Non-metabolic causes of steatotic liver disease

Patrik Nasr1 2, Cecilia Jönsson1, Mattias Ekstedt1 2, Stergios Kechagias1 2

1 Department of Gastroenterology and Hepatology, Department of Health, Medicine and Caring Sciences, Linköping University, Linköping SE-581 85, Sweden.
2 Wallenberg Centre for Molecular Medicine, Linköping University, Linköping SE-581 85, Sweden.

Correspondence to: Dr. Patrik Nasr, Department of Gastroenterology and Hepatology, University Hospital, SE-581 85 Linköping, Sweden. E-mail: Patrik.nasr@liu.se

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Abstract

Hepatic steatosis is caused by exaggerated hepatic lipid accumulation and is a common histological and radiological finding. Non-alcoholic fatty liver disease (NAFLD), or metabolic dysfunction associated steatotic liver disease (MASLD), is highly associated with metabolic syndrome and represents the most common cause of hepatic steatosis. However, since several comorbidities, lifestyle factors, and drugs can cause hepatic steatosis, MASLD is, to some extent, a diagnosis of exclusion. Nevertheless, initiatives have been taken to encompass positive (instead of negative) criteria for diagnosis - such as the presence of cardiometabolic risk factors together with hepatic steatosis. Nonetheless, before confirming a patient with MASLD, it is essential to map and evaluate other causes of fatty liver disease or steatotic liver disease. Several causes of hepatic steatosis have been identified in studies; however, the study cohorts are scarce and often anecdotal. Additionally, many studies have shown correlation without proving causation, and many are retrospective without reporting relevant patient characteristics and comorbidities - making it difficult to draw conclusions regarding the underlying etiology or present comorbidity of hepatic steatosis. In this narrative review, we aimed to identify and summarize present studies evaluating the impact of the most common and often suggested causes of hepatic steatosis.

Keywords: Hepatic steatosis, SLD, alcohol-related liver disease, alcohol-associated liver disease, ALD, methotrexate, tamoxifen, non-alcoholic fatty liver disease, NAFLD, metabolic-dysfunction associated liver disease, MASLD, MetALD, fatty liver disease

INTRODUCTION

Steatotic liver disease (SLD) is caused by hepatic lipid accumulation and is a common finding encountered
during histopathological evaluation of liver biopsies and imaging examinations (e.g., ultrasonography, computed tomography, and magnetic resonance imaging). The most common cause of elevated liver enzyme levels is SLD, which is present in approximately a third of the population\(^5\). The most common cause of hepatic lipid accumulation is non-alcoholic fatty liver disease (NAFLD)\(^{[2,3]}\), recently renamed to metabolic-dysfunction associated steatotic liver disease (MASLD)\(^{[4,5]}\), with an estimated global prevalence of 30%\(^6\). The difference between NAFLD and MASLD is small, with a high overlap\(^7\), but with the common denominator being the presence of hepatic steatosis with the absence of other steatogenic causes. In addition, in MASLD, the presence of at least one cardiometabolic risk factor (i.e., overweight/obesity, hyperglycemia/insulin resistance, hypertension, and dyslipidemia) is a prerequisite for the diagnosis\(^8\). Additionally, a new entity of increased alcohol intake in combination with MASLD was also introduced, labeled MetALD - which includes a continuum of alcohol consumption where the contribution of MASLD and alcohol-related liver disease (ALD) will vary\(^9\).

Steatotic liver disease can be defined as an accumulation of fat, mainly triglycerides, exceeding 5% of the liver weight\(^9\). Even though this definition is appealing, it is not feasible in a common clinical setting. After liver biopsy is performed, the histopathological diagnosis of SLD is set if more than 5% of the hepatocytes contain lipid vacuoles\(^{[10,11]}\). Because liver biopsy is associated with adverse events (both minor and serious), several non-invasive techniques for defining hepatic triglyceride content have emerged, such as magnetic resonance imaging\(^{[12,13]}\) and controlled attenuation parameter\(^{[14]}\).

