Metabolic dysfunction-associated steatotic liver disease: heterogeneous pathomechanisms and effectiveness of metabolism-based treatment

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The global epidemic of metabolic dysfunction-associated steatotic liver disease (MASLD) is increasing worldwide. People with MASLD can progress to cirrhosis and hepatocellular carcinoma and are at increased risk of developing type 2 diabetes, cardiovascular disease, chronic kidney disease, and extrahepatic cancers. Most people with MASLD die from cardiac-related causes. This outcome is attributed to the shared pathogenesis of MASLD and cardiometabolic diseases, involving unhealthy dietary habits, dysfunctional adipose tissue, insulin resistance, and subclinical inflammation. In addition, the steatotic and inflamed liver affects the vasculature and heart via increased glucose production and release of procoagulant factors, dyslipidaemia, and dysregulated release of hepatokines and microRNAs. However, there is substantial heterogeneity in the contributors to the pathophysiology of MASLD, which might influence its rate of progression, its relationship with cardiometabolic diseases, and the response to therapy. The most effective non-pharmacological treatment approaches for people with MASLD include weight loss. Paradoxically, some effective pharmacological approaches to improve liver health in people with MASLD are associated with no change in bodyweight or even with weight gain, and similar response heterogeneity has been observed for changes in cardiometabolic risk factors. In this Review, we address the heterogeneity of MASLD with respect to its pathogenesis, outcomes, and metabolism-based treatment responses. Although there is currently insufficient evidence for the implementation of precision medicine for risk prediction, prevention, and treatment of MASLD, we discuss whether knowledge about this heterogeneity might help achieving this goal in the future.

Introduction

The overall global prevalence of metabolic dysfunction-associated steatotic liver disease (MASLD) has steadily increased during past decades and is now estimated at 38%.[1,2] A progressive subset of MASLD, metabolic dysfunction-associated steatohepatitis (MASH), poses an immense and growing clinical and economic burden worldwide[3,4] because of its risk of progression to advanced fibrosis, cirrhosis, and hepatocellular carcinoma.[5,6] Furthermore, people with MASLD, and especially those with MASH and hepatic fibrosis, are at increased risk of developing type 2 diabetes, cardiovascular disease, chronic kidney disease, and specific types of extrahepatic cancers.[7–9]

Hepatic steatosis is strongly associated with cardiometabolic risk factors, particularly abdominal obesity, dyslipidaemia, hyperglycaemia, insulin resistance, and subclinical inflammation.[7–15] In addition, the highest global pooled prevalence of MASLD is observed in people with obesity (75%, 95% CI 71–79%)[16] and type 2 diabetes (69%, 95% CI 63–74%).[17] These associations led to a proposal in 2020 to focus on metabolic risks in the diagnosis of hepatic steatosis and the term metabolic (dysfunction) associated fatty liver disease (MAFLD) was proposed.[18] In 2023, in a collaborative process including clinicians, public health experts, regulatory agencies, industry representatives, and patient advocacy groups, the terms non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) were changed to MASLD and MASH respectively.[19] Subsequent analyses have shown that the MASLD and MASH nomenclature can be applied to populations previously characterised as having NAFLD and NASH,[20–22] and this Review uses the MASLD nomenclature to describe previous studies.

Heterogeneity in the pathophysiology and outcomes of major non-communicable diseases, such as obesity, type 2 diabetes, and cardiovascular disease, has become a focus of research during the past decade.[23–30] Particularly for obesity[23–27] and type 2 diabetes,[28,29] approaches have been proposed to implement precision medicine for their prevention, diagnosis, and treatment. Similarly, there is also growing interest in understanding the heterogeneity of the pathophysiology of MASLD.[7,31–34] Furthermore, data dimensionality reduction strategies and pathophysiology-based phenotyping have been studied recently for their effectiveness in predicting outcomes in patients with MASLD.[35]

In this narrative Review, we address the heterogeneity of MASLD concerning its pathogenesis, risk prediction, and metabolism-based treatment response. We specifically focus on understanding the shared mechanisms contributing to the pathogenesis of hepatic steatosis, steatohepatitis, type 2 diabetes, and cardiovascular disease. Furthermore, we discuss whether hepatic steatosis might be involved in the pathogenesis of type 2 diabetes and cardiovascular disease since these are linked epidemiologically, and whether the benefits of metabolism-based treatments of hepatic steatosis can be separated mechanistically from their benefits on type 2 diabetes and cardiovascular disease in people with MASLD.

Risks of liver disease progression and cause-specific mortality in patients with MASLD

Risk of liver disease progression

People with hepatic steatosis are at an increased risk of developing cirrhosis and hepatocellular carcinoma. About 20% of people with MASH can progress to decompensated cirrhosis[5,6,36] and the severity of hepatic fibrosis is an important predictor of adverse liver-related outcomes. In this respect, fibrosis stages F3 (severe fibrosis) and F4 (cirrhosis) were associated with increased risks of liver-related complications and death.[37] Furthermore, in patients with hepatic fibrosis, the presence of diabetes strongly increases this risk. In a large prospective observational study (n=2016) conducted in patients diagnosed with fibrosis by magnetic resonance elastography, patients with type 2 diabetes had a substantially higher risk of incident hepatic decompensation (hazard ratio [HR] 3·29, 95% CI 2·21–4·90) and incident hepatocellular carcinoma (HR 7·72, 95% CI 2·61–22·87), compared with patients without diabetes. Importantly and unexpectedly, this risk remained strongly elevated (HR for hepatic decompensation 1·90, 95% CI 1·21–2·96, and HR for hepatocellular carcinoma 5·50, 1·63–15·67) after adjustment for liver stiffness on magnetic resonance elastography.[38] These findings support the concept that the underlying metabolic abnormalities that lead to insulin resistance and overt type 2 diabetes also contribute to the progression of MASLD.

Cause-specific mortality

Among people with MASLD, fewer than 10% develop liver-related complications and the major causes of death are cardiovascular disease and cancer.[1,6,39] In small cohort studies, cardiovascular disease was identified as the leading cause of mortality in adults with MASLD.[40] Recently, Younossi and colleagues conducted a systematic review and meta-analysis of population-based studies published between 1990 and 2019 and established the total and cause-specific mortality in people with MASLD. In five studies with diagnosis of MASLD by ultrasound, the fatty liver index, or liver biopsy, the pooled all-cause mortality rate was 17·05 (95% CI 10·31–28·05) per 1000 person-years. While the cause-specific mortality rate was 1·75 (95% CI 0·58–2·91) for liver-specific mortality and 4·21 (95% CI 1·94–6·48) for extrahepatic cancer-specific mortality, it was 5·54 (95% CI 2·72–8·35), and thereby highest, for cardiac-specific mortality (figure 1).[1] These findings indicate that insulin resistance, impaired lipid metabolism, and subclinical inflammation, all of which are established cardiovascular disease risk factors, might also be the main drivers of MASLD-related clinical outcomes.

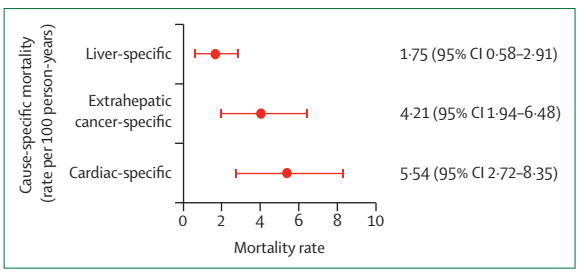

Figure 1: **The pooled cause-specific mortality rate in people with MASLD**
Mortality rate among MASLD patients per 1000 person-years. Data are from a systematic review and meta-analysis conducted by Younossi and colleagues[1] of population-based studies published between 1990 and 2019. MASLD=metabolic dysfunction-associated steatotic liver disease.

