, et al. Diet-induced hepatic steatosis abrogates cell-surface LDLR by inducing de novo PCSK9 expression in mice. J Biol Chem 2019;294(23):9037–47.

[83] Momtazi-Borojeni AA, Banach M, Ruscica M, Sahebkar A. The role of PCSK9 in NAFLD/NASH and therapeutic implications of PCSK9 inhibition. Expert Rev Clin Pharmacol 2022;15(10):1199–208.

[84] Calkin AC, Tontonoz P. Transcriptional integration of metabolism by the nuclear sterol-activated receptors LXR and FXR. Nat Rev Mol Cell Biol 2012;13(4):213–24.

[85] Wang X, Cai B, Yang X, Sonubi OO, Zheng Z, Ramakrishnan R, et al. Cholesterol stabilizes TAZ in hepatocytes to promote experimental non-alcoholic steatohepatitis. Cell Metab 2020;31(5):969–986.e7.

[86] Gan LT, Van Rooyen DM, Koina ME, McCuskey RS, Teoh NC, Farrell GC. Hepatocyte free cholesterol lipotoxicity results from JNK1-mediated mitochondrial injury and is HMGB1 and TLR4-dependent. J Hepatol 2014;61(6):1376–84.

[87] Fabbrini E, Mohammed BS, Magkos F, Korenblat KM, Patterson BW, Klein S. alterations in adipose tissue and hepatic lipid kinetics in obese men and women with nonalcoholic fatty liver disease. Gastroenterology 2008;134(2):424–31.

[88] Mittendorfer B, Yoshino M, Patterson BW, Klein S. VLDL triglyceride kinetics in lean, overweight, and obese men and women. J Clin Endocrinol Metab 2016;101(11):4151–60.

[89] Li Z, Zhang B, Liu Q, Tao Z, Ding L, Guo B, et al. Genetic association of lipids and lipid-lowering drug target genes with non-alcoholic fatty liver disease. eBioMedicine [Internet] 2023 [cited 2023 Oct 25];90. Available from: https://www.thelancet.com/journals/ebiom/article/PIIS2352-3964(23)00108-1/fulltext.

[90] Younossi ZM, Golabi P, de Avila L, Paik JM, Srishord M, Fukui N, et al. The global epidemiology of NAFLD and NASH in patients with type 2 diabetes: A systematic review and meta-analysis. J Hepatol 2019;71(4):793–801.

[91] Abeysekera KWM, Valenti L, Younossi Z, Dillon JF, Allen AM, Nourredin M, et al. Implementation of a liver health check in people with type 2 diabetes. Lancet Gastroenterol Hepatol 2024;9(1):83–91.

[92] Ciardullo S, Monti T, Perseghin G. High prevalence of advanced liver fibrosis assessed by transient elastography among U.S. adults with type 2 diabetes. Diabetes Care 2021;44(2):519–25.

[93] Kwok R, Choi KC, Wong GLH, Zhang Y, Chan HLY, Luk AOY, et al. Screening diabetic patients for non-alcoholic fatty liver disease with controlled attenuation parameter and liver stiffness measurements: a prospective cohort study. Gut 2016;65(8):1359–68.

[94] European Association for the Study of the Liver (EASL). Electronic address: easloffice@easloffice.eu, European Association for the Study of Diabetes (EASD), European Association for the Study of Obesity (EASO), European Association for the Study of the Liver (EASL). EASL-EASD-EASO Clinical Practice Guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD). J Hepatol 2024;S0168-8278(24)00329-5.

[95] Cusi K, Isaacs S, Barb D, Basu R, Caprio S, Garvey WT, et al. American Association of Clinical Endocrinology Clinical Practice Guideline for the Diagnosis and Management of Nonalcoholic Fatty Liver Disease in Primary Care and Endocrinology Clinical Settings: Co-Sponsored by the American Association for the Study of Liver Diseases (AASLD). Endocr Pract Off J Am Coll Endocrinol Am Assoc Clin Endocrinol 2022;28(5):528–62.