Nonetheless, in the wake of a growing body of research in the field of MASLD, focus on other causes of SLD has been set aside [Table 1]. Therefore, in this review, we will focus on other common (and uncommon but clinically important) causes of hepatic lipid accumulation that are important to exclude, or take into consideration, when diagnosing MASLD.

**Alcohol**

Consumption of alcohol is common in the Western world, with nearly two-thirds of all adults in the United States consuming alcohol (approximately 4 drinks per week)\(^{[15]}\). The corresponding numbers in Sweden show that nine out of ten adults in Sweden consume approximately 9 drinks per week\(^{[16,17]}\). Alcohol consumption can lead to hepatic lipid accumulation. However, it is uncertain how much, how long, and at what rate alcohol consumption induces SLD. Although acute alcohol consumption induces SLD in mouse models\(^{[18,19]}\), it does not, over a period of 5-12 weeks, seem to induce similar traits in humans\(^{[20,21]}\). Therefore, it is probable that chronic consumption of alcohol, rather than acute, induces significant SLD. Nevertheless, in studies of patients with confirmed alcohol overconsumption who have undergone liver biopsy, approximately one in three have no histological signs of SLD\(^{[22,23]}\).

Initially, alcohol-induced SLD was thought to be a result of oxidative stress and diminished lipid oxidation secondary to enzymatic metabolism of ethanol. However, new discoveries have shed light on the complex multifactorial process that leads to ethanol-induced lipid accumulation in hepatocytes\(^{[24]}\). Many mechanisms are similar to that of MASLD, which, to some extent, explains the hurdle of separating the entities.

It is important to exclude excessive alcohol consumption in diagnosing MASLD. However, it is difficult to define excessive alcohol consumption in order to separate MASLD, or MetALD, from alcohol-related liver disease (ALD). The threshold for defining excessive alcohol consumption has ranged from abstinence\(^{[25-27]}\) to 252 g/week in different studies\(^{[28]}\). However, the European Association for the Study of the Liver (EASL) reached a consensus in 2016 suggesting a cut-off of 210 and 140 grams per week for men and women, respectively, for the diagnosis of NAFLD\(^{[29]}\). These cut-offs are also suggested for the diagnosis of MASLD,
Table 1. Factors, other than metabolic dysfunction-associated steatotic liver disease, that have been associated with hepatic lipid accumulation

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AFLP: acute fatty liver of pregnancy; CESD: cholesterol ester storage disease; DH: diethylaminoethoxyhexestrol; GI: gastrointestinal; HELLP: hemolysis, elevated liver enzymes, low platelet count; HIV: human immunodeficiency virus; HPD: hypothalamic-pituitary disorder; IBD: inflammatory bowel syndrome; LAL-D: lysosomal acid lipase deficiency; LCAT: lecithin-cholesterol acetyltransferase; NRTI: nucleoside reverse transcriptase inhibitors; NSAID: nonsteroidal anti-inflammatory drug; PA: physical activity; PCOS: polycystic ovary syndrome; SIBO: small intestinal bacterial overgrowth; TPN: total parenteral nutrition; WD: Wolman’s disease.

and if consumption exceeds these thresholds but is below 420 g/week for men and 350 g/week for women, the diagnosis of MetALD is used. However, if alcohol consumption exceeds the thresholds for MetALD, the diagnosis of ALD is recommended.[8]