Heterogeneity in the pathogenesis of MASLD

Shared pathomechanisms

The pathogenesis of MASLD has been extensively studied and well reviewed elsewhere.[10–15,41–44] In most cases, an excessive intake of glucose and fructose contributes to fatty acid production via hepatic de novo lipogenesis. Together with higher intake of saturated fatty acids, this process results in subclinical inflammation in adipose tissue and the liver, and insulin resistance in adipose tissue, liver, and skeletal muscle. The mechanisms involved include increased signalling via fatty acids, diacylglycerols, and ceramides. The resulting insulin resistance-associated hyperinsulinaemia and hyperglycaemia amplify hepatic de novo lipogenesis. Furthermore, increased saturated fatty acids and hyperglycaemia promote hepatic mitochondrial dysfunction, increased oxidative stress, and uncoupling of oxidative phosphorylation. The resulting cell stress and macrophage activation directly and indirectly activates a fibrogenic response in hepatic stellate cells that can promote the progression to cirrhosis. In addition to insulin resistance, hyperinsulinaemia, and proinflammatory lipid signalling, dysregulated release of adipokines and cytokines from inflamed adipose tissue and exposure to inflammatory mediators from Western diet-induced changes in the gut microbiome further fuel this pathogenic process in the liver.[10–15,41–44]

Besides these global metabolic mechanisms, intrahepatic pathways are involved in the pathophysiology of MASLD. This knowledge is predominantly derived from genome-wide association and exome sequencing studies in people with hepatic steatosis, and with supportive mechanistic studies in animals and in vitro. The identified genetic variants and the associated altered pathways are often involved in the regulation of the mobilisation of triglycerides from lipid droplets (*PNPLA3*), assembly and secretion of VLDLs (*TM6SF2*), hepatic phosphatidylinositol acylchain remodelling (*MBOAT7*), de novo lipogenesis (*GCKR*), or as yet unknown mechanisms (*HSD17B13*).[45,46] Of note, adiposity was found to amplify the effects of genetic risk alleles for hepatic steatosis, steatohepatitis, and the progression to cirrhosis, but, importantly, not to other adiposity-associated traits.[47] Furthermore, even normal weight carriers of the *PNPLA3* rs738409 (Ile148Met) GG MASLD-risk polymorphism were found to have increased liver fat content.[48] Thus, recognising the

complex heterogeneity of the pathophysiology of MASLD could be important for the risk prediction and possibly also the treatment of the disease.[49] Many approaches to categorising patients with MASLD have been proposed based on clinical features, laboratory findings, and genetic variants, and we next highlight three of the best-established major contributors to the pathogenesis of MASLD. One challenge to the desire to segregate patients into separate categories is that the dietary, anthropomorphic, clinical, and genetic drivers are not mutually exclusive, therefore, individual patients have varying degrees of the various drivers. Nonetheless, if patients can be characterised by their dominant underlying mechanisms, this could facilitate therapies directed towards those mechanisms.

MASLD with a dominant hepatic genetic component

Studies have shown that people with MASLD based on a strong hepatic genetic component, have an increased risk of hepatic steatosis, inflammation, fibrosis, and hepatocellular carcinoma. In this respect, recently in a study of people homozygous for the *PNPLA3* Ile148Met (*PNPLA3* rs738409 G) MASLD-risk allele were found to have hepatic mitochondrial dysfunction leading to reduced *de novo* lipogenesis and channeling of carbons to ketogenesis.[50] However, people with MASLD based on a strong hepatic genetic component often do not have an increased risk of cardiovascular disease, an observation that suggests that MASLD per se is not a contributor to cardiovascular disease despite the strong epidemiological association (figure 2). In a Mendelian randomisation study, MASLD due to the *PNPLA3* rs738409 G MASLD-risk allele, was not causally linked to ischaemic heart disease.[51] In addition, in a large exome-wide association study of plasma lipids, the *PNPLA3* rs738409 G MASLD-risk allele and the *TM6SF2* rs58542926 T MASLD-risk allele were strongly associated with steatosis and progression to MASH, cirrhosis, and hepatocellular carcinoma. Both alleles were also associated with the incidence of type 2 diabetes but with low blood triglycerides, low LDL cholesterol concentration, and protection from coronary artery disease.[52] Mechanisms that could explain this protective effect from cardiovascular disease and insulin resistance, but the increased risk of type 2 diabetes associated with these MASLD-risk alleles, have previously been discussed.[45,53] For example,

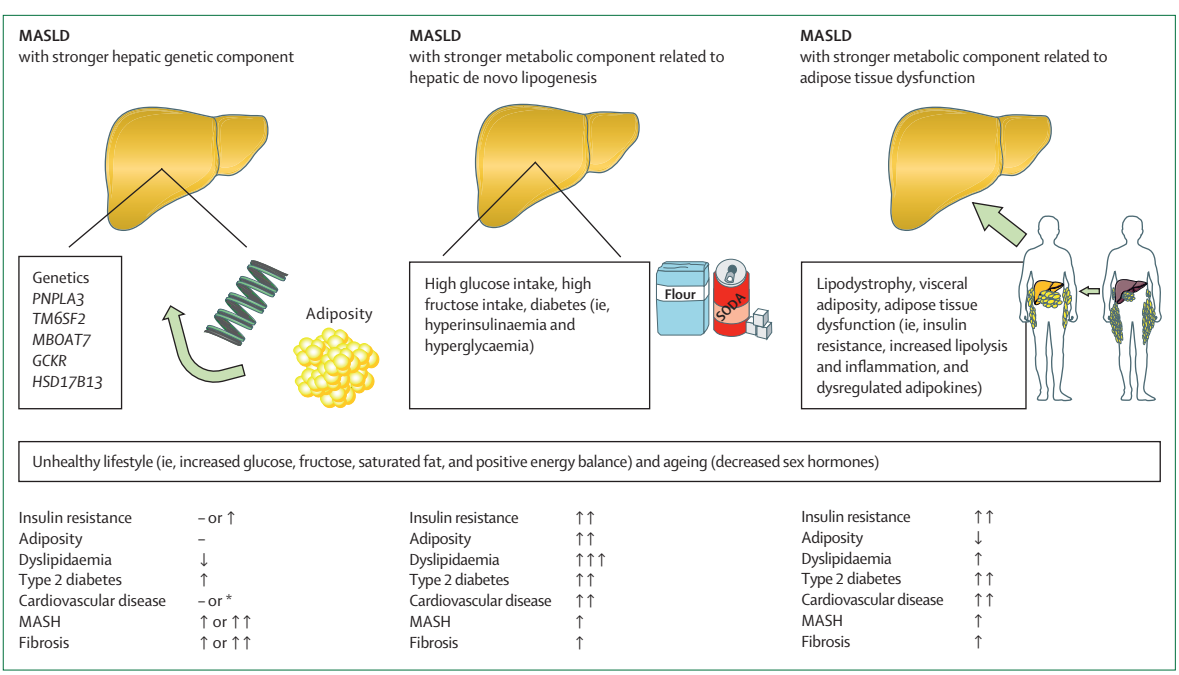

***Figure 2*: Major pathways inducing MASLD and their association with insulin resistance, adiposity, dyslipidaemia, type 2 diabetes, cardiovascular disease, MASH, and fibrosis**

In patients with MASLD with a strong hepatic genetic component, hepatic lipid content is high but insulin resistance, adiposity, and the risk of type 2 diabetes are not. The risk of cardiovascular disease is associated with the severity of obesity. The risk of MASH and fibrosis is moderate to strongly increased in patients with MASLD with a strong hepatic genetic component. In patients with MASLD with a strong metabolic component related to hepatic de novo lipogenesis (ie, high intake of glucose, diabetes-associated hyperinsulinaemia, and hyperglycaemia), often increased insulin resistance and adiposity, severe dyslipidaemia, hyperglycaemia, and an increased risk of cardiovascular disease are observed. In patients with MASLD with a strong metabolic component related to adipose tissue dysfunction (ie, lipodystrophy, high amount of visceral fat and low amount of gluteofemoral fat, adipose tissue with insulin resistance, increased lipolysis, inflammation, and dysregulated adipokines) a high prevalence of insulin resistance, type 2 diabetes, and cardiovascular disease, but a low amount of adiposity and moderate dyslipidaemia are observed. Both MASLD phenotypes with a strong metabolic component have a moderately increased risk of MASH and fibrosis. MASH=metabolic dysfunction-associated steatohepatitis. MASLD=metabolic dysfunction-associated steatotic liver disease. ↑=moderate increase. ↓=moderate decrease. ↑↑=strong increase. ↑↑↑=very strong increase of prevalence or risk of disease. –= no change of prevalence or risk of disease. *Variability in *PNPLA3* and *TM6SF2* are associated with decreased risk of cardiovascular disease.

