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Metabolic dysfunction and alcohol-associated liver disease (MetALD)

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ABSTRACT

Metabolic dysfunction and alcohol-associated liver disease (MetALD) is a recently implemented nomenclature and disease terminology for patients with metabolic dysfunction-associated steatotic liver disease, who consume greater amounts of alcohol. MetALD is diagnosed in individuals who have at least one metabolic risk factor (such as obesity, type 2 diabetes mellitus, hypertension, etc) and consume 140–350 g/week of alcohol for women or 210–420 g/week for men. Conversely, alcohol-associated liver disease is diagnosed in individuals who consume >350 g/week of alcohol for women and >420 g/week for men. MetALD represents a heterogeneous spectrum of liver disease, with variations in clinical presentation and severity driven by differences in metabolic profiles, drinking patterns and individual susceptibility. Alcohol and metabolic risk factors are thought to act synergistically to accelerate steatohepatitis, fibrosis and hepatocellular carcinoma. However, the precise mechanisms underlying liver injury in MetALD still remain poorly understood. In this comprehensive review, we summarise the current definition, diagnostic criteria and clinical management of MetALD. We also discuss emerging insights into understanding its pathogenesis, examine relevant experimental models and highlight future challenges and research priorities in this evolving field.

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INTRODUCTION

Alcohol-associated liver disease (ALD)[1 2] and metabolic dysfunction-associated steatotic liver disease (MASLD)[3 4] are the two major causes of liver cirrhosis, which has a major impact on global health and is among the leading causes of death worldwide.[5] Many individuals with MASLD also consume significant amounts of alcohol, in which both alcohol and metabolic dysfunction likely contribute to the pathogenesis of liver injury. Therefore, a new category targeting individuals with MASLD who consume greater amounts of alcohol per week has been established and is called metabolic dysfunction and alcohol-associated liver disease (MetALD).[6 7] This new terminology and diagnostic criteria for MetALD can help identify separate patient groups with the coexistence of MASLD and ALD, which will facilitate the design of more effective therapeutical interventions for MASLD, MetALD and ALD. The clinical diagnosis and treatment of MetALD have been reviewed in several excellent articles,[8–13] which are briefly summarised in the current paper. Molecular and cellular factors that contribute to the pathogenesis of ALD and MASLD have been extensively investigated in preclinical models and patients.[1 14–18] However, the research on MetALD pathogenesis is in its infancy. In this critical review, we discuss recent advances in understanding MetALD and propose potential mechanisms underlying MetALD development and progression. We also summarise current preclinical models used to study MetALD, although they do not fully recapitulate human MetALD. Lastly, we discuss the current clinical, translational and basic research challenges and propose future research directions for MetALD.

DEFINITION AND DIAGNOSIS

MetALD refers to patients with hepatic steatosis who meet criteria for metabolic dysfunction and report alcohol consumption above the 'non-significant' thresholds for MASLD but below the 'very heavy' drinking range for ALD (figure 1). According to the 2023 multisociety nomenclature, this roughly corresponds to 140–350 g ethanol per week in women and 210–420 g per week in men, positioning MetALD on a continuum between MASLD and ALD.[6 7] Conceptually, MetALD acknowledges that alcohol and metabolic dysregulation act synergistically to exacerbate steatohepatitis, fibrosis, hepatocellular carcinoma and extrahepatic outcomes. Even alcohol intake considered 'non-severe' can

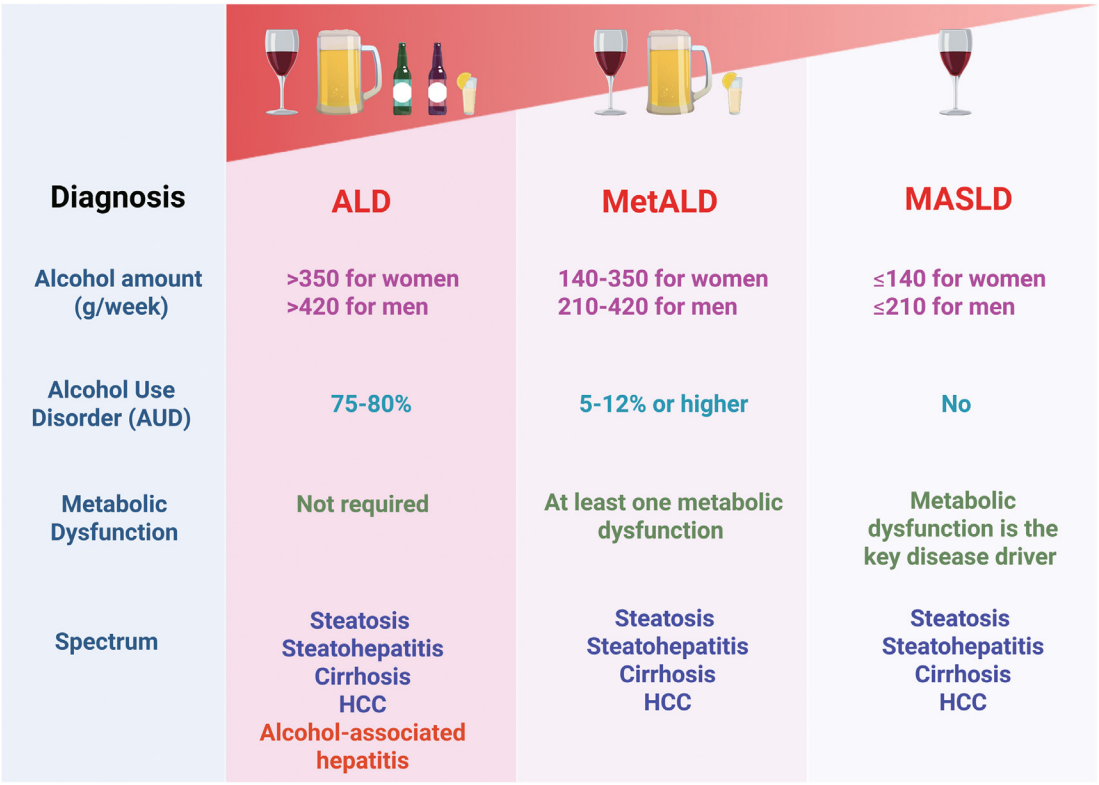

Figure 1 Comparison of ALD, MetALD and MASLD. The schematic images were created with BioRender (https://www.biorender.com). ALD, alcohol-associated liver disease; HCC, hepatocellular carcinoma; MASLD, metabolic dysfunction-associated steatotic liver disease; MetALD, metabolic dysfunction and alcohol-associated liver disease.

significantly worsen prognosis when metabolic risk factors are present.[10] Recent expert guidance has formalised the practical implications of this construct and emphasised the need for precise phenotyping to guide clinical care.[8 12]

Diagnosis

Diagnosis begins with confirmation of hepatic steatosis (eg, by imaging) and documentation of metabolic dysfunction, including obesity, prediabetes or type 2 diabetes mellitus (T2DM), dyslipidaemia and hypertension, followed by rigorous quantification of alcohol exposure, in which beverage types and container sizes are translated into grams per day/week and typical, peak and binge patterns are recorded.[8 19] The detailed diagnosis of MetALD is described in recently published guidelines that delineate the detailed assessment of alcohol use and metabolic dysfunction in individuals with suspected steatotic liver disease (SLD).[8 12] Because the accuracy of self-reported alcohol intake may be limited, structured instruments such as the Timeline Followback[20–22] and Alcohol Use Disorder Identification Test (AUDIT),[20 23] as well as collateral information from family members or medical records, should be employed to improve ascertainment. Documentation of binge drinking patterns further refines risk stratification.[6] Alcohol use and metabolic risk should be reassessed longitudinally, as trajectories change and patients may migrate between MASLD, MetALD and ALD categories.[8 12 24]