[96] Rinella ME, Neuschwander-Tetri BA, Siddiqui MS, Abdelmalek MF, Caldwell S, Barb D, et al. AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease. Hepatol Baltim Md 2023;77(5):1797–835.
[97] El Sayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, et al. 4. Comprehensive medical evaluation and assessment of comorbidities: standards of care in diabetes-2023. Diabetes Care 2023;46(Suppl 1):S49–67.
[98] Ciardullo S, Perseghin G. Prevalence of elevated liver stiffness in patients with type 1 and type 2 diabetes: A systematic review and meta-analysis. Diabetes Res Clin Pract 2022;190:109981.
[99] Harman DJ, Kaye PV, Harris R, Suzuki A, Gazis A, Aithal GP. Prevalence and natural history of histologically proven chronic liver disease in a longitudinal cohort of patients with type 1 diabetes. Hepatol Baltim Md 2014;60(1):158–68.
[100] Zaharia OP, Strassburger K, Strom A, Bönhof GJ, Karusheva Y, Antoniou S, et al. Risk of diabetes-associated diseases in subgroups of patients with recent-onset diabetes: a 5-year follow-up study. Lancet Diabetes Endocrinol 2019;7(9):684–94.
[101] Dewidar B, Kahl S, Pafili K, Roden M. Metabolic liver disease in diabetes - From mechanisms to clinical trials. Metabolism 2020;111S:154299.
[102] Koliaki C, Roden M. Hepatic energy metabolism in human diabetes mellitus, obesity and non-alcoholic fatty liver disease. Mol Cell Endocrinol 2013;379(1–2):35–42.
[103] Vacca M, Kamzolas I, Harder LM, Oakley F, Trautwein C, Hatting M, et al. An unbiased ranking of murine dietary models based on their proximity to human metabolic dysfunction-associated steatotic liver disease (MASLD). Nat Metab 2024;6(6):1178–96.
[104] Abuduyimiti T, Goto H, Kimura K, Oshima Y, Tanida R, Kamoshita K, et al. Diabetes accelerates steatohepatitis in mice: liver pathology and single-cell gene expression signatures. Am J Pathol 2024;194(5):693–707.
[105] Kupriyanova Y, Zaharia OP, Bobrov P, Karusheva Y, Burkart V, Szendroedi J, et al. Early changes in hepatic energy metabolism and lipid content in recent-onset type 1 and 2 diabetes mellitus. J Hepatol 2020.
[106] Bódis K, Roden M. Energy metabolism of white adipose tissue and insulin resistance in humans. Eur J Clin Invest 2018;48(11):e13017.
[107] McGlinchey AJ, Govaere O, Geng D, Ratziu V, Allison M, Bousier J, et al. Metabolic signatures across the full spectrum of non-alcoholic fatty liver disease. JHEP Rep Innov Hepatol 2022;4(5):100477.
[108] Ter Horst KW, Gilijamse PW, Versteeg RI, Ackermans MT, Nederveen AJ, la Fleur SE, et al. Hepatic diacylglycerol-associated protein kinase Cε translocation links hepatic steatosis to hepatic insulin resistance in humans. Cell Rep 2017;19(10):1997–2004.
[109] Lyu K, Zhang Y, Zhang D, Kahn M, Ter Horst KW, Rodrigues MRS, et al. A membrane-bound diacylglycerol species induces PKCε-mediated hepatic insulin resistance. Cell Metab 2020;32(4):654–664.e5.
[110] Brandon AE, Liao BM, Diakanastasis B, Parker BL, Raddatz K, McManus SA, et al. Protein kinase C epsilon deletion in adipose tissue, but not in liver, improves glucose tolerance. Cell Metab 2019;29(1):183–191.e7.
[111] Pafili K, Kahl S, Mastrototaro L, Strassburger K, Pesta D, Herder C, et al. Mitochondrial respiration is decreased in visceral but not subcutaneous adipose tissue in obese individuals with fatty liver disease. J Hepatol 2022;77(6):1504–14.
[112] Carruthers NJ, Strieder-Barboza C, Caruso JA, Flesher CG, Baker NA, Kerk SA, et al. The human type 2 diabetes-specific visceral adipose tissue proteome and transcriptome in obesity. Sci Rep 2021;11(1):17394.
[113] Coombes JD, Choi SS, Swiderska-Syn M, Manka P, Reid DT, Palma E, et al. Osteopontin is a proximal effector of leptin-mediated non-alcoholic steatohepatitis (NASH) fibrosis. Biochim Biophys Acta 2016;1862(1):135–44.
[114] Saxena NK, Ikeda K, Rockey DC, Friedman SL, Anania FA. Leptin in hepatic fibrosis: evidence for increased collagen production in stellate cells and lean littermates of ob/ob mice. Hepatol Baltim Md 2002;35(4):762–71.
[115] Aleffi S, Petrai I, Bertolani C, Parola M, Colombatto S, Novo E, et al. Upregulation of proinflammatory and proangiogenic cytokines by leptin in human hepatic stellate cells. Hepatol Baltim Md 2005;42(6):1339–48.
[116] Jiménez-Cortegana C, García-Galey A, Tami M, del Pino P, Carmona I, López S, et al. Role of leptin in non-alcoholic fatty liver disease. Biomedicines 2021;9(7):762.
[117] Boutari C, Perakakis N, Mantzoros CS. Association of adipokines with development and progression of nonalcoholic fatty liver disease. Endocrinol Metab 2018;33(1):33–43.
[118] Angulo P, Alba LM, Petrovic LM, Adams LA, Lindor KD, Jensen MD. Leptin, insulin resistance, and liver fibrosis in human nonalcoholic fatty liver disease. J Hepatol 2004;41(6):943–9.
[119] Chitturi S, Farrell G, Frost L, Kriketos A, Lin R, Fung C, et al. Serum leptin in NASH correlates with hepatic steatosis but not fibrosis: a manifestation of lipotoxicity? Hepatol Baltim Md 2002;36(2):403–9.
[120] Rotundo L, Persaud A, Feurdean M, Ahlawat S, Kim HS. The Association of leptin with severity of non-alcoholic fatty liver disease: A population-based study. Clin Mol Hepatol 2018;24(4):392–401.
[121] Ferrante SC, Nadler EP, Pillai DK, Hubal MJ, Wang Z, Wang JM, et al. Adipocyte-derived exosomal miRNAs: a novel mechanism for obesity-related disease. Pediatr Res 2015;77(3):447–54.
[122] Zhang T, Hu J, Wang X, Zhao X, Li Z, Niu J, et al. MicroRNA-378 promotes hepatic inflammation and fibrosis via modulation of the NF-κB-TNFα pathway. J Hepatol 2019;70(1):87–96.
[123] Cani PD, Amar J, Iglesias MA, Poggi M, Knauf C, Bastelica D, et al. Metabolic endotoxemia initiates obesity and insulin resistance. Diabetes 2007;56(7):1761–72.