Since differentiating between MASLD, MetALD, and ALD, histopathologically, is difficult, one must rely on patient history, standardized questionnaires, or biomarkers for the correct diagnosis. When diagnosing MASLD, the proposed tool for excluding excessive alcohol consumption is the AUDIT (i.e., Alcohol Use Disorder Inventory Test), which has an adequate test-retest agreement (kappa (κ) agreement of 0.7) [30,31]. The AUDIT consists of ten questions exploring consumption (Q1-3), dependence (Q4-6), and alcohol-related problems (Q7-10).[32] Abbreviated forms have been developed, where the one most regularly used is the AUDIT-C (i.e., AUDIT-Consumption) questionnaire, which includes Q1-3 of the AUDIT.[33]
Furthermore, in addition to both AUDIT or the abbreviated AUDIT-C, indirect alcohol markers, such as mean corpuscular volume, gamma-glutamyl transferase, and aspartate and alanine aminotransferase, are occasionally used. However, indirect alcohol markers all depend on chronic excessive drinking over an extended period, and they are usually associated with multiple confounders resulting in an inadequate accuracy, specificity, and sensitivity. Additionally, carbohydrate-deficient transferrin (CDT) is occasionally used to diagnose or screen for (chronic) excessive alcohol consumption. However, CDT mainly indicates heavy alcohol consumption (50-80 g/day or 350-560 g/week) over a period of more than 1-2 weeks, reflecting a threshold above the limit for MASLD (i.e., 210 g/week for men and 140 g/week for women). Moreover, CDT is susceptible to inaccurate levels secondary to confounding factors.

Direct alcohol markers portray a much higher sensitivity and specificity in comparison to questionnaires (e.g., AUDIT) and indirect alcohol markers (e.g., CDT), since they are direct products of the non-oxidative metabolism of ethanol. In addition, compared to direct determination of ethanol in exhaled air or blood/serum, direct alcohol markers have a much wider window of detection [4-12 h vs. 3-90 days (and up to 6 months)]. There are several direct biomarkers for ethanol, one of which is phosphatidylethanol (PEth), a direct biomarker showing both high specificity and sensitivity. In a study by Schröck et al., 16 volunteers received one dose of vodka (ranging from 34 to 72 g of alcohol) in order to attain a blood ethanol concentration of circa 1 g/kg of weight. Phosphatidylethanol was measured every other hour from intake and up to eight hours after intake. The highest value of PEth was reported and ranged from 0.06 to 0.31 μmol/L (reference value in Sweden for moderate alcohol consumption ranges from 0.05 to 0.30 μmol/L). Moreover, in a study by Kechagias et al., 44 subjects were randomized to abstaining from alcohol or consuming 32 g or 16 g (if male or female, respectively) of wine per day for three months. Most of the participants in the consumption group had values of PEth below 0.04 μmol/L (< 0.05 μmol/L is according to Swedish reference values defined as low or no alcohol consumption), while three subjects had elevated (signs of moderate) PEth values of 0.07, 0.12, and 0.17 μmol/L.

Both the studies by Schröck et al. and Kechagias et al. suggest that long-standing or occasional intake of up to 30 g of alcohol per day results in classifying alcohol consumption as low to moderate according to current clinical decision thresholds for PEth, while consumption exceeding 70 g/day will almost certainly result in values of PEth above 0.30 μmol/L, which is considered heavy alcohol consumption in clinical practice. This is corroborated in a study by Walther et al. that showed an almost linear association between alcohol consumption and PEth.

The more commonly used direct alcohol marker is ethyl glucuronide (EtG), where, to date, the determination of conjugated EtG in urine (uEtG) is applied in several European countries. Depending on the consumption of alcohol, uEtG is detectable for up to 80 hours. However, in contrast, measurement of EtG in hair (hEtG) provides a more reliable means of estimating chronic consumption over a period of 3 to 6 months, where 1 cm of hair represents 1 month (however, hair length below 3 cm or more than 6 cm should be interpreted with caution). In recent years, the interest in hEtG has increased, however, mostly in forensic settings.

Consumption of alcohol is not uncommon in individuals with MASLD, and it also seems to increase the risk of incident steatosis in individuals with presumed MASLD, with an almost direct dose-response relationship between alcohol consumption and hepatic steatosis. As mentioned, the gold standard for excluding patients with excessive alcohol consumption (i.e., disqualifying them from a MASLD diagnosis) is self-reported alcohol consumption. However, in a recent study by Stauffer et al., subjects with presumed MASLD were evaluated with direct alcohol markers. Interestingly, approximately one-third (29%) of the
included MASLD patients showed signs of moderate to excessive alcohol consumption.