Direct alcohol biomarkers are critical for minimising misclassification. Phosphatidylethanol (PEth) in whole blood provides high sensitivity and specificity for moderate-to-heavy drinking and is detectable for approximately 2–4 weeks after alcohol consumption.[25 26] Combining PEth measurement with questionnaires markedly increases the detection of hazardous alcohol consumption and may reclassify patients previously labelled as MASLD into MetALD or ALD.[25 27] Expert recommendations further specify how PEth ranges can contextualise reported intake and support serial testing in ambiguous cases. They also emphasise that PEth measurements complement, but do not replace, careful history and clinical judgement.[8]

Non-invasive assessment of liver injury and fibrosis is essential in MetALD. Simple fibrosis scores such as fibrosis-4 index (FIB-4) can be used for initial triage of patients, followed by elastography, either vibration-controlled transient elastography or magnetic resonance (MR) elastography, to stage fibrosis and guide referral and surveillance.[28] Stiffness thresholds indicating advanced fibrosis should prompt clinicians to initiate enhanced management and targeted screening for related complications.[8] Liver biopsy is reserved for diagnostic uncertainty or suspected competing aetiologies. Histological analysis of liver biopsies typically assesses macrovesicular steatosis, hepatocyte ballooning, lobular inflammation and pericellular ('chicken-wire') fibrosis, although these features overlap substantially between metabolic-predominant

and alcohol-predominant steatohepatitis, making biopsy rarely definitive for determining aetiology in isolation.[10] Practical pitfalls include misattributing alcohol-induced hypertension, hypertriglyceridaemia or hyperglycaemia to metabolic dysfunction alone, and mislabelling heavy drinkers who meet a single metabolic criterion as MASLD rather than MetALD or ALD. Clinicians should carefully assess the causal relationships between cardiometabolic traits and alcohol use when classifying patients.[8]

Epidemiological studies demonstrate that MetALD is widespread globally. It is also associated with higher risks of liver-related and extrahepatic adverse outcomes than MASLD alone.[29 30] These observations underscore the importance of multidisciplinary care addressing both alcohol use disorder (AUD) management and metabolic risk factors, including weight, glycaemic, lipid and blood pressure control.[9]

Clinical management

The management of MetALD requires a multi-targeted, multidisciplinary approach that addresses both the underlying metabolic risk factors and alcohol consumption. This strategy is critical, given the synergistic effect of both aetiologies on liver injury and overall morbidity as well as mortality.[9] A cornerstone of care in MetALD is a comprehensive lifestyle intervention that integrates dietary changes, increased physical activity and sustained weight loss with strategies for alcohol moderation or abstinence.

Lifestyle and behavioural interventions

Weight loss is a pivotal goal in MetALD management, as a reduction of 5%–7% of total body weight has been shown to improve steatosis, while greater weight loss of ≥10% can lead to resolution of steatohepatitis and even regression of fibrosis in patients with MASLD.[19] This is achieved through a combination of a healthy diet (eg, Mediterranean diet) and at least 150 min per week of moderate-intensity aerobic exercise.[31] Bariatric metabolic surgery may be considered for patients with obesity who do not respond to medical and lifestyle interventions, although close monitoring is essential due to the potential risk of new-onset or worsening AUD.[32–34] For the alcohol component, the primary goal is to stop or at least reduce alcohol consumption, as further detailed in the *AUD in MetALD* section.

Pharmacological therapy

Pharmacotherapy in MetALD targets both the metabolic and alcohol-related pathways. For the metabolic component, drugs approved for MASLD, such as the thyroid hormone receptor beta agonist resmetirom, may be considered.[35] In a post hoc analysis, a fraction (10%–15%) of the study cohort in MAESTRO-NASH clinical trial was deemed to have MetALD and the response to resmetirom was the same in this group as the general MASLD group.[36] Additionally, glucagon-like peptide-1 (GLP-1) receptor agonists (GLP-1 RAs), such as semaglutide, have shown efficacy in reducing steatosis and improving liver biochemistry.[37] Emerging evidence also suggests that GLP-1 RAs may reduce alcohol consumption, as further detailed in the *AUD in MetALD* section. It is important to note that many of the medications used for MASLD and AUD have not been formally studied in a dedicated MetALD population, necessitating careful clinical judgement based on the individual patient's risk profile.

Ongoing monitoring and risk stratification

Effective long-term management requires continuous monitoring and risk stratification. Patients should be regularly reassessed for both their alcohol consumption and metabolic status. Non-invasive tests, such as FIB-4 score and transient elastography, should be used to monitor for fibrosis progression. Patients with advanced fibrosis or cirrhosis require intensified management and surveillance for complications.[8 28]

AUD in MetALD

Given the synergistic effects of alcohol and metabolic risk factors in promoting MetALD, comprehensive patient management should explicitly address alcohol consumption. For patients who exhibit alcohol-related injury and harmful drinking patterns but do not meet diagnostic criteria for AUD, brief, low-intensity interventions that emphasise the health risks of ongoing alcohol use can lead to significant improvement in health outcomes.[38] At the other end of the spectrum, significant behavioural disease, including continued use despite knowledge of potentially serious harm, warrants a medical diagnosis of AUD, and in this case treatment is strongly indicated through behavioural or pharmacological approaches, with even greater benefits if these strategies are combined.[38 39] Behavioural and psychological treatments for AUD include motivational interviewing, contingency management, cognitive behavioural treatments and acceptance-based and mindfulness-based approaches.[40] Alcoholics Anonymous and 12-step facilitation, which were designed specifically to connect individuals with mutual support groups, have also been shown to be effective.[41] There is evidence that these behavioural treatments improve outcomes in AUD and reduce harm in people with AUD and comorbid liver diseases.[42]

The Food and Drug Administration (FDA) has approved acamprosate, disulfiram and naltrexone for the treatment of AUD. Disulfiram is indicated only for patients who have achieved abstinence, providing support to sustain complete alcohol abstinence. Because of its potential hepatotoxic effects, disulfiram is not recommended for people with ALD or MetALD, although no studies have formally investigated its use in patients with AUD and liver diseases.[43] Acamprosate and naltrexone have been shown to be effective in treating AUD, especially for relapse prevention and drinking reduction, respectively.[44] Acamprosate is primarily excreted by the kidneys, is considered safe in patients with liver diseases and has been recommended by organisations such as

the American Association for the Study of Liver Diseases (AASLD) for use in patients with AUD and liver diseases.[2] Because of initial concerns about a significant risk of hepatotoxicity, naltrexone use in patients with liver diseases was not recommended. These concerns have been refuted recently, although caution still remains important in patients with more advanced liver disease due to possible active metabolite accumulation.[45] While topiramate, gabapentin and varenicline are not FDA-approved for AUD and have not been formally studied in individuals with coexisting AUD and liver diseases, they may serve as potential second-line therapeutic options. The American Psychiatric Association endorses topiramate and gabapentin as potential second-line treatments for AUD.[46] Studies testing these medications in patients with AUD and liver diseases are needed. Baclofen is approved in France for AUD, and, for reasons that are still unclear, its efficacy appears to be greater in patients with AUD and liver diseases.[47] Despite limited evidence, the potential use of Baclofen in patients with AUD and liver diseases has been endorsed by the AASLD[2] and American College of Gastroenterology.[48]

PATHOGENESIS

Hepatocyte damage

Hepatocyte death plays an important role in promoting the development and progression of MASLD[49] and ALD,[50] and likely MetALD as well. The effect of alcohol and high-fat diet (HFD)/Western diet on hepatocyte injury is not merely additive but rather synergistic, as demonstrated in experimental models. For example, feeding mice with an HFD as short as 3 days markedly aggravated alcohol-induced liver injury and inflammation, especially hepatic neutrophil infiltration.[51] The synergistic effects of alcohol and HFD on hepatocyte injury are mediated by promoting lipotoxicity, oxidative stress, endoplasmic reticulum (ER) stress and inflammatory signals in the liver.[1 49 50] Hence, these mechanisms are involved in the pathogenesis of MetALD.[13]

Inflammation

Chronic liver inflammation is a hallmark of MASLD and ALD, playing a critical role in their pathogenesis.[14 15] In MASLD and ALD, liver inflammation is complex and heterogeneous, marked by infiltration of various inflammatory cell types and elevation of multiple inflammatory mediators.[14 15] Liver inflammation in MASLD and ALD shares many similarities, but there are also pronounced differences. For example, neutrophil inflammation is a hallmark of steatohepatitis in both MASLD and ALD/alcohol-associated hepatitis (AH).[14 15 52] A recent study reported that severe AH is highly infiltrated with self-sustaining interleukin (IL)-8$^+$ neutrophils, which contributes to massive neutrophil infiltration and liver failure in severe AH.[53 54] However, alcohol-associated cirrhosis and MASLD are associated with a low number of IL-8$^+$ neutrophils in the liver.[53] Yet, whether hepatic infiltration of self-sustaining IL-8$^+$ neutrophils in MetALD contributes to the pathogenesis of MetALD should still be investigated.