PNPLA3 was identified as a triglyceride lipase mobilising polyunsaturated fatty acid to facilitate hepatic secretion of large-sized very low density lipoprotein. The *PNPLA3* rs738409 G MASLD-risk allele was less active than the wildtype enzyme, indicating that hepatic steatosis might result from decreased hepatic triglyceride secretion.[54] Furthermore, people with the *PNPLA3* rs738409 G MASLD-risk allele were found to have a less metabolically harmful saturated, ceramide-enriched liver lipidome, compared with people with hepatic steatosis and insulin resitant.[55] Of note, an unweighted genetic risk score based on the number of risk alleles in *PNPLA3*, *TM6SF2*, *MBOAT7*, *HSD17B13*, and *MARC1* associated with increased prevalence of hepatic steatosis, lobular inflammation, and fibrosis, and lower hepatic de novo lipogenesis but not with whole-body and adipose tissue insulin resistance.[56]

MASLD with a dominant metabolic component related to hepatic de novo lipogenesis

Increased hepatic de novo lipogenesis might be the main operative pathway among patients with MASLD that is associated with a strong metabolic component characterised by insulin resistance, hyperglycaemia, and hyperinsulinaemia (figure 2). In 2005, Donnelly and colleagues found in a small study (n=9) that in people with MASLD, 26% of the hepatic triglycerides derived from de novo lipogenesis.[57] In another study, Lambert and colleagues showed that people with high liver fat content had more than 3-fold higher rates of de novo fatty acid synthesis than people with low liver fat content.[58] The authors also discussed data showing that significant stimulation of this pathway in the fed state has been observed in other studies, especially when simple carbohydrates are consumed.[58]

In 2020, Smith and colleagues[41] showed that the contribution of hepatic de novo lipogenesis to intrahepatic triglyceride palmitate was 11% in people with normal weight, 19% in those with obesity, and 38% in people with obesity and MASLD. A subsequent larger stable isotope metabolic study showed that de novo lipogenesis contributed to 40·7% of palmitate production, and this did not decrease with more advanced fibrosis.[59] Importantly, hepatic de novo lipogenesis negatively correlated with hepatic and whole-body insulin sensitivity and positively correlated with 24-h plasma glucose and insulin concentrations. Most recently, in an analysis of data from 37 358 UK Biobank participants, genetic variants associated with enhanced de novo lipogenesis and higher liver triglyceride content were linked to a higher risk of myocardial infarction and coronary artery disease. While genetic variants associated with impaired hepatic triglyceride export and higher liver triglyceride content were linked to a lower risk of coronary artery disease and myocardial infarction, all liver triglyceride content-raising variants were associated with increased risk of non-alcohol-related cirrhosis, hepatocellular carcinoma, and intrahepatic bile duct and gallbladder cancers.[60]

MASLD with a dominant metabolic component related to adipose tissue dysfunction

Although de novo lipogenesis is a contributor to an excess accumulation of lipids in the liver in some patients, a more common contributor might be the excessive delivery of fatty acids to the liver caused by dysregulated lipolysis in adipose tissue.[13,61] Insulin is a primary suppressor of adipocyte lipolysis, and adipose tissue insulin resistance contributes to the dysregulated lipolysis. Dietary oversupply of fat and carbohydrates causes a stress response in adipose tissue that impairs insulin signalling and reduces beneficial adipokine production such as adiponectin.

In some people with lean MASLD, adipose tissue dysfunction might be the predominant pathogenic mechanism (figure 2).[61–66] In this respect, people of normal weight who are metabolically unhealthy and have insulin resistance have a lipodystrophy-like phenotype, which is mainly characterised by a low amount of gluteofemoral and leg fat mass.[62] In addition, severe hepatic steatosis is often found in patients with genetically determined or familial and acquired lipodystrophy.[67] Importantly, acquired lipodystrophy, which is predominantly thought to be autoimmune in origin, might become more relevant as a future disease, considering increasing use of anti-retroviral therapy for HIV and the large increase in cancer immunotherapies that can induce severe MASLD.[68]

In fact, in clinical practice lean MASLD is often underdiagnosed. Based on a 2022 expert review by the American Gastroenterological Association, an estimated 7–20% of people with MASLD have a normal weight body habitus.[69] Patients with lean MASLD are often older and more frequently men. Although the findings are not consistent among several studies, patients with lean MASLD have a similar or higher prevalence of multiple cardiometabolic risk factors, risk scores, and cardiovascular events than patients with overweight and obesity and MASLD.[69] In a 2024 meta-analysis comprising 14 studies with 94 181 patients with MASLD, those with lean MASLD had a higher risk of all-cause mortality than those with non-lean MASLD (random-effects HR 1·61, 95% CI 1·37–1·89). Of note, this risk was independent of age, sex, cardiometabolic risk factors, and estimates of fibrosis stage or cirrhosis.[70] Liver-specific outcomes might be less common as suggested by a study of 1339 patients with biopsy-proven MASLD from four countries (Italy, the UK, Spain, and Australia) in which 4·7% of people with normal weight versus 7·7% of patients with overweight or obesity developed liver-related events (p=0·37). Importantly, most of these patients with normal weight maintained a BMI in the normal weight range during follow-up.[71] A population-based Swedish registry study with nearly

20 years of follow-up showed that at baseline, patients with lean MASLD had lower stages of fibrosis, but paradoxically a higher risk for developing more advanced liver disease compared with patients with non-lean MASLD.[72] Thus, people with lean MASLD are at risk of progressive liver disease, and possibly cardiometabolic disease, independent of change of bodyweight.

Clusters in MASLD based on clinical and laboratory data

Considering heterogeneity in the pathogenesis of MASLD, there is accumulating evidence to support its use for future stratification of MASLD-associated risk of diseases. However, to implement such characterisation in a clinical setting, effective and reproducible procedure stratification of patients with MASLD should be established. Because of the complexity of the many factors influencing outcomes, data dimensionality reduction strategies have been used to cluster people with MASLD as has been done in the fields of obesity and type 2 diabetes research.[23,25] In a study that investigated the serum metabolome from 1154 people with biopsy-proven MASLD, three metabolic subtypes labelled A (47%), B (27%), and C (26%) were identified using a hierarchical clustering algorithm.[73] While the percent of patients with MASH and fibrosis was comparable among subtypes, and insulin resistance and HbA_{1c} also did not differ among the subtypes, serum VLDL-triglyceride levels and secretion rates were lower in subtype A compared with subtypes B and C. Serum triglyceride, cholesterol, VLDL, small dense LDL, and remnant lipoprotein cholesterol were lower among subtype A compared with subtypes B and C. The 10-year risk of cardiovascular disease, estimated with the Framingham risk score, and the frequency of the *PNPLA3* rs738409 G MASLD-risk allele were lower in subtype A.[73]