There is an ongoing debate on the impact of alcohol consumption and its effect on the prognosis of MASLD, with studies proposing both positive\cite{51-56} and negative effects\cite{57-60}, and with some of the studies suggesting a J-shaped curve where modest levels of alcohol consumption might be beneficial. This is in concordance with earlier studies reporting that modest alcohol consumption is associated with decreased risk of cardiovascular disease and mortality\cite{61}. However, in a recent study including 28 million individuals, it was suggested that any level of alcohol use is linked to negative outcomes\cite{62}. Moreover, in two recent studies, it was shown that alcohol consumption (mostly moderate use) was associated with fibrosis progression in patients with MASLD\cite{63,64}. Additionally, in a study by Younossi et al., they found that more than 3 or 1.5 (for men and women, respectively) drinks per day was associated with increased mortality - an association that was more evident amongst individuals with metabolic syndrome\cite{65}.

In summary, alcohol does not seem to attenuate the presence of SLD but rather aggravates the accumulation of steatosis and the progression to fibrosis. Although alcohol seems to be associated with decreased cardiovascular disease, real-world data on alcohol consumption indicate an increased all-cause mortality. Even though these two entities are histopathologically similar, treatment and management vastly differ. Therefore, separating MASLD from MetALD and ALD is of outermost importance, and using the recommended questionnaire (i.e., AUDIT) to estimate a patient’s alcohol consumption can be lined with non-differential misclassification bias\cite{66}. Nevertheless, differentiating ALD from MASLD, or MetALD, is probably more complicated than previously perceived, and the use of direct alcohol markers (e.g., PEth) should be considered.

**Methotrexate**

Methotrexate (MTX) is an effective and widely used drug in the management of autoimmune and dermatological disorders. The notion of liver damage has been attributed to MTX on the basis of accumulation of MTX-polyglutamate - a metabolite that triggers oxidative stress, inflammation, steatosis, fibrosis, and apoptosis\cite{67}. Albeit high-dose MTX treatment (used for its cytotoxic-antiproliferative action in adult and childhood malignancies) has been reported to cause liver damage in up to 80%\cite{68}, the evidence of low-dose MTX treatment and hepatotoxicity is debatable, with fluctuations of liver enzyme levels often returning to normal despite continuation of MTX\cite{69}.

In a Swedish study, the most prominent predictor of elevated aminotransferases was signs of elevated aminotransferases pre-treatment, use of statins, and increased body mass index (BMI)\cite{70}. Similarly, a German study of patients with inflammatory bowel disease noted that the presence of hepatic steatosis verified by ultrasound, and not MTX treatment, predicted elevated aminotransferases\cite{71}. Both these studies indicate that pre-existing risk factors for elevated liver enzymes are often the cause of elevated aminotransferases, which was also shown by Mori et al., who reported that chronically elevated aminotransferases were not associated with the cumulative dose of MTX but rather with BMI, dyslipidemia and type 2 diabetes mellitus (T2DM)\cite{72}. Similarly, in follow-up studies with repeat liver biopsy, the effect of MTX on current and future histopathological changes is mild, and in patients with concomitant SLD, secondary causes such as alcohol overconsumption or obesity are often present\cite{73-76}.

In a Danish population-based cohort study, approximately 40,000 individuals (70% rheumatoid arthritis [RA], 16% psoriatic arthritis [PsA], and 14% psoriasis [PsO]) with MTX treatment were followed for a mean of 6.5-8.4 years\cite{77}. Although cumulative MTX dose was higher in the RA population, liver disease outcomes were more common in the PsO and PsA groups, with alcohol abuse and the presence of T2DM acting as the
strongest predictors. These findings could be related to the findings of psoriasis being strongly associated with MASLD, socioeconomic status, steatogenic treatment, metabolic syndrome, and alcohol consumption pattern\textsuperscript{[79,80].} Furthermore, metabolic components, such as central adiposity or insulin resistance, and not MTX, seem to be of great importance in predicting elevated elastographic values\textsuperscript{[79,80].} Although several studies on MTX and liver damage often focus on fibrosis or elastographic values, few focus on steatosis. However, in a study by Choi et al., 368 patients with RA were evaluated with ultrasound, of whom 92 had SLD. There was no difference in cumulative dose between patients with and without SLD (1.9 ± 1.8 vs. 1.9 ± 2.1 g)\textsuperscript{[81].} However, BMI and hypercholesterolemia were significantly associated with the presence of SLD. Furthermore, in two studies investigating the association of steatosis and MTX treatment, there was a significant difference in cumulative dose, but no adjustment for metabolic features or alcohol consumption was undertaken - making these data difficult to interpret\textsuperscript{[82,83].}