In experimental models, few neutrophils are detected in the livers of chronically ethanol-fed mice or rats; however, binge ethanol administration to chronically ethanol-fed mice causes marked elevation of circulating and hepatic neutrophil infiltration.[55] Interestingly, binge ethanol intake also induces hepatic neutrophil infiltration and liver injury in mice fed an HFD[51 56] or a Western diet.[57] Mechanistically, an HFD combined with acute alcohol binge synergistically causes liver injury and inflammation through the elevation of hepatic or circulatory free fatty acids and subsequent C-X-C motif chemokine ligand 1 (CXCL1)-mediated hepatic neutrophil infiltration.[51 56] Furthermore, alcohol consumption promotes neutrophil extracellular trap (NET) formation, which activates hepatic stellate cells (HSCs) and macrophages via NLR family pyrin domain containing 3 (NLRP3) sensing.[58] Neutrophil depletion or NET disruption diminishes macrophage and HSC activation, thus mitigating MetALD-related liver damage and liver fibrosis in mice. In addition, a high-fat, high-cholesterol and high-sucrose diet plus alcohol gavage induces NLRP3-IL-1β activation in neutrophils, subsequently promoting the development of MetALD.[59]

Interestingly, a recent study reported two distinct histopathological phenotypes of severe AH in patients based on their unique liver immune characteristics.[60] Patients with high hepatic neutrophils but low CD8$^+$ T cells exhibit higher Model for End-Stage Liver Disease (MELD) scores and serum alanine aminotransferase (ALT) levels but have less fibrosis compared with those with low hepatic neutrophils but high CD8$^+$ T cells.[60] It is plausible to predict that different hepatic histopathological immune phenotypes also exist in MetALD. Characterisation of these diverse immune phenotypes could facilitate the identification of precision medicine approaches for MetALD.

The liver is particularly prone to alcohol-induced damage due to its central role in metabolising alcohol and filtering toxins from the circulation.[61] Although acetaldehyde is the primary metabolite of alcohol, other metabolites may also contribute to MetALD development. For example, fatty acid ethyl esters (FAEEs) were reported to exacerbate alcohol-induced liver injury by promoting hepatic ER stress, adipocyte death and lipolysis.[62] Understanding how ethanol and its metabolites influence the immune microenvironment in the liver and impair metabolic homeostasis during MetALD remains an open and compelling question. In addition, alcohol and its metabolites directly induce hepatocellular damage and disrupt the intestinal mucosa and impair gut microbiota balance. This ultimately leads to liver inflammation by generating damage-associated molecular patterns (DAMPs) and facilitating the translocation of pathogen-associated molecular patterns (PAMPs) from the gut to the liver.[14 63] For example, alcohol-driven lipopolysaccharide (LPS) release promotes neutrophilic inflammation and liver injury by inducing IκBζ-mediated CXCL1 expression

in hepatocytes.[64] Alcohol consumption can also alter gut inflammation, thereby exacerbating ALD.[65] Recent studies have demonstrated that duodenal $CD8^+$ T cells are depleted in patients with ALD but not in patients with MASLD, and such depletion was shown to exacerbate ALD progression by disrupting gut barrier function and increasing bacterial translocation.[66 67] Furthermore, data from experimental models revealed that duodenal $CD8^+$ T cell depletion requires high concentrations of ethanol post binge ethanol intake.[67] Because MetALD is associated with moderate alcohol consumption, it is not clear whether duodenal $CD8^+$ T cell depletion also occurs and contributes to its pathogenesis.

Besides T cells and as a part of the innate immune system, macrophages in the liver and the gut can respond to a wide variety of physiological and/or pathological stimuli.[68 69] RNA sequencing (RNA-seq) analysis confirmed the existence of a variety of hepatic macrophage subsets including pro-inflammatory and anti-inflammatory phenotypes, playing diverse roles in controlling ALD and MASLD development and progression.[14 15 70–72] Like their counterparts in the liver, intestinal macrophages are involved in pathogen clearance and tissue remodelling as well as in maintaining gut homeostasis.[69] Immune-mediated disruption of the intestinal barrier promotes microbial translocation to the liver, triggering crosstalk between gut-derived signals and hepatic macrophages. This interaction promotes liver inflammation and contributes to the pathogenesis of ALD and MASLD.[15 68 73] How alcohol or the occurrence of MASLD affects the intestinal macrophage compartment remains largely unknown. In parallel to $CD8^+$ T cell depletion in the duodenum, it has been reported that the number of intestinal macrophages is also reduced in patients with AUD.[66] Yet, the reasons for the depletion of intestinal macrophages and their role in liver disease progression remain unknown.

Although ALD and MASLD share similarities including aberrant activation of the immune system,[14 15] MetALD represents a distinct category separate from pure MASLD or ALD. Whether or which of the reported immune changes in the gut and the liver also play a role in the pathogenesis of MetALD remains to be formally investigated. Caution is also required before extrapolating animal data to humans since some of the functions of macrophages differ between humans and mice, whereas others are similar.

In summary, the combination of metabolic syndrome and moderate alcohol consumption predisposes individuals to the development of liver inflammation and advanced MetALD (figure 2). Therefore, understanding the pathophysiological mechanisms of the synergistic effect of alcohol and metabolic risk factors on MetALD, especially distinct metabolic and inflammatory responses, may provide a more accurate prognosis and effective management of MetALD.

Liver fibrosis in MetALD

Liver fibrosis is a feature of all types of chronic liver diseases including MetALD and is a strong predictor of patient morbidity and mortality.[74] There is a male preponderance and high smoking prevalence in MetALD. Both are associated with alcohol consumption and are also independently associated with liver fibrosis.[75 76] It might therefore be expected that the MetALD population will have, in general, greater liver fibrosis than the MASH population, but a significant difference in the degree of liver fibrosis or the rate of fibrosis progression has not been identified.[77 78] However, the recognition of MetALD as a distinct entity is relatively new and these questions have not been comprehensively addressed.

The cellular, inflammatory, epigenetic, matrix and other biological changes associated with liver fibrosis have been extensively investigated in human livers and have also been manipulated in animal models. This has resulted in the development of a model of fibrosis that is relatively stereotypical and centres around the activation of HSCs from a quiescent state into final myofibroblasts, which are predominantly responsible for deposition of a fibrotic liver matrix. This is a complex process and has been covered in detail in several dedicated reviews.[79–81] Recent developments have been marked by novel concepts and novel technologies. Two novel concepts are the functional roles of quiescent HSCs and the development of a stellate cell syncytium with autocrine signalling on activation.[82 83] The traditional view of the quiescent HSCs being functionally inert has been shown to be incorrect, and quiescent HSCs have recently been shown to control hepatic zonation, liver size, regeneration and cytochrome P450 enzymes. This is dependent on HSC-specific expression of the molecule R-spondin 3, with its loss resulting in changes that replicate the loss of quiescent HSCs, worsening ALD.[82] The second conceptual change is that it is now known that on activation, HSCs develop a syncytium with multiple autocrine interactions that are conserved between mice and humans.[83] The development of this syncytium has many functional implications as it enhances the interaction of HSCs with many other liver cell populations. The impact of the alcohol-driven changes in the functional roles of quiescent HSCs and the development of a myofibroblast syncytium is yet to be explored.