In an analysis of data from the US Third National Health and Nutrition Examination Survey where fatty liver was diagnosed by abdominal ultrasound and linked to mortality data up until December 2019, a two-stage cluster analysis was performed.[74] Using 21 baseline clinical and laboratory variables, such as BMI, waist circumference, waist-to-hip ratio, haemoglobin, HbA_{1c}, uric acid, HDL cholesterol, and homeostasis model assessment of insulin resistance, three distinct clusters were identified. Compared with patients in cluster 1 (younger with mean age 40 years, normal weight with mean BMI 24 kg per m², more females [76%] with a low cardiometabolic risk profile), patients in cluster 2 (older people with mean age 50 years, people with obesity, insulin-resistance, and high prevalence of diabetes) and cluster 3 (older people with mean age 49 years, people with obesity, lower prevalence of insulin resistance, low prevalence of diabetes, hypertension, and atherogenic dyslipidaemia) had higher all-cause and cardiovascular mortality after the adjustment for age, sex, BMI, and race or ethnicity. No differences in all-cause mortality were observed between patients in clusters 2 and 3. Whether the people with normal weight, who were insulin-sensitive and normolipidaemic with MASLD in cluster 1 mostly had a strong hepatic genetic component of MASLD and whether incident fibrosis or cirrhosis also differed between the clusters, could not be established. Furthermore, it would have been interesting to know whether the high insulin resistance in cluster 2 might predominantly be driven by adipose tissue dysfunction and the atherogenic dyslipidaemia and hypertension in cluster 3 by increased de novo lipogenesis.[74]

In another study, using the parameters of age, HbA_{1c}, total cholesterol or HDL cholesterol ratio to total cholesterol, triglycerides, and lipoprotein (a) levels, five clusters of MAFLD were identified in a Chinese cohort and validated in the UK Biobank database.[75] Patients in different clusters showed different risks of type 2 diabetes, coronary heart disease, and all-cause mortality. Patients in cluster 3, which was referred to as severe insulin resistance-related MAFLD, had considerably worse survival outcomes and higher cardiometabolic risks than those in other clusters. The other clusters were referred to as mild obesity and dyslipidaemia-related MAFLD (cluster 1), age-related MAFLD (cluster 2), high lipoprotein (a)-related MAFLD (cluster 4), and severe mixed hyperlipidaemia-related MAFLD (cluster 5).[75] Altogether, the results of these studies of clustering based on clinical parameters highlight that the allocation of the patients with hepatic steatosis to specific clusters strongly depends on the parameters that are used to generate the clusters and that in the future precise liver phenotypes need to be used for clustering MASLD.

Clusters in MASLD that incorporate genetic variants

Luukkonen and colleagues performed extensive metabolic and genetic analyses of a large cohort of Finnish patients to identify a group with a dominant component of metabolic drivers (MetComp) and another group with a dominant component of genetic drivers (GenComp), and as might be expected since these drivers are not mutually exclusive, a group with features of both.[56] The patients in the GenComp cluster were characterised by the excessive metabolic substrate (fatty acids, carbohydrates and amino acids) availability with increased peripheral lipolysis or increased de novo lipogenesis whereas those in the GenComp cluster did not have these dysmetabolic characteristics, but had evidence of redox imbalance characterised by a high β-hydroxybutyrate to acetoacetate ratio suggesting impaired mitochondrial function. Others have identified this reductive stress as a cause of cell stress and increased lipogenesis.[76] A more recent study of phenotypic characteristics and a diverse array of genetic variants clustered patients into seven metabolic categories with additive influences of genetic variants.[77] Most recently, a data-driven cluster analysis, using a simple algorithm

based on six widely available traits: age, BMI, HbA1c, alanine aminotransferase, LDL cholesterol, and triglycerides, identified two types of MASLD characterised by distinct clinical trajectories. The liver-specific cluster, which was enriched by the PNPLA3 rs738409 G MASLD-risk allele, showed a rapid progression of chronic liver disease, but a relatively low risk of cardiovascular disease. The cardiometabolic cluster, which was predominantly characterised by elevated glycaemia and high levels of triglycerides, had a similar incidence of chronic liver disease, but a higher risk of cardiovascular disease and type 2 diabetes. Analyses of liver transcriptomics and plasma metabolomics showed that these two types of MASLD clusters had distinct liver transcriptomic profiles and plasma metabolomic signatures, respectively.[78] Another most recently published study used a genetic approach and identified two partitioned polygenic risk scores based on the presence of lipoprotein retention in the liver. The two polygenic risk scores indicate the presence of at least two different types of MASLD phenotypes. The one, a so-called liver-specific or discordant (ie, high liver fat content but relatively low circulating triglycerides) MASLD phenotype, is characterised by liver lipid retention. This phenotype strongly associated with more aggressive liver disease, but a lower risk of cardiovascular disease. Of note, a higher mRNA expression of the genes generating this score in liver versus visceral adipose further supports that the major pathophysiology of the liver-specific or discordant MASLD phenotype is corresponding to the liver. The other, a so-called systemic or concordant MASLD phenotype, also associated with a similarly increased risk of more aggressive liver disease, but a higher risk of cardiometabolic disease (ie, cardiovascular disease and type 2 diabetes).[79] These novel findings further highlight the heterogeneity of MASLD with respect to its pathogenesis and risk of diseases.

MASLD heterogeneity and non-pharmalogical treatments

The importance of understanding the diverse contributors to the pathogenesis of MASLD is based on the assumption that this knowledge will influence individualised treatment approaches. For the treatment of MASH, the US Food and Drug Administration (FDA) published a whitepaper in 2011 detailing the roadmap of drug approval, stating that for conditional approval, at least one of the following histologic endpoints should be reached: resolution of MASH (defined as an inflammation score of 0 or 1 and a ballooning score of 0) without worsening of fibrosis or improvement in fibrosis by one stage or more, without worsening of MASH.[80] While the FDA accepts either the resolution of MASH or improvement in fibrosis as the primary endpoint, the European Medicine Agency requires both endpoints.[81]

Here we mainly focus on metabolism-based treatment approaches of MASH, as we assume that they also strongly affect cardiometabolic risk parameters due to their shared underlying metabolic abnormalities. Liver-directed therapeutic targets such as inflammation and fibrosis, have been well discussed in other reviews.[82–84] With the exception of thyroid hormone receptor-β (THR-β) agonists and fatty acid synthase inhibitors, liver-directed therapies such as anti-inflammatory and anti-cell death agents (eg, ASK-1, PDE-4, CCR2/5, and JNK inhibitors, anti-TNFα approaches, and caspase inhibitors) have been disappointing despite encouraging data in preclinical mouse models.

MASLD and pharmacological treatments

Potential treatments associated with weight loss

During the past decade, pharmacological treatment with sodium–glucose co-transporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists has revolutionised the therapy of type 2 diabetes.[85–87] A reduction in major adverse cardiovascular events and mortality has been observed with SGLT2 inhibitors and GLP-1 receptor agonists. Furthermore, protection from progressive chronic kidney disease and symptoms from and hospitalisation due to heart failure have been observed with these therapies in patients with or without type 2 diabetes.[85–87] In addition, the GLP-1 receptor agonists semaglutide and the glucose-dependent insulinotropic polypeptide (GIP) receptor and GLP-1 receptor co-agonist tirzepatide have been approved for the treatment of obesity.[87] In patients with preexisting cardiovascular disease and overweight or obesity but without diabetes, semaglutide decreased the incidence of death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke.[88] Drugs that are approved for the treatment of cardiometabolic diseases or are being tested for the treatment of MASH and for which data from clinical trials in patients with MASLD are available, are shown in the table.