The assumption that MTX is a steatogenic drug in the absence of overweight/obesity, T2DM, dyslipidemia and alcohol overconsumption is disputable. Further studies determining the association of low-dose MTX and steatosis while adjusting for known steatogenic co-morbid diseases are needed.

**Tamoxifen**

Tamoxifen (TMX) is an effective selective estrogen receptor modulator used to treat estrogen receptor-positive breast cancer. It has been linked to liver toxicity mainly through the induction of SLD\textsuperscript{[84,85].} The effect of TMX on hepatic lipid metabolism and accumulation remains unclear. However, animal studies have proposed both inhibition of fatty acid oxidation and increased triglyceride synthesis\textsuperscript{[86,87].} This was, however, questioned in a study by Cole et al., where mice injected with TMX had higher hepatic triacylglycerol compared to controls but unchanged fatty acid uptake, triacylglycerol secretion, and fatty acid oxidation\textsuperscript{[88].} These data would suggest that TMX increases de novo fatty acid synthesis, causing hepatic lipid accumulation. Furthermore, in human subjects, TMX is highly associated with SLD. In a meta-analysis by Lee et al., data on 6,962 patients and 975 controls were analyzed\textsuperscript{[85].} The incidence rate for SLD in TMX-treated patients and controls was 40.25 and 12.37 per 100 patients, respectively, with an incidence rate ratio of 3.12. However, the main risk factors for concomitant SLD were body mass index (BMI) and hypercholesterolemia. Similar results were observed in a multicenter trial of more than 5,000 women, where TMX treatment was associated with a two-fold risk of developing MASLD\textsuperscript{[89].} This risk, however, seemed synergistic, since patients with a normal BMI had no increased risk of TMX-induced SLD, compared to patients with overweight or obesity, where TMX treatment was associated with an increased risk of MASLD development compared to controls. Similarly, hypercholesterolemia, dyslipidemia, and glucose intolerance seem to predict TMX-induced SLD and/or elevated enzyme levels\textsuperscript{[88,89].} Albeit SLD is often benign and the risk of severe liver damage in TMX-treated patients is absent (or at best anecdotal), the co-morbidly associated metabolic syndrome entails an increased risk of T2DM and cardiovascular disease\textsuperscript{[90].} Although risk mitigation with lipid-lowering drugs may have a theoretical place in the management of these patients, further studies are required before such treatment can be proposed.

**Corticosteroids**

Corticosteroids are used in a variety of medical conditions for their anti-inflammatory effects and are commonly prescribed. At present, approximately 1% of the general population receives corticosteroids, with a more than two-fold increase in senior citizens\textsuperscript{[82,83].}

The use of corticosteroids is associated with an adverse metabolic profile, including insulin resistance and T2DM, conditions also associated with hepatic lipid accumulation\textsuperscript{[44].} The means by which corticosteroids induce fatty liver is not fully understood, although corticosteroids are often referred to as steatogenic\textsuperscript{[44].} Rodent studies have shown that corticosteroids increase appetite and caloric intake as well as
gluconeogenesis and lipogenesis, and also the release of free fatty acids from adipose tissue to the liver - trademarks similar to metabolic syndrome associated with MASLD\textsuperscript{[95-97]}. However, in a study from 2003, Rockall et al. investigated 50 patients with Cushing’s syndrome for the presence of SLD using computed tomography\textsuperscript{[90]}. Only 20% were found to have SLD, and although it was not associated with BMI, it did correlate with both visceral and total fat volume. Furthermore, the prevalence of SLD among patients with Cushing’s syndrome does not exceed the estimated global prevalence of MASLD (i.e., 30%)\textsuperscript{[9],99]. Additionally, of interest, cortisol levels did not differ between patients with and without SLD, results which are corroborated by Hubel et al.\textsuperscript{[100]}. Hence, the main cause of SLD in patients with short\textsuperscript{[111]} and long-term corticosteroid treatment\textsuperscript{[102]} is the disruption of the metabolic equilibrium leading to hyperglycemia, insulin resistance and central obesity, and ultimately SLD\textsuperscript{[97]}.