The technological advances of single cell RNA-seq and spatial transcriptomics are changing our understanding of liver fibrosis.[84 85] Single-cell RNA-seq of human MASH livers has allowed subcategorisation of HSCs to provide greater functional understanding.[86 87] In addition to the established quiescent HSCs (expressing *LRAT*, *SYNM* and *NGRF*), activated HSCs can be identified into separate functional clusters. These include a classic activated cluster (expressing alpha-smooth muscle actin (a-SMA) and fibrillar collagen), and an intermediate activated cluster. There is also an inflammatory cluster (expressing *CD36*, *CLEC* and *CREM*) with relatively low expression of collagen genes, which is relatively small

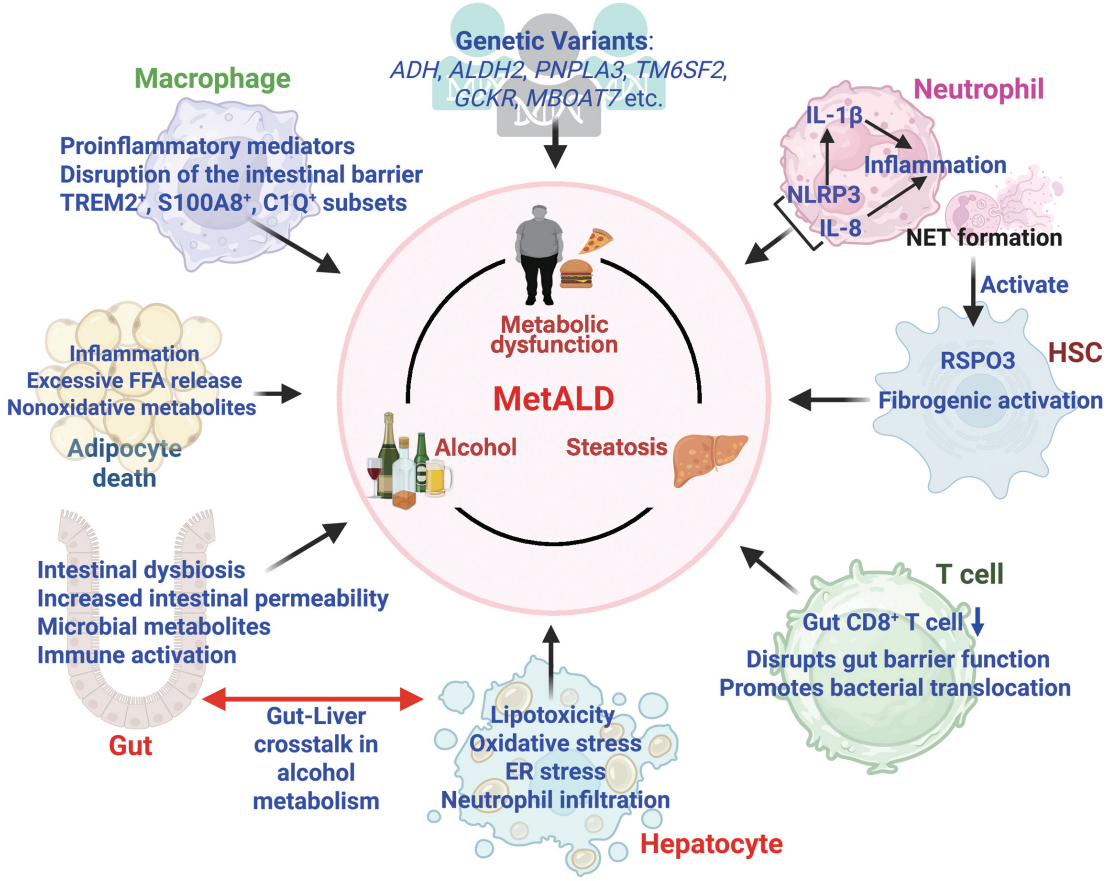

Figure 2 Pathogenesis of MetALD. Various molecular and cellular mechanisms contribute to the pathogenesis of MetALD. The schematic images were created with BioRender (https://www.biorender.com/). ADH, alcohol dehydrogenase; ALDH2, aldehyde dehydrogenase 2; C1q, complement component 1q; ER, endoplasmic reticulum; FFA, free fatty acid; GCKR, glucokinase regulatory protein; HSC, hepatic stellate cell; IL-1β, interleukin 1β; IL-8, interleukin 8; MBOAT7, membrane-bound O-acyltransferase 7; MetALD, metabolic dysfunction and alcohol-associated liver disease; NET, neutrophil extracellular trap; NLRP3, NLR family pyrin domain containing 3; PNPLA3, patatin-like phospholipase domain-containing 3; RSPO3, R-spondin 3; S100A8, S100 calcium binding protein A8; TM6SF2, transmembrane 6 superfamily member 2; TREM2, triggering receptor expressed on myeloid cells 2. The schematic images were created with BioRender (https://www.biorender.com/).

compared with the others. A small cluster of senescent cells is also present (expressing *GLB1*, *TP35* and *SPI1*). The identification of functional subgroups of HSC along with the morphological data on syncytia formation raises the important question of what types of interactions are occurring between these subpopulations. Answers to such questions will be more accessible with the application of spatial transcriptomics.[88]

With the removal of the pathological stimulus, liver fibrosis can reverse, at least at the precirrhotic stage. This has been documented in effective therapies, such as direct-acting antivirals for HCV.[89] The same is true for MASH and MetALD, but the issue here is that removing the pathogenic stimuli is much more challenging.[1 90] The recent approval of semaglutide for F2-F3 MASH is encouraging and given the initial evidence supporting a role of GLP-1RAs for AUD, there is the potential for this class of medications to address both the liver disease and the underlying AUD (also see *AUD in MetALD* section).[37 91–93]

Gut-liver crosstalk in MetALD

The pathophysiology of MetALD goes beyond the hepatocyte and is affected by the gut-liver axis. This bidirectional communication system plays an important role in controlling alcohol metabolism[94] and integrates host, microbial, immune and metabolic signals. Disruption of this crosstalk contributes to steatosis, inflammation, fibrosis and cirrhosis.[95] Excessive alcohol consumption is known to induce alcohol-associated bowel disease that can exacerbate liver disease.[96] Here, we summarise the key mechanisms by which alcohol and metabolic risk factors synergistically converge to alter the gut-liver interface, exacerbating MetALD. We highlight microbial dysbiosis, increased intestinal permeability, microbial metabolites and immune activation as central pathways.

Intestinal dysbiosis

Both alcohol and metabolic dysfunction alter the gut microbiome, and their combination might exacerbate intestinal dysbiosis. Chronic alcohol consumption decreases bacterial diversity, reduces beneficial taxa

and promotes expansion of pathobionts like *Enterococcus faecalis* and *Escherichia coli*.[97 98] Virulence factors from pathobionts directly cause hepatocyte damage or allow them to escape immune surveillance.[97 98] Similarly, patients with MASLD shift the microbiome towards a reduced prevalence of anti-inflammatory microbes (such as *Coprococcus, Faecalibacterium* and *Ruminococcus*) and a higher abundance of potentially inflammatory microbes (such as *Escherichia, Prevotella* and *Streptococcus*).[17] Although evidence for synergistic effects of bacterial perturbations in patients with MetALD is lacking, emerging data suggest that alcohol plays a role in modulating the intestinal virome of patients with MASLD. Patients with MASLD have decreased viral diversity and a lower proportion of bacteriophages compared with other intestinal viruses.[99] Low-to-moderate alcohol consumption increased the viral diversity in patients with MASLD to a level comparable to patients with AUD.[100]

Increased intestinal permeability

A hallmark of gut-liver crosstalk in ALD and MASLD is the disruption of the intestinal barrier. The ethanol metabolite acetaldehyde might directly impair tight junction proteins,[101] while low-grade inflammation in the lamina propria might further compromise epithelial cell integrity.[102] Together, these effects may lead to increased translocation of bacterial products, including LPS, peptidoglycan and bacterial DNA into the portal circulation. Interestingly, while systemic LPS is elevated in preclinical models of ALD and MASLD, bacterial DNA could only be detected in the livers of ethanol-fed mice.[103] Elevated bacterial products may synergistically increase liver inflammation and cause progression of liver disease in patients with MetALD.[104]

Microbial metabolites

Gut microbes metabolise dietary components into metabolites that affect the host locally in the gut or after absorption in the liver. These microbial metabolites, including short-chain fatty acids, bile acids, acetate and indole derivatives, are dysregulated in patients with ALD and MASLD.[17] These disturbances contribute to inflammation, steatosis and fibrosis in both ALD and MASLD, and likely in MetALD as well. Endogenous ethanol production by intestinal bacteria has also been suggested as a relevant factor linking dysbiosis to liver damage including MASLD.[105] However, endogenous ethanol concentrations are likely much lower compared with those in heavy drinkers, thus potentially playing only a minor role in MetALD pathogenesis.