SGLT2 inhibitors

Uptake of glucose and fructose by the liver can contribute to de novo lipogenesis and the development of MASLD. Thus, reducing the burden of circulating glucose by promoting its renal excretion could be beneficial. In a randomised, open-label, active-controlled trial conducted in Japan,[89] patients with biopsy-proven MASLD and type 2 diabetes were randomly assigned to receive tofogliflozin once daily at a dose of 20 mg or glimepiride at an initial dose of 0·5 mg for 48 weeks. There was a tendency (all p=0·06–0·17) for a greater improvement in steatosis, hepatocellular ballooning, lobular inflammation, and fibrosis in the tofogliflozin group compared with the glimepiride group. Reductions in aspartate transaminase, γ-glutamyl transferase, the fibrosis 4 index, and bodyweight were greater in the tofogliflozin group compared with the glimepiride group, while the reductions in glucose levels and HbA_{1c} did not differ between the groups.[89] Based on a 2022 systematic review,[100] seven trials of SGLT2 inhibitors

	Drug	Indication	Phase	Resolution of NASH or MASH	Clinical effect						
					Steatosis score	Inflammation score	Fibrosis score	Hepatic enzymes	Bodyweight	HbA_{1c}	insulin resistance
Treatments associated with decrease in bodyweight											
SGLT2 inhibitors	Tofogliflozin *vs* glimepirid[89]	Biopsy-proven NAFLD	2	Yes	(↓)	(↓)	(↓)	↓	↓	↓	NA
GLP-1 receptor agonist	Liraglutide *vs* placebo[90]	Biopsy-proven NASH	2	Yes	–	–	(↓)	(↓) ALT; ↓ GGT	↓	↓	–
GLP-1 receptor agonist	Semaglutide *vs* placebo[91]	Biopsy-proven NASH and liver fibrosis (F1–F3)	2	Yes	↓	↓	– or (↓)	↓	↓	↓	NA
GLP-1 receptor agonist	Semaglutide *vs* placebo[92]	Biopsy-proven MASH and liver fibrosis (F2, F3)	3	Yes	NA	NA	↓	↓	↓	↓	NA
GLP-1 receptor agonist	Semaglutide *vs* placebo[93]	Biopsy-proven NASH and liver cirrhosis	2	No	↓	–	–	↓	↓	↓	NA
GIP and GLP-1 receptor co-agonist	Tirzepatide *vs* placebo[94]	Biopsy-proven MASH and liver fibrosis (F2, F3)	2	Yes	↓	↓	↓	↓	↓	↓	NA
Glucagon and GLP-1 receptor co-agonist	Survodutide *vs* placebo[95]	Biopsy-proven MASH and liver fibrosis (F2, F3)	2	Yes	↓	↓	(↓)	↓	↓	↓	NA
Treatments associated with no change in bodyweight											
Fibroblast growth factor 21	Pegozafermin *vs* placebo[96]	Biopsy-proven NASH + liver fibrosis (F2, F3)	2	Yes	↓	↓	↓	↓	–	–	NA
THR-β receptor agonist	Resmetirom *vs* placebo[97]	Biopsy-proven NASH and liver fibrosis (F1B, F2, F3)	3	Yes	↓	↓	↓	↓	–	–	–
Treatments associated with increase in bodyweight											
PPAR agonist	Pioglitazone (PPARγ *vs* control[96]	Biopsy-proven NASH	4	Yes	↓	↓	↓	↓	↑	↓	↓
PPAR agonist	Lanifibranor (PPARα, PPARδ, and PPARγ, pan-PPAR) agonist *vs* placebo[97]	Biopsy-proven NASH (76% moderate or advanced fibrosis	2	Yes	↓	↓	↓	↓	↑	↓	↓

↓ or ↑=statistical difference versus comparator. (↓) or (↑)=statistical trend versus comparator ($p<0·2$) or no consistent effects among treatment groups. –=not altered. ALT=alanine aminotransferase. F1=mild fibrosis. F1B=moderate perisinusoidal fibrosis. F2=moderate fibrosis. F3=severe fibrosis. GGT=γ-glutamyl transferase. GIP=glucose-dependent insulinotropic polypeptide. GLP=glucagon-like peptide. MASH=metabolic dysfunction steatohepatitis. MASLD=metabolic dysfunction-associated steatotic liver disease. NA=not assessed. NASH=non-alcoholic steatohepatitis. NAFLD=non-alcoholic fatty liver disease. PPAR=peroxisome proliferator-activated receptor. SGLT2=sodium–glucose co-transporter 2. THR-β=thyroid hormone receptor-β.

Table: **Selected agents with suspected beneficial metabolic effects that were studied in active controlled clinical trials in patients with biopsy-proven MASLD or MASH**

to specifically treat MASLD in patients with obesity and type 2 diabetes (n=569, not including the trial referenced here by Takeshita and colleagues)[89] were identified. In this analysis, treatment with SGLT2 inhibitors was associated with an improvement in liver fat content, aminotransferase levels, bodyweight, and HbA_{1c} levels. A large population study in South Korea has also shown reduced liver-related adverse outcomes in people treated with SGLT2 inhibitors compared with sulfonylureas.[101] These data indicate that SGLT2 inhibitors might be effective in treating MASLD, most probably via their glucose and bodyweight-lowering effects. However, there is also accumulating data showing that SGLT2 inhibitors might directly decrease inflammation, induce ketogenesis, increase glucagon production, and increase adiponectin levels.[102,103]

GLP-1 receptor agonists

Two clinical trials investigated the efficacy of the GLP-1 receptor agonists liraglutide and semaglutide (both compounds are approved for the treatment of type 2 diabetes and obesity) to treat MASH with fibrosis and examined liver histology outcomes. In a small phase 2 trial,[90] treatment with subcutaneous 1·8 mg liraglutide once daily for 48 weeks led to MASH resolution in nine (39%) of 23 patients in the liraglutide group compared with two (9%) of 22 in the placebo group (relative risk 43, 95% CI 1·0–17·7). No improvement of fibrosis, but a lower rate of worsening of fibrosis, was observed in the liraglutide group. Decreases of bodyweight and HbA_{1c} were larger in the liraglutide group, while the change of insulin resistance (estimated with homoeostasis model assessment-estimated insulin resistance) was not different among the groups. In a larger phase 2 trial with semaglutide in 320 patients with MASH and liver fibrosis of stage F1–F3 (mild, moderate, and severe fibrosis),[91] treatment with subcutaneous 0·1 mg, 0·2 mg, or 0·4 mg semaglutide per day for 72 weeks resulted in a significantly higher proportion of patients with MASH resolution without worsening of fibrosis than placebo (in 40%, 36%, and 59% of patients treated with doses of 0·1 mg, 0·2 mg, or 0·4 mg per day, respectively, compared with 17% in the placebo group). Improvement

of liver fibrosis stage with no worsening of MASH was not found in this study.

Three clinical trials investigated the efficacy of semaglutide. A phase 2 trial of 2·4 mg semaglutide once-weekly for 48 weeks in 71 patients with MASH cirrhosis showed liver fat reduction but did not result in larger improvement in liver fibrosis of one stage or more without worsening of MASH compared with placebo.[93] There was also no significant difference between groups in the proportion of patients who had MASH resolution. Decreases of body weight (–8·83% in the semaglutide group *vs* –0·09% in the placebo group) and HbA_{1c} were larger with semaglutide compared with placebo. Most recently in an interim analysis of 800 of 1200 patients with MASH and fibrosis F2 or F3 of an ongoing phase 3 trial, once-weekly treatment with semaglutide 2·4 mg for 72 weeks resulted in a statistically higher proportion of patients with MASH resolution without worsening of liver fibrosis than placebo (ie, in 63% of patients treated with semaglutide compared with 34% in the placebo group). Treatment with semaglutide also resulted in a statistically higher proportion of patients having an improvement of liver fibrosis without worsening of MASH (ie, in 37% of patients treated with semaglutide compared with 23% in the placebo group.[92]

Clinical, demographic, and genetic factors that affect treatment response with respect to liver histology or liver-related events with the GLP-1 receptor agonist have not been reported. Of note, variants in *GLP1R* and its associated signalling molecule *ARRB1* (β-arrestin1) have been identified as having a significant effect on glycaemic control in a genome-wide analysis of pooled samples from multiple large clinical trials.[104] Whether these variants alter target engagement and would influence MASH treatment response has not been described.