[124] Thaiss CA, Levy M, Grosheva I, Zheng D, Soffer E, Blacher E, et al. Hyperglycemia drives intestinal barrier dysfunction and risk for enteric infection. Science 2018;359(6382):1376–83.
[125] Gomes JMG, Costa J de A, Alfenas R de CG. Metabolic endotoxemia and diabetes mellitus: A systematic review. Metabolism 2017;68:133–44.
[126] Niederreiter L, Tilg H. Cytokines and fatty liver diseases. Liver Res 2018 1;2(1):14–20.
[127] Yuan J, Baker SS, Liu W, Alkhouri R, Baker RD, Xie J, et al. Endotoxemia unrequired in the pathogenesis of pediatric nonalcoholic steatohepatitis. J Gastroenterol Hepatol 2014;29(6):1292–8.
[128] León-Mimila P, Villamil-Ramírez H, Li XS, Shih DM, Hui ST, Ocampo-Medina E, et al. Trimethylamine N-oxide levels are associated with NASH in obese subjects with type 2 diabetes. Diabetes Metab 2021;47(2):101183.
[129] Hai S, Li X, Xie E, Wu W, Gao Q, Yu B, et al. Intestinal IL-33 promotes microbiota-derived trimethylamine N-oxide synthesis and drives metabolic dysfunction–associated steatotic liver disease progression by exerting dual regulation on HIF-1α. Hepatology:10.1097/HEP.0000000000000985.
[130] Jang JW, Capaldi E, Smith T, Verma P, Varga J, Ho KJ. Trimethylamine N-oxide: a meta-organismal axis linking the gut and fibrosis. Mol Med Camb Mass 2024;30(1):128.
[131] Forlano R, Martinez-Gili L, Takis P, Miguens-Blanco J, Liu T, Triantafyllou E, et al. Disruption of gut barrier integrity and host–microbiome interactions underlie MASLD severity in patients with type-2 diabetes mellitus. Gut Microbes. 16(1):2304157.
[132] Aron-Wisnewsky J, Vigliotti C, Witjes J, Le P, Holleboom AG, Verheij J, et al. Gut microbiota and human NAFLD: disentangling microbial signatures from metabolic disorders. Nat Rev Gastroenterol Hepatol 2020;17(5):279–97.
[133] Boursier J, Mueller O, Barret M, Machado M, Fizanne L, Araujo-Perez F, et al. The severity of NAFLD is associated with gut dysbiosis and shift in the metabolic function of the gut microbiota. Hepatol Baltim Md 2016;63(3):764–75.
[134] Mouzaki M, Comelli EM, Arendt BM, Bonengel J, Fung SK, Fischer SE, et al. Intestinal microbiota in patients with nonalcoholic fatty liver disease. Hepatol Baltim Md 2013;58(1):120–7.
[135] Gurung M, Li Z, You H, Rodrigues R, Jump DB, Morgun A, et al. Role of gut microbiota in type 2 diabetes pathophysiology. EBioMedicine 2020;3(51):102590.
[136] Zhu L, Baker SS, Gill C, Liu W, Alkhouri R, Baker RD, et al. Characterization of gut microbiomes in nonalcoholic steatohepatitis (NASH) patients: A connection between endogenous alcohol and NASH. Hepatology 2013;57(2):601–9.
[137] Nair S, Cope K, Risby TH, Diehl AM. Obesity and female gender increase breath ethanol concentration: potential implications for the pathogenesis of nonalcoholic steatohepatitis. Am J Gastroenterol 2001;96(4):1200–4.
[138] Clifford BL, Sedgeman LR, Williams KJ, Morand P, Cheng A, Jarrett KE, et al. FXR activation protects against NAFLD via bile-acid-dependent reductions in lipid absorption. Cell Metab 2021;33(8):1671–1684.e4.
[139] Prawitt J, Abdelkarim M, Stroeve JHM, Popescu I, Duez H, Velagapudi VR, et al. Farnesoid X receptor deficiency improves glucose homeostasis in mouse models of obesity. Diabetes 2011;60(7):1861–71.
[140] Enooku K, Tsutsumi T, Kondo M, Fujiwara N, Sasako T, Shibahara J, et al. Hepatic FATP5 expression is associated with histological progression and loss of hepatic fat in NAFLD patients. J Gastroenterol 2020;55(2):227–43.
[141] Hubbard B, Doege H, Punreddy S, Wu H, Huang X, Kaushik VK, et al. Mice deleted for fatty acid transport protein 5 have defective bile acid conjugation and are protected from obesity. Gastroenterology 2006;130(4):1259–69.
[142] Smith GI, Shankaran M, Yoshino M, Schweitzer GG, Chondronikola M, Beals JW, et al. Insulin resistance drives hepatic de novo lipogenesis in nonalcoholic fatty liver disease. J Clin Invest 2020;130(3):1453–60.
[143] Sanders FWB, Griffin JL. De novo lipogenesis in the liver in health and disease: more than just a shunting yard for glucose. Biol Rev 2016;91(2):452–68.
[144] Jelenik T, Kaul K, Sequaris G, Flogel U, Phielix E, Kotzka J, et al. Mechanisms of insulin resistance in primary and secondary nonalcoholic fatty liver. Diabetes 2017;66(8):2241–53.
[145] Higuchi N, Kato M, Shundo Y, Tajiri H, Tanaka M, Yamashita N, et al. Liver X receptor in cooperation with SREBP-1c is a major lipid synthesis regulator in nonalcoholic fatty liver disease. Hepatol Res Off J Jpn Soc Hepatol 2008;38(11):1122–9.
[146] Caballero F, Fernández A, De Lacy AM, Fernández-Checa JC, Caballería J, García-Ruiz C. Enhanced free cholesterol, SREBP-2 and StAR expression in human NASH. J Hepatol 2009;50(4):789–96.
[147] Benhamed F, Denechaud PD, Lemoine M, Robichon C, Moldes M, Bertrand-Michel J, et al. The lipogenic transcription factor ChREBP dissociates hepatic steatosis from insulin resistance in mice and humans. J Clin Invest 2012;122(6):2176–94.
[148] Loomba R, Friedman SL, Shulman GI. Mechanisms and disease consequences of nonalcoholic fatty liver disease. Cell 2021;184(10):2537–64.
[149] Apostolopoulou M, Gordillo R, Koliaki C, Gancheva S, Jelenik T, De Filippo E, et al. Specific hepatic sphingolipids relate to insulin resistance, oxidative stress, and inflammation in nonalcoholic steatohepatitis. Diabetes Care 2018;41(6):1235–43.
[150] Luukkonen PK, Zhou Y, Sädevirta S, Leivonen M, Arola J, Orešič M, et al. Hepatic ceramides dissociate steatosis and insulin resistance in patients with non-alcoholic fatty liver disease. J Hepatol 2016;64(5):1167–75.
[151] Haus JM, Kashyap SR, Kasumov T, Zhang R, Kelly KR, Defronzo RA, et al. Plasma ceramides are elevated in obese subjects with type 2 diabetes and correlate with the severity of insulin resistance. Diabetes 2009;58(2):337–43.