Immune activation and inactivation in the gut

Intestinal homeostasis depends on the interplay between epithelial barrier integrity and mucosal immune activity.[106] Chronic alcohol consumption disrupts epithelial function by increasing the number of goblet cells, inducing excessive mucin secretion and impairing the formation of small intestinal goblet cell-associated antigen passages (GAPs).[61 107] GAPs are dynamic, columnar transcytotic structures induced by muscarinic acetylcholine receptor 4 (mAChR4) activation. They mediate the controlled delivery of luminal antigens to lamina propria antigen-presenting cells, thereby fostering immune tolerance while supporting adaptive immune responses.[108 109] Chronic alcohol use downregulates mAChR4 expression, limiting GAP formation and impairing immune education, thereby increasing susceptibility to alcohol-induced bacterial translocation and the development of ALD. Restoring mAChR4 activity, either through direct pharmacological activation or by targeting upstream pathways such as interleukin-6 signal transducer (IL6ST), reinstates GAP formation, enables antigen sampling by antigen-presenting cells and, in turn, induces innate group 3 innate lymphoid cell (ILC3)-derived IL-22 and antimicrobial Reg3 proteins, thereby limiting mucosa-associated bacteria and protecting against ALD.[108] In MASLD models, goblet cell-specific mAChR4 ablation exacerbates the disease, whereas activation ameliorates it. Although the precise mechanism remains to be elucidated, they might be different from ALD.[108] Whether GAPs play a role in MetALD remains unknown, but restoring intestinal homeostasis through GAP formation may represent a promising strategy to alleviate this disease. In the same line as discussed above, duodenal $CD8^+$ T cells are markedly depleted in patients with ALD, which results in enhanced gut bacterial translocation and subsequent exacerbated ALD.[60 66] Duodenal macrophages are also markedly depleted in patients with ALD, but the roles of such depletion in ALD pathogenesis remain unknown. Depletion of duodenal $CD8^+$ T cells and macrophages may also occur in patients with MetALD, and the significance of such depletions in MetALD deserves further investigation.

In summary, alcohol-induced and metabolic-driven alterations in the gut-liver axis lead to gut dysbiosis, barrier dysfunction, microbial metabolite dysregulation and immune activation in the intestine and the liver. These processes may cause or contribute to the progression of steatosis, steatohepatitis and fibrosis in MetALD.

Adipose-liver crosstalk

The adipose tissue-liver axis constitutes an evolutionarily conserved regulatory network that governs systemic nutrient partitioning and lipid homeostasis. Under conditions of caloric excess, adipose tissue functions as the primary storage site for neutral lipids, sequestering potentially lipotoxic free fatty acids (FFAs) in the form of triglycerides. In contrast, the liver functions as a central metabolic organ, integrating dietary and endogenous lipid flux through triglyceride synthesis, the synthesis of lipoproteins and redistribution of energy substrates to extrahepatic tissues. This bidirectional regulation—mediated by insulin signalling, lipoprotein metabolism and the capacity of adipose tissue to undergo controlled expansion—is fundamental to the maintenance of metabolic health.[110 111]

In metabolically healthy states, adipose tissue accommodates caloric surplus through a combination of adipocyte hypertrophy and hyperplasia, supported by angiogenesis, extracellular matrix remodelling and low-level immune surveillance. This adaptive microenvironment permits efficient clearance and storage of fatty acids, limiting spillover of FFAs into the systemic circulation effectively, thereby shielding the liver from excessive FFA influx, preventing ectopic triglyceride deposition and hepatocellular stress.[112 113]

With sustained energy excess, the storage capacity of adipocytes becomes compromised. Hypertrophic, hypoxic adipocytes activate stress pathways that promote the release of chemokines such as chemokine (C-C motif) ligand 2 (CCL2), which recruit circulating monocytes. Inflammatory macrophages that accumulate in adipose tissue frequently form crown-like structures around necrotic adipocytes. Together with stressed adipocytes, these macrophages secrete cytokines including tumour necrosis factor-α, IL-6 and resistin, which disrupt insulin receptor signalling.[114–117] In response, the replenishment of metabolically protective macrophage subsets is impaired, which coincides with a breach of adipose vascular integrity, leading to albumin leakage and impaired immune-endothelial interactions, thereby aggravating adipose tissue inflammation.[118] Similarly, the extent of adipose tissue inflammation in individuals with obesity strongly correlates with the histological severity of MASLD.[115] As a consequence, inflamed adipose tissue becomes insulin resistant, with impaired suppression of hormone-sensitive lipase activity and elevated basal lipolysis resulting in excessive flux of FFAs into the circulation, imposing an increased metabolic load on the liver.[114 119] The liver responds to this lipid oversupply by esterifying FFAs into triglycerides, thereby promoting hepatic steatosis. In parallel, adipose-derived cytokines and adipokines enter the portal circulation, activating Kupffer cells and HSCs. These events potentiate hepatic inflammation, insulin resistance and fibrogenesis.[111 116] Adipocyte death is frequently observed in obese individuals. Apoptotic adipocytes release a variety of factors, such as fatty acids, extracellular vesicles and DAMPs. It has recently been documented that fatty acids released by apoptotic adipocytes cause the elevation of $S100A8^{+}$ macrophages in the liver, which in turn leads to the upregulation of *CD36* in hepatocytes, promoting hepatic steatosis and lipotoxicity.[72]

Superimposed alcohol consumption further enhances dysregulated metabolism and inflammation in the liver. Alcohol metabolism in the liver elevates the NADH/NAD^{+} ratio, enhancing de novo lipogenesis while suppressing β-oxidation of fatty acids. Alcohol also induces cytochrome P450 family 2 subfamily E member 1 (CYP2E1) activity, generating reactive oxygen species that exacerbate oxidative stress and increase intestinal permeability, facilitating the translocation of LPS into the portal circulation. This, in turn, amplifies toll-like receptor 4 (TLR4)-mediated inflammatory signalling in hepatic macrophages.[120] Importantly, alcohol also exerts direct effects on adipose tissue. Park *et al* demonstrated that alcohol and its non-oxidative metabolites, FAEEs, promote acute alcohol-induced liver injury by inducing adipocyte death in association with hepatic ER stress and lipolysis.[62] Chronic alcohol exposure impairs insulin-mediated glucose uptake, promotes adipocyte apoptosis and further accelerates lipolysis, thereby increasing FFA flux to the liver.[121] Comparative gene identification-58 (CGI-58) is a lipid droplet-associated protein that contributes to adipocyte lipolysis. Adipose tissue-specific deletion of the *Cgi58* gene protected against liver injury and steatosis induced by chronic plus binge ethanol feeding in mice, suggesting a critical role of adipose tissue lipolysis in the development of ALD.[122] Alcohol additionally stimulates macrophage infiltration into adipose tissue and suppresses secretion of adiponectin, a key anti-inflammatory adipokine that normally enhances hepatic fatty acid oxidation.[121 123] Moreover, emerging evidence indicates that alcohol directly impacts adipose tissue endothelium, reducing vascular barrier integrity, increasing permeability and altering endothelial-immune cell interactions.[124 125] Beyond barrier dysfunction, activated adipose endothelium facilitates leucocyte adhesion and transmigration through upregulation of adhesion molecules such as intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1). This process is well documented in obesity, where it contributes to macrophage and lymphocyte infiltration into adipose depots.[126] Experimental evidence also suggests that alcohol amplifies similar pathways through oxidative stress and endotoxin-mediated TLR4 activation.[120 125] These endothelial changes further accelerate immune cell trafficking into adipose tissue, reinforcing inflammation and impairing its lipid-buffering function.