**Viral hepatitis-associated steatosis**

Chronic infection with hepatitis C virus (HCV), genotype 3, is commonly associated with SLD. The prevalence of SLD in patients with chronic hepatitis C varies between 40\%-80\%, depending on the prevalence of alcohol consumption, overweight, T2DM, and other risk factors of hepatic lipid accumulation\textsuperscript{[103]}. Several observations also indicate a correlation between the grade of hepatic steatosis and elevated aminotransferases\textsuperscript{[104,105]}. Furthermore, the steatogenic effect seems to be cytopathic, with an increased grade of hepatic steatosis being associated with HCV RNA levels in both serum and liver\textsuperscript{[106,107]}, and attenuation occurring after sustained therapeutic response\textsuperscript{[108]}. Furthermore, chronic HCV infection seems to be associated with acquired hypobetalipoproteinemia and hypocholesterolemia, the latter often normalizing after therapeutic response\textsuperscript{[109-111]}.

Hepatitis C virus has an intertwined connection with hepatic and systemic metabolism. Genotype 3 HCV proteins have been proven to interact with glucose and lipid metabolism by stimulating de novo lipogenesis, and synthesis of phospholipids, via activation of several transcription factors to favor HCV assembly\textsuperscript{[112]}. Furthermore, HCV assembly interferes with VLDL assembly and export by interfering with the VLDL secretion pathway\textsuperscript{[113]}.

Overweight and T2DM are frequently present\textsuperscript{[107,114,115]} and often exaggerate HCV-associated SLD, irrespective of genotype. Further, the presence of SLD in chronic HCV infection is independently associated with an increased risk of HCC\textsuperscript{[116]}.

In recent years, effective direct-acting antiviral treatment has changed the HCV landscape, where sustained virologic response (SVR) is often achieved after an 8-12 (-24) weeks course of treatment. In contrast to cholesterol, SVR does not seem to attenuate steatosis in responders to a significant degree\textsuperscript{[117]}; but instead appears to increase steatosis\textsuperscript{[118,119]}. This could be partly attributed to the weight gain often observed after sustained virological response\textsuperscript{[120]}. Hence, chronic HCV infection with genotype 3 is independently associated with SLD, a trait associated with disrupted hepatic metabolism, and is exaggerated by comorbidities associated with the metabolic syndrome.

**HIV-associated hepatic steatosis**

The presence of SLD in patients living with human immunodeficiency virus (HIV) is common, affecting approximately 35\%-80\%\textsuperscript{[121,122]}. Although SLD secondary to traditional risk factors is common among patients living with HIV, the presence of SLD is also seen in normal or underweight patients living with HIV\textsuperscript{[123]}. Therefore, it is suggested that the exact etiology may differ from patients with MASLD, but the pathophysiological mechanism is still unclear\textsuperscript{[122]}. Yet, in lipodystrophic patients with HIV, insulin resistance is highly prevalent, showing signs of impaired glucose tolerance and T2DM in 35\% and 7\%, respectively\textsuperscript{[124]}. The proposed mechanism is theorized to be related to defect lipid metabolism and active inflammation,
indicating that lipotoxicity and inflammation lead to metabolic dysregulation associated with insulin resistance, a hallmark for hepatic lipid accumulation [129].