[152] Fromenty B, Roden M. Mitochondrial alterations in fatty liver diseases. J Hepatol 2023;78(2):415–29.
[153] Koliaki C, Szendroedi J, Kaul K, Jelenik T, Nowotny P, Jankowiak F, et al. Adaptation of hepatic mitochondrial function in humans with non-alcoholic fatty liver is lost in steatohepatitis. Cell Metab 2015;21(5):739–46.
[154] Pedersen JS, Rygg MO, Chrøis K, Sustarsic EG, Gerhart-Hines Z, Wever Albrechtsen NJ, et al. Influence of NAFLD and bariatric surgery on hepatic and adipose tissue mitochondrial biogenesis and respiration. Nat Commun 2022;13 (1):2931.
[155] Pérez-Carreras M, Del Hoyo P, Martín MA, Rubio JC, Martín A, Castellano G, et al. Defective hepatic mitochondrial respiratory chain in patients with nonalcoholic steatohepatitis. Hepatology 2003;38(4):999–1007.
[156] Lund MT, Kristensen M, Hansen M, Tveskov L, Floyd AK, Støckel M, et al. Hepatic mitochondrial oxidative phosphorylation is normal in obese patients with and without type 2 diabetes. J Physiol 2016;594(15):4351–8.
[157] Petersen KF, Befroy DE, Dufour S, Rothman DL, Shulman GI. Direct assessment of hepatic mitochondrial oxidation and pyruvate cycling in non alcoholic fatty liver disease by 13C magnetic resonance spectroscopy. Cell Metab 2016;24(1):167–71.
[158] Gancheva S, Kahl S, Pesta D, Mastrototaro L, Dewidar B, Strassburger K, et al. Impaired hepatic mitochondrial capacity in nonalcoholic steatohepatitis associated with type 2 diabetes. Diabetes Care 2022;45(4):928–37.
[159] Cortez-Pinto H, Chatham J, Chacko VP, Arnold C, Rashid A, Diehl AM. Alterations in liver ATP homeostasis in human nonalcoholic steatohepatitis: a pilot study. Jama 1999;282(17):1659–64.
[160] Traussnigg S, Kienbacher C, Gajdošík M, Valkovič L, Halilbasic E, Stift J, et al. Ultra-high-field magnetic resonance spectroscopy in non-alcoholic fatty liver disease: Novel mechanistic and diagnostic insights of energy metabolism in non-alcoholic steatohepatitis and advanced fibrosis. Liver Int 2017;37(10):1544–53.
[161] Szendroedi J, Chmelik M, Schmid AI, Nowotny P, Brehm A, Krssak M, et al. Abnormal hepatic energy homeostasis in type 2 diabetes. Hepatology 2009;50(4): 1079–86.
[162] Schmid AI, Szendroedi J, Chmelik M, Krssák M, Moser E, Roden M. Liver ATP synthesis is lower and relates to insulin sensitivity in patients with type 2 diabetes. Diabetes Care 2011;34(2):448–53.
[163] Roehlen N, Crouchet E, Baumert TF. Liver fibrosis: mechanistic concepts and therapeutic perspectives. Cells 2020;9(4):875.
[164] Uribarri J, Cai W, Peppa M, Goodman S, Ferrucci L, Striker G, et al. Circulating glycotoxins and dietary advanced glycation endproducts: two links to inflammatory response, oxidative stress, and aging. J Gerontol A Biol Sci Med Sci 2007;62(4):427–33.
[165] Paradis V, Perlemuter G, Bonvoust F, Dargere D, Parfait B, Vidaud M, et al. High glucose and hyperinsulinemia stimulate connective tissue growth factor expression: a potential mechanism involved in progression to fibrosis in nonalcoholic steatohepatitis. Hepatology 2001;34(4, Part 1):738–44.
[166] Dewidar B, Mastrototaro L, Englisch C, Ress C, Granata C, Rohbeck E, et al. Alterations of hepatic energy metabolism in murine models of obesity, diabetes and fatty liver diseases. EBioMedicine 2023;94:104714.
[167] Lebeaupin C, Vallée D, Hazari Y, Hetz C, Chevet E, Bailly-Maitre B. Endoplasmic reticulum stress signalling and the pathogenesis of non-alcoholic fatty liver disease. J Hepatol 2018;69(4):927–47.
[168] Su Q, Tsai J, Xu E, Qiu W, Bereczki E, Santha M, et al. Apolipoprotein B100 acts as a molecular link between lipid-induced endoplasmic reticulum stress and hepatic insulin resistance. Hepatol Baltim Md 2009;50(1):77–84.
[169] Koo JH, Lee HJ, Kim W, Kim SG. Endoplasmic reticulum stress in hepatic stellate cells promotes liver fibrosis via PERK-mediated degradation of HNRNPA1 and up-regulation of SMAD2. Gastroenterology 2016;150(1):181–193.e8.
[170] Ryu D, Seo WY, Yoon YS, Kim YN, Kim SS, Kim HJ, et al. Endoplasmic reticulum stress promotes LIPIN2-dependent hepatic insulin resistance. Diabetes 2011;60 (4):1072–81.