In obesity, where adipose tissue is already characterised by heightened inflammation and insulin resistance, alcohol acts as a synergistic 'second hit' amplifying hepatic lipid accumulation, promoting oxidative stress and accelerating fibrosis. These convergent insults may accelerate downstream progression from steatosis to steatohepatitis and beyond. Experimental models of MetALD have demonstrated the synergistic interaction between metabolic dysfunction and alcohol intake in promoting liver disease progression.[13] During this process, exacerbated adipose tissue inflammation has been recognised as a critical component. Xu *et al* reported that combined intragastric overfeeding and alcohol administration synergistically induced macrophage infiltration in both liver and adipose tissue of mice, with predominant inflammatory macrophage accumulation in the liver, and elevations in both mixed macrophage populations in adipose tissue.[127] Similarly, Benedé-Ubieto *et al* demonstrated that co-exposure to ethanol and a Western diet additively enhanced hepatic injury, inflammation and fibrosis, accompanied by increased infiltration of leucocytes and macrophages in adipose tissue.[128]

Table 1 Mouse models of MetALD

Model [ref]	Diet	Period	Alcohol dose	Phenotypes	Pros	Cons
HFDA[51 56]	HFD+single or multiple gavage ethanol	3 days or 3 months	Up to 5 g/kg	Increased ALT, AST, inflammation, neutrophil infiltration, fibrogenic responses	Easy to handle	No/Mild fibrosis, relevance to human MetALD unclear
MASHA[59]	MASH+three ethanol gavages	3 days	Up to 5 g/kg	Increased ALT, AST, inflammation, neutrophil infiltration, NET formation	Easy to handle	No fibrosis, relevance to human MetALD unclear
WDA[130]	WD+ethanol in drinking water	Up to 16 weeks	10%/20%, v/v	Increased ALT, AST, inflammation, fibrosis, hepatocyte degeneration	Easy to handle, mimic MASLD/MetALD histology	Long period, large variations, no obvious bodyweight gain
DUAL[128]	WD+ethanol in drinking water	23 weeks	10%, v/v	Adipocyte hypertrophy, hypercholesterolaemia, hyperglycaemia, hepatocyte ballooning, cell death, inflammation and advanced fibrosis	Easy to handle, mimic MASLD/MetALD histology	Long period, large variations
SMAFLD[176]	FFC+ethanol in drinking water+gavage	16 weeks	5%, v/v 2.5 g/kg	Increased weight gain, glucose intolerance, steatosis	Relatively easy to manage, increase bodyweight	Liver fibrosis and inflammation are unclear
MASHAB[57]	MASH+ethanol in drinking water+gavage	12 weeks	10%, v/v 5 g/kg	Steatosis, inflammation, macrophage activation and neutrophil infiltration, fibrosis, ductular reactions and hepatocyte degeneration	Relatively easy to manage, mimic severe human MetALD/AH	Bodyweight reduced compared with MASH, high mortality
WASH[131]	Modified Lieber-Decarli liquid diet with high fat, cholesterol and fructose	5–7 weeks	Gradual ethanol increase from 0 to 4.5% v/v	Increased ALT, AST, inflammation, fibrosis	Mimic MetALD pathology	Not easy to manage. Serum ALT levels are higher than AST
MASHB[58]	High-fat, cholesterol, sucrose diet plus weekly ethanol binge	12 weeks	5 g/kg	Steatosis, inflammation, macrophage and neutrophil activation, NETs, accelerated fibrosis	Easy to manage, accelerates fibrosis	Up to 25% mortality in MetALD

AH, alcoholic hepatitis; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DUAL, alcohol-associated liver disease plus metabolic-associated fatty liver disease model; FFC, high fructose, high fat and high cholesterol diet; HFD, high-fat diet; HFDA, high-fat diet with alcohol gavage; MASHA, MASH-diet with alcohol; MASHAB, MASH-diet with alcohol binge; MASHB, MASH diet-alcohol feeding with binge; MASLD, metabolic dysfunction-associated steatotic liver disease; MetALD, metabolic dysfunction and alcohol-associated liver disease; NET, neutrophil extracellular trap; SMAFLD, syndrome of metabolic and alcohol-associated fatty liver disease; WASH, Western-ASH diet; WD, Western diet; WDA, Western diet with alcohol.

EXPERIMENTAL MODELS

Mouse models

An effective MetALD animal model should accurately reflect key aspects of the human condition. It should exhibit pathological features similar to those found in human MetALD, including significant steatosis, hepatic inflammation and neutrophil infiltration, and various forms of liver injury.[129] Accelerated liver fibrosis should also be present in the animal model to mimic human disease progression. Given the increasing evidence regarding the combined negative effects of an HFD-related metabolic dysfunction and alcohol consumption, several animal models have been developed that combine various types of diet feeding (either short-term or long-term) and alcohol exposure either by gavage (short-term to mimic human binge drinking) or by supplementing alcohol in drinking water (long-term).

As summarised in table 1, several MetALD mouse models have been established to recapitulate key features of MetALD, such as liver injury, steatosis, inflammation, NET formation, hepatocyte degeneration and fibrosis.[51 57 59 128 130 131] Every model has its strengths and limitations. For the HFD with alcohol gavage and MASH diet with alcohol binge models, the feeding and ethanol administration are easy to manage. However, their relevance to human MetALD is unclear, as these models only reflect an acute alcohol binge scenario. The Western diet with alcohol and ALD/MASLD model is relatively straightforward to manage, as it does not require the commonly used Lieber-DeCarli liquid diet, which involves daily changes of feeding bottles. Additionally, complex procedures like gavage or surgically induced intragastric infusion are not needed. However, these mice do not always develop obesity due to decreased food intake. Another

potential drawback is the high variability in results, likely due to difficulties in ensuring that each mouse consistently consumes the same amount of alcohol and a Western diet. Moreover, mice that receive both the MASH diet and alcohol have significantly lower body weight and a higher mortality rate compared with mice that receive only the MASH diet. The MASH diet-alcohol feeding with binge model that combines the MASH diet with weekly alcohol binges to mimic human binge alcohol intake has minimal mortality, preserves obesity and results in accelerated inflammation and liver fibrosis. To evaluate MetALD mouse models based on HFD/MASH diet and alcohol administration, we recommend taking into account the aspartate aminotransferase (AST)/ALT ratio to better understand the obtained phenotypes and differentiate the causes of liver injury. Moreover, and most importantly, it would be highly beneficial if the research community could reach a consensus on a standard MetALD protocol or model, enabling results to be shared and compared across different research groups, thereby improving data robustness and reproducibility.

Human liver spheroid model

New approach methodologies have gained increasing interest as a way to understand human health and disease without relying on animal experimentation. Recently, an in vitro MetALD human liver three-dimensional spheroid model was developed using isolated human hepatocytes, non-parenchymal cells and HSCs, cultured in a MetALD cocktail (MASH cocktail supplemented with 100 mM ethanol) for 9 days.[132] This MetALD in vitro model replicates features of steatosis, inflammation and fibrosis seen in human MetALD. While the model will help test drug candidates for MetALD, it does not recapitulate complex physiological changes, such as ductular reactions or neutrophil-mediated inflammatory responses. Therefore, more advanced MetALD in vitro systems, possibly also including circulatory immune cells within microfluidic components ('liver-on-chip'), need to be developed.

CHALLENGES AND RESEARCH DIRECTIONS

The new nomenclature of MetALD will undoubtedly spur further research into tailored therapeutic interventions and a more personalised treatment approach. However, many challenges remain across clinical, translational and basic research domains, which are discussed herein (box 1).