GLP-1 and GIP receptor co-agonists

GIP and glucagon receptor agonists have additive beneficial metabolic effects to GLP-1 receptor agonists and multiple drugs are available or under investigation that leverage the synergistic benefits.[105] Tirzepatide, a GIP receptor and GLP-1 receptor co-agonist, has been approved for the treatment of type 2 diabetes and obesity.[105] Tirzepatide was not only found superior to GLP-1 receptor agonists to decrease bodyweight, both in people with and without type 2 diabetes, but also HbA_{1c} levels in patients with diabetes.[87,105] Beneficial metabolic effects of tirzepatide, independent of weight loss, include increased insulin secretion and glucagon secretion-induced lipid oxidation. Most importantly, GIP receptor agonism in adipose tissue is thought to enhance lipid storage in white adipose tissue, thereby reducing ectopic lipid deposition in other organs, such as skeletal muscle and the liver,[105] a process that depends on insulinaemia.[106] In a phase 2 trial involving 190 participants with MASH and stage F2 or F3 (moderate or severe) fibrosis, once-weekly subcutaneous tirzepatide (5 mg, 10 mg, or 15 mg) for 52 weeks led to statistically significant MASH resolution without worsening of fibrosis in 44% of 5 mg, 56% of 10 mg, and 62% of 15 mg tirzepatide groups compared with 10% in the placebo group.[94] Similarly, improvement of at least one fibrosis stage without worsening of MASH was found in 55% of 5 mg, 51% of 10 mg, and 51% of the 15 mg tirzepatide groups compared with 30% in the placebo group. However, the change in fibrosis has not been adjusted for multiple comparisons.

GLP-1 and glucagon receptor co-agonists

Survodutide, a GLP-1 and glucagon receptor co-agonist, has not yet been approved for any treatment. In a phase 2 trial involving 293 participants with biopsy-confirmed MASH and fibrosis stage F1–F3, participants received once-weekly subcutaneous injections of survodutide at a dose of 2·4 mg, 4·8 mg, or 6·0 mg or placebo, for 48 weeks.[95] Statistically significant improvement in MASH with no worsening of fibrosis was observed in 47% of 2·4 mg, 62% of 4·8 mg, and 43% of 6·0 mg groups compared with 14% in the placebo group. Improvement of fibrosis was found in 34% of the 6·0 mg group compared to 22% in the placebo group. Another GLP-1 and glucagon receptor co-agonist, pemvidutide which has a greater effect on the GLP-1 receptor than survodutide, is also being studied in patients with MASH.[107]

GLP-1, GIP, and glucagon triple agonists

Retatrutide and efocipegtrutide—GLP-1, GIP, and glucagon triple agonists—are being evaluated as treatments for obesity with retatrutide in early studies for MASH. Liver biopsy results are not available yet but in a phase 2a study of 98 patients, retratrutide treatment for just 24 weeks resulted in a mean relative change in liver fat from baseline of –42·9% (1 mg), –57·0% (4 mg), –81·4% (8 mg), –82·4% (12 mg), and +0·3% for placebo (all $p<0·001$ *vs* placebo). Liver fat normalization (<5% liver fat by proton density fat fraction) was observed in 27% in 1 mg, 52% in 4 mg, 79% in 8 mg, and 86% in 12 mg treatment groups compared with 0% in the placebo group.[108] If future biopsy-based studies show similar MASH resolution, these results might suggest that this treatment type might overcome major genetic drivers in most patients, although much is to be learned about the 14% of patients who did not normalise liver fat.

Potential treatments associated with no change in bodyweight

FGF-21 analogues

Fibroblast growth factor 21 (FGF-21) is a hepatokine that has pleiotropic beneficial effects on metabolism.[109,110] Numerous analogues that target the FGF receptors (ie, FGFR1, FGFR2, and FGFR3) and the β-klotho co-receptor have been shown to increase energy expenditure, improve insulin sensitivity and dyslipidaemia, and increase adiponectin levels. Treatment

of patients with obesity and type 2 diabetes with different FGF-21 analogues resulted in a decrease of bodyweight, hyperlipidaemia, liver fat content, and an increase of adiponectin levels, while changes of glycaemia were not observed.[109,110] Pegbelfermin, a pegylated FGF-21 drug, showed some beneficial effects on secondary endpoints in patients who are pre-cirrhotic[111] and those with well-compensated cirrhotic MASLD,[112] but did not meet primary histological improvement endpoints and its development was stopped. However, in a phase 2b trial of the FGF-21 analogue pegozafermin, FGF-21 linked to a smaller polyethylene glycol molecule and a different linking structure than pegbelfermin, led to MASH resolution in patients treated with 15 mg weekly (37% MASH resolution), 30 mg weekly (23%), or 44 mg every two weeks (25%) compared with 2% in the placebo group.[96] Fibrosis improved in 25% and 44% of patients in the 30 mg and 44 mg groups compared with 7% in the pooled placebo group. No changes in bodyweight or HbA_{1c} levels occurred in the pegozafermin groups or the placebo group.

A study of efruxifermin, a human IgG1 Fc-FGF-21 fusion protein, showed similar results with improved MASH activity and fibrosis in some but not all patients.[113] In a meta-analysis that included five phase 2 placebo-controlled trials involving adults with biopsy-confirmed MASH and stages F1–F4 fibrosis, treatment with the FGF-21 analogues efruxifermin, pegbelfermin, and pegozafermin resulted in a significantly higher percentage of patients with MASH resolution with no worsening of fibrosis, or greater than one stage of fibrosis improvement without worsening of MASH than placebo.[114] Multiple other FGF-21 analogues are in earlier stages of development for MASH.[115]

Resmetirom

Activation of the thyroid hormone receptor-β (THR-β) in the liver improves circulating lipid levels by modulating hepatic lipid metabolism and this signalling pathway has been identified as a promising target to treat MASLD and hypercholesterolaemia.[116] A phase 3 clinical trial of the THR-β agonist resmetirom in 966 patients led to MASH resolution without worsening of fibrosis in 25·9% and 29·9% of patients treated with 80 mg or 100 mg respectively compared with 9·7% of the participants in the placebo group. Fibrosis improvement by at least one stage without worsening of the NAFLD Activity Score was seen in 24·2% and 25·9% in the 80 mg and 100 mg group groups compared with 14·2% in the placebo group. No differences were observed in bodyweight, HbA_{1c} levels, or insulin resistance between the resmetirom and placebo groups.[97] Importantly, on March 14, 2024, the FDA approved resmetirom for the treatment of adults with non-cirrhotic NASH with moderate to advanced liver fibrosis, to be used together with diet and exercise.[117] Thus, resmetirom became the first drug to receive conditional approval in the USA for treating fibrotic MASH. Laboratory, clinical, and genetic factors associated with non-response have not yet been described.