[171] Teratani T, Tomita K, Suzuki T, Oshikawa T, Yokoyama H, Shimamura K, et al. A high-cholesterol diet exacerbates liver fibrosis in mice via accumulation of free cholesterol in hepatic stellate cells. Gastroenterology 2012;142(1):152–164.e10.
[172] Duan NN, Liu XJ, Wu J. Palmitic acid elicits hepatic stellate cell activation through inflammasomes and hedgehog signaling. Life Sci 2017;1(176):42–53.
[173] Ioannou GN, Haigh WG, Thorning D, Savard C. Hepatic cholesterol crystals and crown-like structures distinguish NASH from simple steatosis [S]. J Lipid Res 2013;54(5):1326–34.
[174] Suriano F, Vieira-Silva S, Falony G, Roumain M, Paquot A, Pelicaen R, et al. Novel insights into the genetically obese (ob/ob) and diabetic (db/db) mice: two sides of the same coin. Microbiome 2021;9(1):147.
[175] Seki E, Schwabe RF. Hepatic inflammation and fibrosis: functional links and key pathways. Hepatol Baltim Md 2015;61(3):1066–79.
[176] Melhem A, Muhanna N, Bishara A, Alvarez CE, Ilan Y, Bishara T, et al. Anti-fibrotic activity of NK cells in experimental liver injury through killing of activated HSC. J Hepatol 2006;45(1):60–71.
[177] Tilg H, Moschen AR, Roden M. NAFLD and diabetes mellitus. Nat Rev Gastroenterol Hepatol 2017;14(1):32–42.
[178] Hammoutene A, Rautou PE. Role of liver sinusoidal endothelial cells in non-alcoholic fatty liver disease. J Hepatol 2019;70(6):1278–91.
[179] Tsuchiya K, Accili D. Liver sinusoidal endothelial cells link hyperinsulinemia to hepatic insulin resistance. Diabetes 2013;62(5):1478–89.
[180] Harrison SA, Bedossa P, Guy CD, Schattenberg JM, Loomba R, Taub R, et al. A phase 3, randomized, controlled trial of resmetirom in NASH with liver fibrosis. N Engl J Med 2024;390(6):497–509.
[181] Romero-Gómez M, Zelber-Sagi S, Trenell M. Treatment of NAFLD with diet, physical activity and exercise. J Hepatol 2017;67(4):829–46.
[182] Patel NS, Doycheva I, Peterson MR, Hooker J, Kisselva T, Schnabl B, et al. Effect of weight loss on magnetic resonance imaging estimation of liver fat and volume in patients with nonalcoholic steatohepatitis. Clin Gastroenterol Hepatol Off Clin Pract J Am Gastroenterol Assoc 2015;13(3):561–568.e1.
[183] Musso G, Cassader M, Rosina F, Gambino R. Impact of current treatments on liver disease, glucose metabolism and cardiovascular risk in non-alcoholic fatty liver disease (NAFLD): a systematic review and meta-analysis of randomised trials. Diabetologia 2012;55(4):885–904.
[184] Lean ME, Leslie WS, Barnes AC, Brosnahan N, Thom G, McCombie L, et al. 5-year follow-up of the randomised Diabetes Remission Clinical Trial (DiRECT) of continued support for weight loss maintenance in the UK: an extension study. Lancet Diabetes Endocrinol 2024;12(4):233–46.
[185] Muriel P, López-Sánchez P, Ramos-Tovar E. Fructose and the Liver. Int J Mol Sci 2021;22(13):6969.
[186] Sobiecki JG, Imamura F, Davis CR, Sharp SJ, Koulman A, Hodgson JM, et al. A nutritional biomarker score of the Mediterranean diet and incident type 2 diabetes: Integrated analysis of data from the MedLey randomised controlled trial and the EPIC-InterAct case-cohort study. PLoS Med 2023;20(4):e1004221.
[187] Anania C, Perla FM, Olivero F, Pacifico L, Chiesa C. Mediterranean diet and nonalcoholic fatty liver disease. World J Gastroenterol 2018;24(19):2083–94.
[188] Ryan MC, Itsiopoulos C, Thodis T, Ward G, Trost N, Hofferberth S, et al. The Mediterranean diet improves hepatic steatosis and insulin sensitivity in individuals with non-alcoholic fatty liver disease. J Hepatol 2013;59(1):138–43.
[189] Bozzetto L, Prinster A, Annuzzi G, Costagliola L, Mangione A, Vitelli A, et al. Liver fat is reduced by an isoenergetic MUFA diet in a controlled randomized study in type 2 diabetic patients. Diabetes Care 2012;35(7):1429–35.
[190] Stine JG, DiJoseph K, Pattison Z, Harrington A, Chinchilli VM, Schmitz KH, et al. Exercise training is associated with treatment response in liver fat content by magnetic resonance imaging independent of clinically significant body weight loss in patients with nonalcoholic fatty liver disease: A systematic review and meta-analysis. Am J Gastroenterol 2023;118(7):1204–13.