Box 1 Challenges and research directions of MetALD

Translational and basic research
- ⇒ Develop in vivo and in vitro model systems to study MetALD.
- ⇒ Accurate reflection of cardiometabolic risk factors in animal models of MetALD.
- ⇒ Constitute standardised, well-characterised patient cohorts with ALD, MetALD and MASLD for comparative and longitudinal studies to bridge experimental models to human pathophysiology.
- ⇒ Investigate alcohol metabolism in experimental models and patients with MASLD.
- ⇒ Investigate the pathogenesis of MetALD, including but not limited to gut-liver, adipose-liver crosstalk and genetics.

Clinical diagnosis and research
- ⇒ Identify biomarkers to detect past alcohol consumption in patients with metabolic dysfunction.
- ⇒ Understand the clinical course of AUD in patients with MetALD.
- ⇒ Clinical trials of drugs targeting MASLD or AUD in patients with MetALD.
- ⇒ Identify genetic susceptibility loci for MetALD.
- ⇒ Investigate pathogenesis and explore therapeutic targets.

ALD, alcohol-associated liver disease; AUD, alcohol use disorder; MASLD, metabolic dysfunction-associated steatotic liver disease; MetALD, metabolic dysfunction and alcohol-associated liver disease.

Clinical diagnosis and alcohol amount

Key challenges and opportunities in MetALD include the need for objective diagnostic biomarkers for the diagnosis and risk stratification of MetALD, the role of PEth and diagnostic cut-points for MetALD in SLD.[25] Future research priorities include: (1) establishing population-specific and sex-specific PEth cut-offs; (2) developing point-of-care PEth testing platforms for routine clinical use; (3) validating PEth kinetics and optimal testing intervals for longitudinal monitoring; (4) integrating PEth measurement with structured assessment tools (Timeline Followback, AUDIT) in clinical workflows and (5) determining how PEth thresholds should guide therapeutic decision-making versus serving purely as diagnostic markers.

Key research opportunities include identifying patients who require treatment specifically for AUD versus those needing integrated treatment for both AUD and liver disease. It may be more important to screen and identify harmful alcohol use, and as appropriate, diagnose AUD in patients with MASLD and then let the diagnosis of MetALD follow, rather than the other way around. Quantitative, precise and reproducible biomarkers of pharmacodynamic and pharmacokinetic responses are needed for early phase trials, along with validated surrogate endpoints for registrational trials.[11] Furthermore, the history of heavy alcohol consumption and drinking patterns (particularly binge drinking) is a strong determinant of hepatic progression and liver-related outcomes that must be systematically captured in clinical assessment and research protocols.

Different amounts of alcohol consumption are currently recommended to distinguish MetALD, ALD and MASLD: specific alcohol consumption levels—140–350 g/week for women and 210–420 g/week for men for MetALD; >350 g/week for women and >420 g/week for men for ALD; ≤140 g/week for women, ≤210 g/week for men for MASLD. The current diagnostic thresholds for MetALD are inherently arbitrary and require validation across diverse populations. Moreover, determination of accurate alcohol consumption is challenging, with self-reported intake demonstrating up to 57.7% under-reporting rates

and only one-third of self-reported intake aligning with objective measures. Furthermore, the contribution of moderate alcohol consumption to the pathogenesis of liver injury in patients with MASLD remains poorly understood and likely varies across disease stages. In addition, the history of problematic alcohol use as well as drinking patterns (eg, heavy drinking, very heavy drinking, binge drinking) is also a strong determinant of hepatic progression and liver-related outcomes.[30]

Heterogeneity and complexities of MetALD

Notwithstanding the importance of MetALD as a conceptual framework for considering the synergistic effects of both systemic metabolic dysregulation and alcohol consumption on liver disease progression, the simplicity of the term, masks the complexity of the entity in clinical practice. The principal issue concerns disease labelling as fixed entities in the context of highly dynamic disease pathobiology coupled with a quite wide heterogeneity of this population. In particular, the lifetime history of alcohol consumption is highly variable in any individual with phenotypic variations such as binge drinking patterns adding further complexity. Since alcohol consumption is a relapsing and remitting entity, diagnostic classification can only be made at any single point in time rather than across the life course. Patients may migrate between MASLD, MetALD and ALD categories depending on alcohol consumption trajectories, necessitating longitudinal reassessment strategies. Second, the impact on the liver and disease progression of alcohol consumption at MetALD levels differs dramatically between patients with no fibrosis versus those with cirrhosis. Labelling both scenarios as MetALD simplifies clinical realities and may require stage-specific diagnostic subcategorisation. Third, the interaction between various operational features defining metabolic dysregulation and alcohol consumption varies considerably, including when metabolic factors are treated to target with pharmacotherapy for hypertension or dyslipidaemia. Finally, many factors have been reported to affect ALD and/or MASLD disease progression. These include sex, age, genetics, comorbidity, etc,[1 18] which may have more complex roles in modulating MetALD development and progression. In summary, future studies must incorporate these dynamics, harnessing multi-omics data, electronic health records and artificial intelligence-powered large data integration to enable precision determination of disease progression dynamics and outcome prediction.

Addressing AUD in MetALD

Problematic alcohol use ranges from harmful drinking without formal AUD to progressively more serious clinical manifestations of AUD (mild to severe), including alcohol dependence.[133 134] Addressing problematic alcohol use is critical when alcohol-related harm, including ALD or MetALD, manifests. Effective treatments exist, ranging from brief interventions and behavioural/psychological interventions to pharmacotherapies, including FDA-approved medications and additional therapeutic options. However, several challenges persist. First, despite the availability of effective treatments, their implementation in clinical practice remains very limited.[135] The shortcoming is particularly evident in liver clinics, where addressing alcohol use is especially vital, yet efforts are hindered by persistent barriers and lack of broadly implemented multidisciplinary models despite evidence that simultaneous management of AUD and liver disease improves outcomes.[136–138] Second, as the integration of addiction and hepatology gains attention, growing research interest is directed towards understanding the crosstalk between obesity and AUD to guide new therapeutic strategies.[139] The emerging role of GLP-1 receptor agonists for AUD[92] raises important questions about their utility in patients with comorbid liver diseases.[93] Several other targets are under investigation, including non-selective mineralocorticoid receptor antagonist spironolactone,[140] immune-modulating drugs[141] and neuromodulation approaches.[38 142 143] As this field moves forward, it will be critical to test these drugs' safety and efficacy specifically in patients with comorbid ALD or MetALD. Third, with the new hepatology nomenclature, it is not well established whether addressing alcohol use should differ between people with comorbid ALD vs MetALD. This question is more relevant than ever, given mounting evidence showing health benefits (including liver-related) of non-abstinent outcomes and the recent FDA qualification of risk drinking levels as primary end point for alcohol pharmacotherapy trials.[144] Nonetheless, it remains foundational to personalise treatment approaches and goals according to multiple factors, including severity of problematic alcohol use, diagnosis of AUD, alcohol-related harm, type of liver disease (ALD or MetALD), severity of liver disease and, importantly, shared decision-making between patients and physicians.

Experimental models

Current preclinical models provide valuable insights but have significant limitations in fully recapitulating human MetALD pathophysiology. Alcohol feeding induces only mild to moderate ALD in mouse models. Although alcohol intake exacerbates liver injury in mouse models of MASLD as listed in table 1, HFD/MASH diets remain the dominant factors causing liver damage while alcohol plays a less important role. Moreover, high doses of ethanol are used in most of these models, differing from the moderate consumption defining MetALD. In addition, species differences in gut microbiota, microbiota-related metabolites and bile acids may hamper translatability from mice to humans.[145]

Alcohol metabolism is approximately five times faster in mice than in humans. In addition, alcohol metabolism is much more complicated in humans, with three *ADH1* genes and one *ALDH2* gene containing numerous variants, while mice have only single *Adh1* and *Aldh2* genes without variants. Thus, moderate alcohol consumption may play a significant role in contributing to liver injury

in patients with MASLD than current models suggest. Humanised knock-in mice expressing human alcohol-metabolising enzyme genes may be required to develop more severe and clinically relevant ALD and MetALD models.