COVID-19 and hepatic steatosis

In December 2019, the emergence of coronavirus disease 2019 (COVID-19), caused by the Severe Acute Respiratory Syndrome (SARS) Coronavirus (CoV) 2 (SARS-CoV-2), led to a major global health and economic crisis[126]. Although the respiratory tract was considered the main target of SARS-CoV-2 infection, other organs, including the liver, have also been shown to be affected[126,127].

Elevated liver transaminases in COVID-19 patients are seen in approximately 20% of patients[128]. Furthermore, elevated transaminases are often accompanied by elevated cholestatic liver enzymes, probably reflecting systemic inflammatory response syndrome (SIRS). The cause of elevated liver enzymes can be directly associated with COVID-19 but is most often multifactorial.

COVID-19-associated liver injury includes a broad spectrum of potential mechanisms of action, such as active viral replication of SARS-CoV-2 in the liver with subsequent cytotoxicity, liver damage due to SIRS, respiratory failure with induced hypoxic liver damage, vascular changes due to coagulopathy, endothelial dysfunction or cardiac congestion from right heart failure, drug-induced liver injury, and exacerbation of underlying liver disease[129,130].

So far, information on underlying histopathological alterations is scarce. Hepatic steatosis appears to be commonly encountered in the livers of patients with SARS-CoV-2 infection, both radiologically and histopathologically, either alone or together with inflammation[131-134]. To date, more than 20 studies with histological samples of the liver are present[131]. Most samples are retrieved postmortem and reflect a very selected population, and furthermore, most studies are written on available data during autopsy; hence, clinical data are limited. Nevertheless, histological samples on approximately 270 patients who died secondary to COVID-19 can be found in the literature, of whom 57% have hepatic steatosis, often mild, and difficult to distinguish from, e.g., shock/SIRS, drug-induced liver injury, or metabolic syndrome[130,131,134-153]. In studies where some clinical data is present, the majority of individuals are elderly, and more than a third have type 2 diabetes and/or are obese, with almost two-thirds having hypertension. This is not surprising since cardiometabolic risk factors were seen as a risk factor for COVID-19 mortality[154]. Similarly, in radiological studies (utilizing either magnetic resonance imaging or computed tomography), hepatic steatosis seems to be associated with the severity of COVID-19 illness, but is often of collinearity with obesity, type 2 diabetes, and hypertension[132,133].

Steatotic liver disease is a common finding in patients with COVID-19. Although COVID-19 does not seem to have any steatogenic properties, it is unknown if hepatic steatosis is a risk factor for more severe COVID-19, including increased mortality. Even though the incidence of hepatic steatosis is common in autopsies of patients who have died secondary to COVID-19, this is probably secondary to co-morbid conditions associated with increased mortality in COVID-19 (such as obesity and type 2 diabetes).

Environmental toxin-associated steatosis

A wide variety of environmental toxins can induce steatosis and steatohepatitis. Among these are metals (arsenic, cadmium, lead, mercury), pesticides/fungicides (e.g., fludioxonil, triflumizole), herbicides (e.g., dioxin), polychlorinated biphenyls, and chloroalkenes (e.g., perchloroethylene, trichloroethylene, and vinyl chloride)[155-157]. These agents may induce hepatic fat accumulation but also aggravate pre-existing MASLD.
Among the pathophysiological mechanisms reported to be involved in toxicant-associated SLD are disturbances of endocrine metabolic regulation and interactions between nutrients and chemicals that may aggravate metabolic irregularities\(^{[155]}\). Chemicals and toxins may also induce metabolic disturbances by influencing hepatokine production (e.g., fibroblast growth factor-21, insulin growth factor-1), or by interfering with anabolism and catabolism of lipids or with nuclear hormone receptors required in metabolic regulation\(^{[155,158]}\).

**Endocrine disorders associated with steatosis**

Besides T2DM, some endocrine disorders predispose to steatosis. Among them are hypothyroidism, growth hormone (GH) deficiency, and hypopituitarism\(^{[159-161]}\). In the latter condition, it has been reported that 2.3% had evidence of SLD in the absence of other hepatic diseases or excessive alcohol consumption\(^{[162]}\). After the diagnosis of pituitary/hypothalamic disease, most patients exhibited weight gain, and developed T2DM or glucose intolerance and hypertriglyceridemia. These consequences are most likely associated with GH deficiency or supplementation therapy with corticosteroids\(^{[162]}\).