[191] van der Windt DJ, Sud V, Zhang H, Tsung A, Huang H. The effects of physical exercise on fatty liver disease. Gene Expr 2018;18(2):89–101.
[192] Verrastro O, Panunzi S, Castagneto-Gissey L, Gaetano AD, Lembo E, Capristo E, et al. Bariatric–metabolic surgery versus lifestyle intervention plus best medical care in non-alcoholic steatohepatitis (BRAVES): a multicentre, open-label, randomised trial. Lancet 2023;401(10390):1786–97.
[193] Lautenbach A, Wernecke M, Mann O, Wagner J, Wolter S, Stoll F, et al. Low-grade hepatic steatosis is associated with long-term remission of type 2 diabetes independent of type of bariatric-metabolic surgery. Obes Surg 2023;33(2):530–8.
[194] Ferguson D, Finck BN. Emerging therapeutic approaches for the treatment of NAFLD and type 2 diabetes mellitus. Nat Rev Endocrinol 2021;17(8):484–95.
[195] Ratziu V, Giral P, Jacqueminet S, Charlotte F, Hartemann-Heurtier A, Serfaty L, et al. Rosiglitazone for nonalcoholic steatohepatitis: one-year results of the randomized placebo-controlled Fatty Liver Improvement with Rosiglitazone Therapy (FLIRT) Trial. Gastroenterology 2008;135(1):100–10.
[196] Neuschwander-Tetri BA, Brunt EM, Wehmeier KR, Oliver D, Bacon BR. Improved nonalcoholic steatohepatitis after 48 weeks of treatment with the PPAR-gamma ligand rosiglitazone. Hepatol Baltim Md 2003;38(4):1008–17.
[197] Belfort R, Harrison SA, Brown K, Darland C, Finch J, Hardies J, et al. A placebo-controlled trial of pioglitazone in subjects with nonalcoholic steatohepatitis. N Engl J Med 2006;355(22):2297–307.
[198] Sanyal AJ, Chalasani N, Kowdley KV, McCullough A, Diehl AM, Bass NM, et al. Pioglitazone, vitamin E, or placebo for nonalcoholic steatohepatitis. N Engl J Med 2010;362(18):1675–85.
[199] Cusi K, Orsak B, Bril F, Lomonaco R, Hecht J, Ortiz-Lopez C, et al. Long-term pioglitazone treatment for patients with nonalcoholic steatohepatitis and prediabetes or type 2 diabetes mellitus: A randomized trial. Ann Intern Med 2016; 165(5):305–15.
[200] Musso G, Cassader M, Paschetta E, Gambino R. Thiazolidinediones and advanced liver fibrosis in nonalcoholic steatohepatitis: A meta-analysis. JAMA Intern Med 2017;177(5):633–40.
[201] Kawaguchi-Suzuki M, Bril F, Kalavalapalli S, Cusi K, Frye RF. Concentration-dependent response to pioglitazone in nonalcoholic steatohepatitis. Aliment Pharmacol Ther 2017;46(1):56–61.
[202] Kawaguchi-Suzuki M, Cusi K, Bril F, Gong Y, Langaee T, Frye RF. A Genetic Score Associates With Pioglitazone Response in Patients With Non-alcoholic Steatohepatitis. Front Pharmacol [Internet]. 2018 [cited 2023 Nov 26];9. Available from: https://www.frontiersin.org/articles/10.3389/fphar.2018.00752.
[203] Divakaruni AS, Wiley SE, Rogers GW, Andreyev AY, Petrosyan S, Loviscach M, et al. Thiazolidinediones are acute, specific inhibitors of the mitochondrial pyruvate carrier. Proc Natl Acad Sci U S A 2013;110(14):5422–7.
[204] McCommis KS, Hodges WT, Brunt EM, Nalbantoglu I, McDonald WG, Holley C, et al. Targeting the mitochondrial pyruvate carrier attenuates fibrosis in a mouse model of nonalcoholic steatohepatitis. Hepatol Baltim Md 2017;65(5):1543–56.
[205] Harrison SA, Alkhouri N, Davison BA, Sanyal A, Edwards C, Colca JR, et al. Insulin sensitizer MSDC-0602K in non-alcoholic steatohepatitis: A randomized, double-blind, placebo-controlled phase IIb study. J Hepatol 2020;72(4):613–26.
[206] Liu H, Sridhar VS, Boulet J, Dharia A, Khan A, Lawler PR, et al. Cardiorenal protection with SGLT2 inhibitors in patients with diabetes mellitus: from biomarkers to clinical outcomes in heart failure and diabetic kidney disease. Metabolism 2022;126:154918.
[207] Radlinger B, Ress C, Folie S, Salzmann K, Lechuga A, Weiss B, et al. Empagliflozin protects mice against diet-induced obesity, insulin resistance and hepatic steatosis. Diabetologia 2023;66(4):754–67.