The rapid development of 'in vitro model systems'" offers new opportunities for translationally relevant mechanistic understanding in MetALD.[146] Ariño *et al* established patient-derived liver organoids from individuals with ALD that preserve cellular and transcriptional heterogeneity of the human liver, enabling precision modelling of ALD. This platform reveals cell type-specific injury responses and intercellular signalling mechanisms, thereby providing a powerful tool to study epithelial and macrophage interactions in metabolic and inflammatory liver disorders such as MetALD.[147] In addition, many other in vitro model systems have been used to study ALD and MASLD, including liver-on-chip, precision-cut liver slices, co-culture system, microphysiological systems and advanced multitissue organoids.[148 149] Many of these systems can be used to study the MetALD pathogenesis and therapeutic targets in the future.

Alcohol metabolism in MetALD

Alcohol metabolism plays a key role in the pathogenesis of ALD.[150 151] It is not clear whether alcohol metabolism is altered in MASLD and individuals with obesity. One recent study reported that alcohol dehydrogenase 1 (ADH1) activity was markedly reduced in the livers and sera from patients with MASLD compared with those from healthy controls.[152] However, in addition to the liver, several other organs also express ADH1, and multiple organ ADH1 may have a redundant role in metabolising ethanol. Hence, it is not clear whether the reduced liver ADH1 activity in MASLD markedly affects ethanol metabolism and MetALD progression. It will also be important to examine other oxidative pathways (such as aldehyde dehydrogenase 2 (ALDH2), CYP2E1, etc)[153] and non-oxidative pathways (such as FAEE synthase, etc)[154] to determine if alcohol metabolism is altered in MetALD and whether such alterations contribute to MetALD progression.

ADH1 and *ALDH2* variants in MetALD

Alcohol is first metabolised by ADH1 to generate acetaldehyde, which is further metabolised by *ALDH2* to produce acetate. Human *ADH1* and *ALDH2* have many variants that have significantly different enzyme activities to metabolise alcohol.[153 155 156] Some of these variants also modulate metabolic functions independent of their enzyme activities. These factors likely contribute to the complexities and heterogeneity of MetALD diagnosis and pathogenesis. For example, the relationship between alcohol consumption and T2DM has been investigated by meta-analyses, but the data from Eastern and Western ethnic groups yield conflicting results for moderate drinking.[157 158] This discrepancy may be related to genetic factors affecting alcohol-metabolising enzymes. A recent meta-analysis of data from genome-wide association studies indicated that *ALDH2*1/*1* is a susceptibility variant for T2DM in East Asian male populations.[159] Moreover, compared with *ALDH2*2* carriers, *ALDH2*1/*1* carriers increase alcohol intake, reduce fasting blood glucose clearance and promote hepatic insulin resistance, elevating fasting glucose levels and T2DM's susceptibility.[160] Additionally, ALDH2 plays a multifaceted role in lipid metabolism, particularly in cholesterol homeostasis and lipoprotein regulation.[161–165] However, how *ALDH2* variants affect ALD and MetALD has not been carefully examined.

Integration of polygenic risk scores for MetALD

An area of research that will be important is the genetic underpinnings that drive MetALD. In this regard, there are no specific genetic studies devoted to characterising the MetALD population, a term coined after the era of major Genome-Wide Association Study (GWAS). Given that MetALD arises from the convergence of metabolic dysfunction and alcohol exposure, integrating polygenic risk scores (PRS) from both MASLD and ALD may enhance risk prediction and mechanistic understanding. PRS for ALD capture variants in alcohol-metabolising enzymes (eg, *ADH1B, ADH1C, ALDH2*)[166] and inflammatory pathways, while MASLD PRS include metabolic and lipid-related genes (eg, *PNPLA3, TM6SF2, GCKR, MBOAT7*).[167 168] Some patients previously diagnosed with MASLD can be re-diagnosed as MetALD because they also had moderate alcohol consumption. However, the functions of these variants have not been specifically evaluated in patients with MetALD.[169] Future studies combining these variant scores could help identify individuals at a high risk of MetALD even with moderate alcohol consumption, guide personalised prevention strategies and uncover shared molecular pathways contributing to liver injury. However, challenges remain, including population-specific variability of PRS, complex gene-environment interactions with alcohol intake and the need for large, well-phenotyped cohorts with precise measures of metabolic status, alcohol consumption and liver outcomes. Addressing these issues will be crucial for translating integrated PRS into clinical risk assessment and personalised interventions in MetALD. Determining whether these variants or new variants are relevant in MetALD would be of value.

The gut-liver axis and gut microbiome in MetALD

The gut microbiome has been extensively investigated in MASLD[17] and ALD,[170] playing important roles in their pathogenesis, but the roles of the gut microbiome in MetALD have not been evaluated. Little is currently known about the precise interactions between alcohol, its principal metabolite acetaldehyde and metabolic factors in gut inflammation, induction of gut barrier dysfunction and microbiome composition. Studies assessing the gut barrier usually focus on epithelial changes such as tight junction alterations to explain microbial translocation,

whereas the contribution of other components of the gut barrier, for instance, the gut immune barrier or the vascular barrier, remains largely understudied. Heavy alcohol consumption induces intestinal architectural and immune alterations, which have not been found in patients with MASLD.[66 96 171] Whether those modifications also occur with lower amounts of alcohol consumed, as classically encountered in MetALD, remains unknown. Although some synergistic mechanisms have been identified, the field lacks preclinical studies directly comparing the effects of alcohol in well-characterised MASLD models, or vice versa. Future research should focus on several directions: (a) mechanistic studies dissecting how microbial, immune and metabolic alterations interact at the gut-liver axis in MetALD and (b) comparative and longitudinal human studies of microbiome composition and function as well as gut barrier changes in standardised, well-characterised patient cohorts with ALD, MASLD and MetALD. Such work is essential to characterise additive or synergistic effects of ethanol and metabolic dysfunction in liver injury, which may help identify effective therapies for MetALD targeting the gut-liver axis.

The adipose-liver axis in MetALD

Adipocyte death and adipose inflammation play important roles in the pathogenesis of both ALD and MASLD.[117 172] The adipose-liver crosstalk may play more important roles in inducing liver inflammation and injury in MetALD than in either ALD or MASLD, which deserves further investigation, particularly given the increasing obesity prevalence worldwide.

Liver cancer in MetALD

Another challenge in the field is the need for natural history studies of MetALD populations to determine disease trajectories to adverse outcomes, especially primary liver cancer. The impact of alcohol might be quite different and more worrisome for liver cancer than for fibrosis-related liver outcomes. Such studies are complex to undertake and would require both detailed and regular clinical histories supplemented by quantitative measurements of alcohol consumption. Although it has been well documented that both ALD and MASLD are among the leading causes of liver cancer,[173 174] liver cancer in MetALD has not been systematically evaluated. It remains largely unknown whether alcohol consumption and metabolic dysfunction have additive or synergistic effects in promoting liver cancer development and progression. Experimental models of MetALD-associated liver cancer are lacking.

CONCLUSIONS

MetALD represents a critical paradigm shift in the understanding of SLD, acknowledging the synergy between metabolic dysfunction and alcohol consumption. Its diagnosis necessitates a holistic approach, moving beyond simple diagnostic labels to an integrated assessment of steatosis, metabolic risk factors and rigorously quantified alcohol use, often with the aid of biomarkers like PEth. This precise phenotyping is fundamental to guiding a multi-targeted management strategy, which combines comprehensive lifestyle interventions and behavioural support for alcohol use with pharmacological therapies that address both the metabolic and alcohol-related underlying conditions.[175] The formal recognition of MetALD provides a framework for more accurate risk stratification and underscores the need for a collaborative, multidisciplinary care model to improve both hepatic and extrahepatic (eg, metabolic, alcohol-related) outcomes in these patients. Ensuring that the new nomenclature is incorporated into diagnostic coding and clinical practice guidelines will further facilitate its adoption in routine care. Further preclinical and clinical research on MetALD will help develop better therapeutic strategies and clinical care for these patients.

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