Treatments associated with an increase of bodyweight

Peroxisome proliferator-activated receptors (PPARs) are a group of nuclear receptors that are important modulators of glucose and lipid metabolism, but are also involved in the regulation of inflammatory and fibrotic processes. Three different PPAR isotypes exist

Panel: Lifestyle interventions

There is scarce clinical trial data on tailoring dietary and exercise recommendations based on clinical phenotype or the presence of genetic variants. Based on major society recommendations, in all adults with metabolic dysfunction-associated steatotic liver disease (MASLD) and overweight or obesity, dietary and behavioural therapy-induced weight loss should aim at a sustained reduction of 5% or more to reduce liver lipid content, 7–10% to improve liver inflammation, and 10% or more to improve fibrosis,[120,123] but in people with lean MASLD, the recommended targeted weight loss is 3–5%.[69]

Bariatric surgery is usually reserved for people with substantial obesity with comorbidities and is already tailored to a subset of patients with MASLD based on phenotypic features.[127] For example, in a French study that included 180 patients, 5 years after bariatric surgery with liver biopsies available in 64 patients, resolution of MASH without worsening fibrosis was observed in 54 (84%) of patients (95% CI 73·1–92·2%).[128] In addition, fibrosis decreased in 45 (70·2%) of patients (95% CI 56·6–81·6%). In an Italian study, 288 patients with obesity and biopsy-proven MASH were assigned to lifestyle modification plus best medical care (n=96), Roux-en-Y gastric bypass (n=96), or sleeve gastrectomy (n=96).[127] Resolution of MASH without worsening of fibrosis at 1-year follow-up was observed in 54 (56%) of patients in the Roux-en-Y gastric bypass group and in 55 (57%) of patients in the sleeve gastrectomy group, but in only 15 (16%) of patients in the lifestyle modification group.

An important and intensively discussed aspect in the field of MASLD treatment is the question of whether the treatment of MASLD also improves clinical outcomes. In the SPLENDOR study,[130] in patients without cirrhosis at baseline, bariatric surgery (Roux-en-Y gastric bypass or sleeve gastrectomy) showed a marked reduction in the rate of major adverse liver outcomes (adjusted hazard ratio 0·12, 95% CI 5·5–11·4%), versus nonsurgical care, but some patients still progressed to liver-related adverse events. In addition, bariatric surgery largely reduced major adverse cardiovascular events (adjusted hazard ratio 0·30, 95% CI 0·12–0·72), compared with the nonsurgical group.

(α, β/δ, and γ). Single, dual, and pan-PPAR agonists have been studied for the treatment of MASH and hepatic fibrosis. Mechanisms of action of these PPAR agonists and results of the respective clinical trials have been well summarised before.[118] Clinical, laboratory, and genetic factors that correlate with response or non-response to the various PPAR agonists have not been described.

Pioglitazone

The PPARγ agonist pioglitazone is approved for the treatment of type 2 diabetes and is also protective of myocardial infarction and ischaemic stroke and improves MASLD. A meta-analysis showed an odds ratio (OR) of 3·65 (95% CI 2·32–5·74) for MASH resolution and an OR of 10·17 (95% CI 2·8–36·5) for improvement in advanced fibrosis (stages F3–F4) compared with control groups.[98] Weight gain, particularly subcutaneous fat rather than visceral fat, is often observed during pioglitazone treatment,[119] however, pioglitazone has not been approved to treat MASLD. The USA practice guidance statement on treating MASH states that pioglitazone can be used to treat patients with biopsy-proven MASH, with or without type 2 diabetes.[120] The European guidelines on the management of MASLD states that pioglitazone is safe to use in adults with non-cirrhotic MASH but given the absence of robust evidence of histological efficacy on steatohepatitis and liver fibrosis in large phase 3 trials, pioglitazone cannot be recommended as a MASH-targeted therapy.[121]

Other PPAR ligands

Fibrates are considered pure PPARα ligands and do not promote MASH resolution. The PPARα and PPARδ drug elafibranor has dominant PPARα effects and progressed to a phase 3 trial for MASH, but its development for the treatment of MASH was stopped in 2023 due to failure to meet key endpoints on interim analysis. The PPARα and PPARγ drug saroglitazar improved liver fat content and alanine aminotransferase but was associated with weight gain in a phase 2a trial.[122] Saroglitazar is now being evaluated in a phase 2b trial and has been approved in India for treatment of MASH. A phase 2b study of the PPARα, PPARδ, and PPARγ (pan-PPAR) agonist lanifibranor for MASH showed disease improvement in 55% of patients treated with the highest dose compared with 33% in the placebo group.[99] Fibrosis improvement without worsening of MASH was found in 48% at the highest dose compared with 29% in the placebo group. Treatment improved liver fat content, reduced liver enzymes, HbA_{1c} levels, insulin resistance, and increased adiponectin, but also led to a 2·8% weight gain.

Management of patients with MASLD considering the heterogeneity in its pathogenesis and cardiometabolic risk

The care of patients with MASLD is best done based on the medical guidelines and guidance statements (eg, European,[121] USA,[120,123] Latin American,[124] and Asia-Pacific clinical practice guidelines or guidances)[125,126] for diagnosis and treatment of MASLD. Lifestyle modifications that focus on a healthier diet, increased

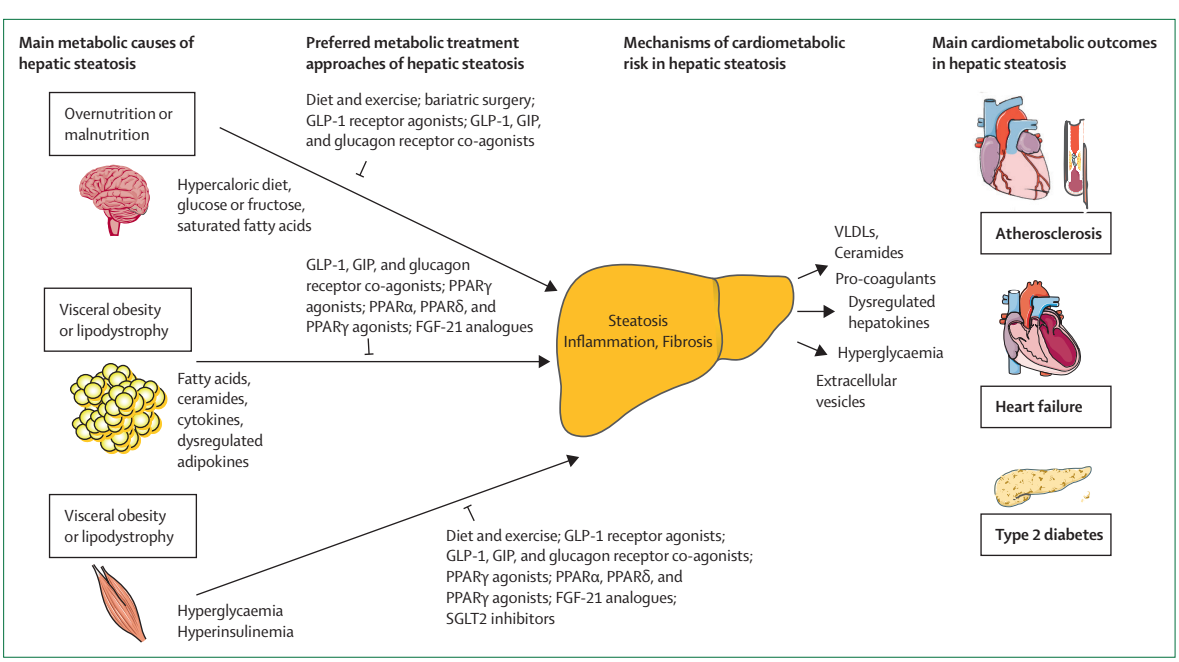

***Figure 3*: Main metabolic causes, consequences, and treatment approaches for people with MASLD**

FGF-21=fibroblast growth factor 21. GIP=glucose-dependent insulinotropic polypeptide. GLP=glucagon-like peptide. MASLD=metabolic dysfunction-associated steatotic liver disease. PPAR=peroxisome proliferator-activated receptor. SGLT2=sodium–glucose co-transporter-2.

physical activity, and weight reduction are recommended for all patients and pharmacotherapy or bariatric surgery can be recommended to individual patients based on their disease severity and comorbidities (panel).[131] Unfortunately, we do not yet have established methods to easily detect the different major pathomechanisms that contribute to MASLD and categorise patients into respective groups or clusters. In the future, using new data reduction approaches along with established measures of liver health and cardiometabolic risk (eg, elastography, non-invasive tests of steatohepatitis and fibrosis, precise measurements of insulin sensitivity, and body fat distribution) we could reach this goal. Nevertheless, from a clinical point of view, such basic stratification can already be done.