[208] Shen Y, Cheng L, Xu M, Wang W, Wan Z, Xiong H, et al. SGLT2 inhibitor empagliflozin downregulates miRNA-34a-5p and targets GREM2 to inactivate hepatic stellate cells and ameliorate non-alcoholic fatty liver disease-associated fibrosis. Metabolism 2023;146:155657.
[209] Packer M. Critical reanalysis of the mechanisms underlying the cardiorenal benefits of SGLT2 inhibitors and reaffirmation of the nutrient deprivation signaling/autophagy hypothesis. Circulation 2022;146(18):1383–405.
[210] Latva-Rasku A, Honka MJ, Kullberg J, Mononen N, Lehtimäki T, Saltevo J, et al. The SGLT2 inhibitor dapagliflozin reduces liver fat but does not affect tissue insulin sensitivity: a randomized, double-blind, placebo-controlled study with 8-week treatment in type 2 diabetes patients. Diabetes Care 2019;42(5):931–7.
[211] Cusi K, Bril F, Barb D, Polidori D, Sha S, Ghosh A, et al. Effect of canagliflozin treatment on hepatic triglyceride content and glucose metabolism in patients with type 2 diabetes. Diabetes Obes Metab 2019;21(4):812–21.
[212] Kahl S, Gancheva S, Straßburger K, Herder C, Machann J, Katsuyama H, et al. Empagliflozin effectively lowers liver fat content in well-controlled type 2 diabetes: A randomized, double-blind, Phase 4. Placebo-controlled trial. Diabetes Care 2020;43(2):298–305.
[213] Shimizu M, Suzuki K, Kato K, Jojima T, Iijima T, Murohisa T, et al. Evaluation of the effects of dapagliflozin, a sodium-glucose co-transporter-2 inhibitor, on hepatic steatosis and fibrosis using transient elastography in patients with type 2 diabetes and non-alcoholic fatty liver disease. Diabetes Obes Metab 2019;21(2):285–92.
[214] Taheri H, Malek M, Ismail-Beigi F, Zamani F, Sohrabi M, Reza Babaei M, et al. Effect of empagliflozin on liver steatosis and fibrosis in patients with non-alcoholic fatty liver disease without diabetes: A randomized, double-blind, placebo-controlled trial. Adv Ther 2020;37(11):4697–708.
[215] Lai LL, Vethakkan SR, Nik Mustapha NR, Mahadeva S, Chan WK. Empagliflozin for the treatment of nonalcoholic steatohepatitis in patients with type 2 diabetes mellitus. Dig Dis Sci 2020;65(2):623–31.
[216] Akuta N, Watanabe C, Kawamura Y, Arase Y, Saitoh S, Fujiyama S, et al. Effects of a sodium-glucose cotransporter 2 inhibitor in nonalcoholic fatty liver disease complicated by diabetes mellitus: Preliminary prospective study based on serial liver biopsies. Hepatol Commun 2017;1(1):46.
[217] Takahashi H, Kessoku T, Kawanaka M, Nonaka M, Hyogo H, Fujii H, et al. Ipragliflozin improves the hepatic outcomes of patients with diabetes with NAFLD. Hepatol Commun 2022;6(1):120–32.
[218] Takeshita Y, Honda M, Harada K, Kita Y, Takata N, Tsujiguchi H, et al. Comparison of tofogliflozin and glimepiride effects on nonalcoholic fatty liver disease in participants with type 2 diabetes: A randomized, 48-week, open-label. Active-Controlled Trial Diabetes Care 2022;45(9):2064–75.
[219] Lo CWH, Fei Y, Cheung BMY. Cardiovascular outcomes in trials of new antidiabetic drug classes. Card Fail Rev 2021;5(7):e04.
[220] Williams KH, Vieira De Ribeiro AJ, Prakoso E, Veillard AS, Shackel NA, Brooks B, et al. Circulating dipeptidyl peptidase-4 activity correlates with measures of hepatocyte apoptosis and fibrosis in non-alcoholic fatty liver disease in type 2 diabetes mellitus and obesity: A dual cohort cross-sectional study. J Diabetes 2015;7(6):809–19.
[221] Romacho T, Sell H, Indrakusuma I, Roehrborn D, Castañeda TR, Jelenik T, et al. DPP4 deletion in adipose tissue improves hepatic insulin sensitivity in diet-induced obesity. Am J Physiol Endocrinol Metab 2020;318(5):E590–9.
[222] Zheng W, Zhou J, Song S, Kong W, Xia W, Chen L, et al. Dipeptidyl-Peptidase 4 Inhibitor Sitagliptin Ameliorates Hepatic Insulin Resistance by Modulating Inflammation and Autophagy in ob/ob Mice. Int J Endocrinol 2018;2018:8309723.
[223] Kawakubo M, Tanaka M, Ochi K, Watanabe A, Saka-Tanaka M, Kanamori Y, et al. Dipeptidyl peptidase-4 inhibition prevents nonalcoholic steatohepatitis-associated liver fibrosis and tumor development in mice independently of its anti-diabetic effects. Sci Rep 2020;10(1):983.
[224] Joy TR, McKenzie CA, Tirona RG, Summers K, Seney S, Chakrabarti S, et al. Sitagliptin in patients with non-alcoholic steatohepatitis: A randomized, placebo-controlled trial. World J Gastroenterol 2017;23(1):141–50.
[225] Cui J, Philo L, Nguyen P, Hofflich H, Hernandez C, Bettencourt R, et al. Sitagliptin vs. placebo for non-alcoholic fatty liver disease: A randomized controlled trial. J Hepatol 2016;65(2):369–76.
[226] Giugliano D, Longo M, Signoriello S, Maiorino MI, Solerte B, Chiodini P, et al. The effect of DPP-4 inhibitors, GLP-1 receptor agonists and SGLT-2 inhibitors on cardiorenal outcomes: a network meta-analysis of 23 CVOTs. Cardiovasc Diabetol 2022;21(1):42.
[227] Armstrong MJ, Gaunt P, Aithal GP, Barton D, Hull D, Parker R, et al. Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study. Lancet Lond Engl 2016;387(10019):679–90.