Hypothyroidism is often associated with features of the metabolic syndrome, and steatosis, which are at least partly reversible by pharmacological replacement therapy\(^{[159,164-165]}\). Mechanisms contributing to increased hepatic triglyceride content are effects of thyroid stimulating hormone on hepatic lipid metabolism, as well as reduced glucose sensing by pancreatic \(\beta\)-cells due to reduced levels of thyroid hormones resulting in impaired insulin secretion and derepression of lipolysis in adipocytes, which increases the flux of free fatty acids to the liver\(^{[161,166]}\). Selective agonists for the thyroid hormone receptor-\(\beta\) are currently being evaluated for the treatment of non-alcoholic steatohepatitis. Among them, resmetirom has been shown to reduce hepatic triglyceride content after 12 and 36 weeks of treatment in a phase II trial\(^{[167]}\).

Polycystic ovary syndrome (PCOS) is strongly associated with insulin resistance and SLD\(^{[168]}\). A recent meta-analysis concluded that the odds ratio for MASLD in PCOS patients was 2.54 compared to controls\(^{[169]}\). Steatosis in PCOS may be present in the absence of obesity and metabolic syndrome. In these cases, hyperandrogenism may be involved in the pathogenesis\(^{[169,170]}\).

In contrast, low testosterone levels in males have been associated with SLD independently of insulin resistance, BMI, and T2DM\(^{[170,171]}\). Studies in animals have shown that supplementation of testosterone ameliorated high fat diet-induced steatosis in castrated rodents\(^{[172,173]}\).

**Genetic diseases associated with steatosis**

Steatotic liver disease may be caused by hereditary diseases, particularly in children and young adults. Inborn errors of lipid metabolism, such as lysosomal acid lipase deficiency (LAL-D, previously termed cholesteryl ester storage disease in adults/Wolman’s disease in infancy), abetalipoproteinemia, congenital lipodystrophy, familial hypobetalipoproteinemia, and familial hyperlipidemia/hypercholesterolemia may underlie SLD\(^{[174-177]}\).

LAL-D results from mutations in the lipase A (\(LIPA\) gene, which have an estimated minor allele frequency of 0.18%-0.24% and are characterized by a residual enzyme activity of < 1% or 1%-5% in the pediatric and adult phenotypes, respectively. Until recently, treatment for LAL-D was primarily symptomatic and focused on a combination of dietary manipulation and the use of lipid-lowering pharmacological agents. Recently, sebelipase alfa, a recombinant enzyme replacement therapy, was approved after demonstrating positive effects on disease-relevant markers and clinical benefits in clinical trials, including survival benefits in the
Figure 1. A schematic illustration of the included steatogenic causes of hepatic lipid accumulation. Often, several concomitant causes of steatotic liver disease exist where separating the two is difficult. Although some causes only seem to increase hepatic fat infiltration in the presence of insulin resistance (A) some can elicit steatogenic properties by themselves (i.e., in the absence of insulin resistance) (B) or by inducing insulin resistance (C).

most severe cases\textsuperscript{178}.

**SUMMARY**

Most cases of SLD are associated with cardiometabolic risk factors, most commonly insulin resistance. The absence of signs and symptoms of the metabolic syndrome on clinical work-up warrants assessment of secondary causes of SLD. Many of these causes can be considered co-factors that aggravate primary MASLD, but some can trigger hepatic lipid accumulation per se [Figure 1]. Drug treatment and other primary liver diseases need to be evaluated and congenital metabolic defects should be considered, especially in younger people.

**DECLARATIONS**

**Authors’ contributions**

Made substantial contributions to the conception and design of the study: Nasr P, Jönsson C, Ekstedt M, Kechagias S

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All authors declared that there are no conflicts of interest.

**Ethical approval and consent to participate**

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