To date, medical guidelines do not recommend genetic testing for the risk of MASLD because we lack data on how the response to therapy, including lifestyle modification, is influenced by known genetic variants. Because the genetic background of the disease is unlikely to considerably influence the response to therapy regarding the liver phenotype, the lower risk of cardiovascular disease in patients with a strong hepatic genetic component of MASLD might not be relevant.

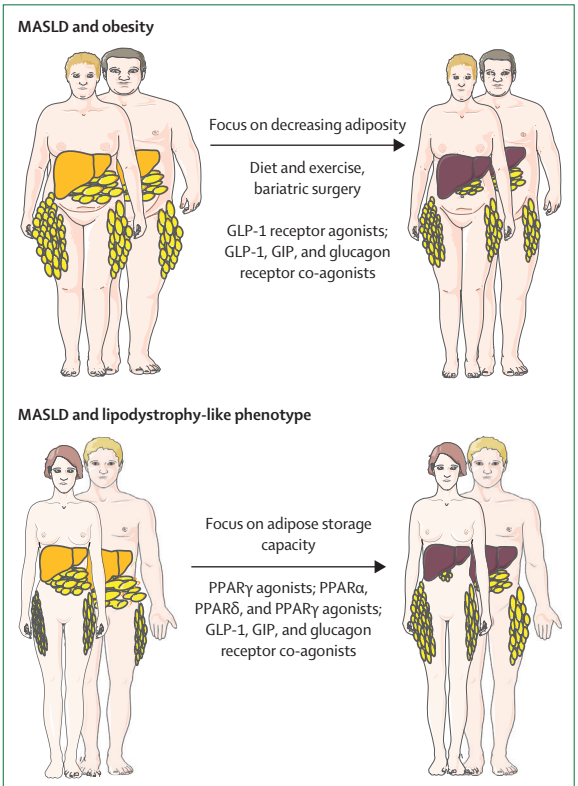

Figure 4: **Main metabolic treatment approaches for people with obesity and normal weight and MASLD**
GIP=glucose-dependent insulinotropic polypeptide. GLP=glucagon-like peptide. MASLD=metabolic dysfunction-associated steatotic liver disease. PPAR=peroxisome proliferator-activated receptor.

Instead, the higher risk of MASH, cirrhosis, and hepatocellular carcinoma in patients with some of the genetic risk variants for MASLD, warrants the use of the most effective pharmacological treatment to decrease hepatic inflammation and fibrosis in these patients.

For people having MASLD with a strong metabolic component related to hepatic de novo lipogenesis, particularly related to overnutrition and malnutrition (figure 2), the greatest focus of intervention might be a modification of diet, particularly decreased glucose and fructose intake and increase in exercise. If sufficient weight loss cannot be achieved, bariatric surgery or mono-incretin or multi-incretin hormone receptor agonists might be preferably recommended. Such treatment might also considerably decrease the elevated cardiometabolic risk in these people (figure 3). Because these patients often have severe insulin resistance, dyslipidaemia and an increased risk of cardiovascular disease, and heart failure, type 2 diabetes-specific treatment of the cardiometabolic risk parameters should be implemented early on.

For patients with MASLD with a strong metabolic component related to adipose tissue dysfunction (particularly those with lean MASLD), diet modification, increased exercise, and weight loss might not be the most effective treatment options. In this respect, if approved in the future, PPAR agonists, multi-incretin hormone receptor agonists, and FGF-21 agonists could be the preferred pharmacological treatment options (figure 3).

For people having MASLD with severe type 2 diabetes-associated hyperglycaemia and hyperinsulinaemia, all aforementioned treatment strategies and SGLT2 inhibitors, should be used, particularly those that decrease glucose levels and improve insulin resistance. Here a diabetes and endocrinology-focused approach identifying extreme phenotypes, such as hypo-insulinaemic type 2 diabetes, and hormone-induced obesity (eg, monogenetic obesity or hypercortisolism) should be used (figure 3).

In summary, besides the general recommendations of the medical guidelines to treat MASLD in the future, sub-phenotypes of MASLD might benefit from targeted therapy.[31] So far, in most cases of MASLD that is accompanied with obesity, the focus of treatment might be to achieve substantial weight loss, brought about by lifestyle intervention and bariatric surgery or mono-incretin or dual-incretin hormone receptor agonists. For people with MASLD that is accompanied by a lipodystrophy-like phenotype (lean MASLD), the focus of treatment should be improvement of adipose tissue storage capacity and increase of ectopic lipid oxidation. Here, preferably PPAR agonists and dual-incretin or triple-incretin hormone receptor agonists can be used (figure 4). Lastly, widely recommended combination therapy[82–84,132] (eg, resmetirom, pegozafermin, and other compounds), might be most effective in reducing the

Search strategy and selection criteria

The PubMed database was searched for full-text original research studies and review articles written in English from Jan 1, 1990 to Dec 11, 2024, and abstracts presented at scientific conferences were screened until Nov 25, 2024 to identify reports about the pathophysiology, the consequences, and the treatment of non-alcoholic fatty liver disease and metabolic dysfunction-associated steatotic liver disease. The search terms used were "non-alcoholic fatty liver disease", "metabolic dysfunction-associated steatotic liver disease", "nonalcoholic steatohepatitis", "metabolic dysfunction-associated steatohepatitis", "liver disease", and "liver fibrosis" together with "hepatocellular carcinoma", "mortality", "cardiovascular mortality", "liver-related mortality", "type 2 diabetes", "insulin resistance", "cardiovascular disease", "prediction", "prevention", "lifestyle intervention", "pharmacogenomics", and "treatment". The reference lists of the identified papers were also used to identify further papers of interest. The final reference list was selected based on relevance to the subject of this Review.

risk of hepatic and cardiometabolic events in patients with MASLD.

Conclusion

The ongoing global epidemic of MASLD and its close pathogenic and predictive relationship with the non-communicable diseases of cardiovascular disease, cancer, obesity, and type 2 diabetes, allow the inclusion of MASLD as a new non-communicable disease. Therefore, knowledge gained from research into the established non-communicable diseases (eg, related to patho-physiology, screening, social, health, economic, and industrial policies, and access to pharmacotherapies), should also be implemented in the field of MASLD research and therapy.[133] Among such knowledge is the idea of the implementation of precision medicine in MASLD, as is ongoing for other non-communicable diseases. Currently there is not enough evidence for the implementation of precision medicine for risk prediction, prevention, and treatment of MASLD. Because considerable heterogeneity in the pathogenesis of MASLD exists, it is probable that precision medicine can be implemented for future risk prediction and treatment, particularly related to the cardiometabolic causes and consequences of MASLD. Clinical, laboratory, and genetic analysis of responders and non-responders to emerging MASLD therapeutics will hopefully provide further guidance in the future.

Contributors

NS, HY-J, and BANT reviewed the published work and wrote the manuscript.

Declaration of interests

NS received fees for consultancy and giving scientific talks from Allergan, AstraZeneca, Boehringer Ingelheim, Gilead, Genkyotex, GSK, Intercept Pharma, Lilly, Merck Sharpe & Dohme, Novartis, Novo Nordisk, Pfizer, and Sanofi; and received research support from AstraZeneca, Boehringer Ingelheim, Sanofi, DSM Nutritional Products, and Roche Diagnostics. HY-J received advisory or consultancy fees from Merck, Lilly, Novo Nordisk, and Hamni Pharmaceuticals. BANT received advisory or consultancy fees from AbbVie, Akero, Aligos, Arrowhead, GSK, Hepion, HistoIndex, Madrigal, Merck, Mirum, Sagimet, Senseion; has stock options with HepGene and HeptaBio; and received institutional research grants from Madrigal.

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