[228] Newsome PN, Buchholtz K, Cusi K, Linder M, Okanoue T, Ratziu V, et al. A Placebo-Controlled Trial of Subcutaneous Semaglutide in Nonalcoholic Steatohepatitis. N Engl J Med 2021;384(12):1113–24.
[229] Kenny PR, Brady DE, Torres DM, Ragozzino L, Chalasani N, Harrison SA. Exenatide in the treatment of diabetic patients with non-alcoholic steatohepatitis: a case series. Am J Gastroenterol 2010;105(12):2707–9.
[230] Armstrong MJ, Hull D, Guo K, Barton D, Hazlehurst JM, Gathercole LL, et al. Glucagon-like peptide 1 decreases lipotoxicity in non-alcoholic steatohepatitis. J Hepatol 2016;64(2):399–408.
[231] Loomba R, Abdelmalek MF, Armstrong MJ, Jara M, Kjær MS, Krarup N, et al. Semaglutide 2·4 mg once weekly in patients with non-alcoholic steatohepatitis-related cirrhosis: a randomised, placebo-controlled phase 2 trial. Lancet Gastroenterol Hepatol 2023;8(6):511–22.
[232] Müller TD, Finan B, Bloom SR, D'Alessio D, Drucker DJ, Flatt PR, et al. Glucagon-like peptide 1 (GLP-1). Mol Metab 2019;30:72–130.
[233] Loomba Rohit, Hartman Mark L., Lawitz Eric J., Vuppalanchi Raj, Boursier Jérôme, Bugianesi Elisabetta, et al. Tirzepatide for Metabolic Dysfunction–Associated Steatohepatitis with Liver Fibrosis. N Engl J Med [Internet]. [cited 2024 Jun 18];0(0). Available from: https://www.nejm.org/doi/full/10.1056/NEJMoa2401943.
[234] Sanyal AJ, Kaplan LM, Frias JP, Brouwers B, Wu Q, Thomas MK, et al. Triple hormone receptor agonist retatrutide for metabolic dysfunction-associated steatotic liver disease: a randomized phase 2a trial. Nat Med 2024;10:1–12.
[235] Nahra R, Wang T, Gadde KM, Oscarsson J, Stumvoll M, Jermutus L, et al. Effects of Cotadutide on Metabolic and Hepatic Parameters in Adults With Overweight or Obesity and Type 2 Diabetes: A 54-Week Randomized Phase 2b Study. Diabetes Care 2021;44(6):1433–42.
[236] Sanyal Arun J., Bedossa Pierre, Fraessdorf Mandy, Neff Guy W., Lawitz Eric, Bugianesi Elisabetta, et al. A Phase 2 Randomized Trial of Survodutide in MASH and Fibrosis. N Engl J Med [Internet]. [cited 2024 Jun 24];0(0). Available from: https://www.nejm.org/doi/full/10.1056/NEJMoa2401755.
[237] McGlone ER, Bloom SR, Tan TMM. Glucagon resistance and metabolic-associated steatotic liver disease: a review of the evidence. J Endocrinol 2024;261(3):e230365.
[238] Dutta D, Kamrul-Hasan ABM, Mondal E, Nagendra L, Joshi A, Bhattacharya S. Role of Resmetirom, a Liver-Directed, Thyroid Hormone Receptor Beta-Selective Agonist, in Managing Nonalcoholic Steatohepatitis: A Systematic Review and Meta-Analysis. Endocr Pract Off J Am Coll Endocrinol Am Assoc Clin Endocrinol. 2024;S1530-891X(24)00506-8.
[239] Mantsiou C, Karagiannis T, Kakotrichi P, Malandris K, Avgerinos I, Liakos A, et al. Glucagon-like peptide-1 receptor agonists and sodium-glucose co-transporter-2 inhibitors as combination therapy for type 2 diabetes: A systematic review and meta-analysis. Diabetes Obes Metab 2020;22(10):1857–68.
[240] Neves JS, Borges-Canha M, Vasques-Nóvoa F, Green JB, Leiter LA, Granger CB, et al. GLP-1 Receptor Agonist Therapy With and Without SGLT2 Inhibitors in Patients With Type 2 Diabetes. J Am Coll Cardiol 2023;82(6):517–25.
[241] Hupa-Breier KL, Dywicki J, Hartleben B, Wellhöner F, Heidrich B, Taubert R, et al. Dulaglutide Alone and in Combination with Empagliflozin Attenuate Inflammatory Pathways and Microbiome Dysbiosis in a Non-Diabetic Mouse Model of NASH. Biomedicines 2021;9(4):353.
[242] Akuta N, Kawamura Y, Fujiyama S, Saito S, Muraishi N, Sezaki H, et al. Favorable impact of long-term SGLT2 inhibitor for NAFLD complicated by diabetes mellitus: A 5-year follow-up study. Hepatol Commun 2022;6(9):2286–97.
[243] Ohki T, Isogawa A, Toda N, Tagawa K. Effectiveness of Ipragliflozin, a Sodium-Glucose Co-transporter 2 Inhibitor, as a Second-line Treatment for Non-Alcoholic Fatty Liver Disease Patients with Type 2 Diabetes Mellitus Who Do Not Respond to Incretin-Based Therapies Including Glucagon-like Peptide-1 Analogs and Dipeptidyl Peptidase-4 Inhibitors. Clin Drug Investig 2016;36(4):313–9.
[244] Harreiter J, Just I, Leutner M, Bastian M, Brath H, Schelkshorn C, et al. Combined exenatide and dapagliflozin has no additive effects on reduction of hepatocellular lipids despite better glycaemic control in patients with type 2 diabetes mellitus treated with metformin: EXENDA, a 24-week, prospective, randomized, placebo-controlled pilot trial. Diabetes Obes Metab 2021;23(5):1129–39.
[245] Gastaldelli A, Repetto E, Guja C, Hardy E, Han J, Jabbour SA, et al. Exenatide and dapagliflozin combination improves markers of liver steatosis and fibrosis in patients with type 2 diabetes. Diabetes Obes Metab 2020;22(3):393–403.
[246] Haukeland JW, Konopski Z, Eggesbø HB, von Volkmann, Raschpichler G, Bjøro K, et al. Metformin in patients with non-alcoholic fatty liver disease: A randomized, controlled trial. Scandinavian Journal of Gastroenterology 2009;44(7):853–60. https://doi.org/10.1080/00365520902845268.