Navigating the landscape of metabolic-associated steatotic liver disease treatment: aspirin as a potential game changer

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Metabolic-associated steatotic liver disease (MASLD) is the most common cause of chronic liver disease in Western countries, with rapidly increasing prevalence worldwide, estimated at around 40% due to modernization and urbanization. MASLD is defined as hepatic steatosis and identified through histology, imaging, blood markers, and in the absence of other secondary causes of hepatic fat accumulation, such as significant alcohol consumption, use of steatogenic medication, or hereditary disorders. The current management strategies addressing MASLD involve lifestyle modifications and treating coexisting conditions such as obesity, hyperlipidemia, insulin resistance, and type 2 diabetes. Several studies demonstrate that antiplatelet drugs, including acetylsalicylic acid, have beneficial effects on hepatocytes by decreasing hepatic inflammation, oxidative stress, and insulin resistance and may prevent hepatic fibrosis progression in MASLD. This review article discusses the impact of aspirin on steatosis and triglyceride accumulation in the hepatocytes. Eur J Gastroenterol Hepatol 37: 10–14

Introduction

The European Association for the Study of the Liver (EASL) recognized that while nonalcoholic fatty liver disease (NAFLD) is typically diagnosed by excluding other causes of chronic liver disease, its strong association with the metabolic syndrome and frequent overlap with other liver conditions called for a reconsideration of its nomenclature. EASL argued that the current terminology does not fully capture the metabolic roots of the disease, and a name change would better reflect its underlying causes and improve the understanding of its link to metabolic dysfunction. The same year, Eslam *et al*. [1] proposed a new term 'metabolic dysfunction-associated liver disease (MAFLD)/metabolic associated steatotic liver disease (MASLD)', which could be diagnosed in adults with hepatic steatosis detected by imaging techniques, blood biomarkers, or liver histology, when overweight or obese, or in the presence of type 2 diabetes (T2DM) or at least two metabolic risk abnormalities.

MASLD is a spectrum of hepatic disorders with a global prevalence of around 25–30% consisting of benign nonalcoholic fatty liver (NAFL) to the more severe nonalcoholic steatohepatitis (NASH) characterized by steatosis, hepatocellular ballooning, lobular inflammation, which may lead to cirrhosis and hepatocellular carcinoma (HCC) that is predicted to become also the most frequent indication for liver transplantation by 2030 along with chronic hepatitis B and alcohol consumption [2]. With the rise of urbanization, westernization, and the increasing prevalence of obesity, diabetes, and hypertension, the prevalence of MASLD has increased significantly in the USA. In 2019, 36000 new HCC cases and 34 700 HCC-related deaths were attributed to MASLD [3]. The most common cause of death among individuals with chronic liver disease is MASLD and mortality associated with MASLD rose from 0.2 per 100 000 people in 1999 to 1.7 per 100 000 in 2022, indicating a notable average annual percentage change of 10.0% [4].

MASLD pathogenesis is multifactorial, with obesity, insulin resistance, and diabetes as the top risk factors and diagnostic criteria involving patients having hepatic steatosis identified through histology, imaging, blood markers, or evidence of fat accumulation and one of the following: being overweight or obese (based on ethnicity-specific cutoffs), having T2DM, or showing signs of metabolic dysregulation. The latter is defined as having two or more of the following conditions: (1) an enlarged waist circumference, (2) elevated blood pressure or taking specific medications, (3) elevated triglycerides (TGs) or taking specific medications, (4) low high-density lipoprotein cholesterol, (5) prediabetes, (6) a high homeostatic model assessment of IR score, or (7) inflammation indicated by elevated levels of high-sensitivity C-reactive protein [5].

Currently, the management of MASLD involves lifestyle modifications and treating coexisting conditions such as obesity, hyperlipidemia, insulin resistance, and

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T2DM. However, various drugs like oral hypoglycemics, statins, and newer drugs, like obeticholic acid 25 mg, which acts as a farnesoid X receptor agonist, have promising results in improving fibrosis and steatosis in patients suffering from MASLD [6,7]. In recent times, preclinical models of chronic liver disease have indicated that platelets play a pivotal role in both liver inflammation and fibrosis [8]. Aspirin, an O-acetyl derivative of salicylic acid (acetylsalicylic acid) has antiplatelet, anti-inflammatory, and antipyretic effects due to inhibition of cyclooxygenase (COX-1) enzymes [9]. Various studies have shown the positive effect of aspirin over steatosis and fibrosis through antiplatelet effects of aspirin by modulating immune cell response and impacting oxidative stress, vascular inflammation, and insulin sensitivity. Due to its anti-inflammatory characteristics, aspirin has been extensively studied for its potential in preventing cancers linked to chronic inflammation and daily aspirin use has been linked to a decreased likelihood of developing HCC in individuals with MASLD [10]. This review article discusses the effects of aspirin over steatosis and TG accumulation in the hepatocytes and subsequent developing pathologies such as MASLD and HCC.

Pathophysiology

MASLD involves a complex interplay of various factors, with inflammation and oxidative stress playing central roles. Aspirin, a widely used medication known for its anti-inflammatory and antiplatelet properties, has demonstrated potential in managing MASLD [11]. While the exact cause of MASLD remains uncertain, the 'two-hit' hypothesis has been widely accepted, where insulin resistance and hepatic steatosis represent the 'first hit', and oxidative stress, lipid peroxidation, inflammation, and fibrosis represent the 'second hit' [12]. On a cellular level, the primary mediators of liver fibrosis are activated hepatic stellate cells (HSCs) and portal fibroblasts, which are stimulated by cytokines released by Kupffer cells [13]. Platelet-derived growth factor-β (PDGF-B) is a potent mitogen for activated HSCs and myofibroblasts, and it functions in synergy with profibrotic signaling from transforming growth factor-β [14]. While platelets are a rich source of PDGF-B, the role of platelet accumulation or aggregation in MASLD specifically is not well established. In conditions such as chronic hepatitis and liver cirrhosis, platelets interact with Kupffer cells, contributing to liver fibrosis through cytokine release, but the direct 'build-up' of platelets in the liver is not a defining feature of MASLD [15,16]. Instead, platelet-derived factors promote fibrogenesis via indirect mechanisms, including cytokine release that activates HSCs. Aspirin's inhibition of the COX-1 enzyme prevents platelet thromboxane production, which, in turn, reduces platelet activation and aggregation [17]. This action decreases inflammation and enhances lipid metabolism, as mediated by the PPARδ-AMPK-PGC-1α oxidative phosphorylation pathway [18]. Moreover, aspirin increases the expression of the mannose receptor, a marker of noninflammatory macrophages that supports tissue repair and helps reverse liver damage, while simultaneously downregulating C-C chemokine receptor 2, which is involved in inflammatory cell chemotaxis [19,20]. Recent studies indicate that low-dose daily aspirin for 6 months significantly reduces hepatic fat content [21]. In addition to aspirin, a Mediterranean diet rich in olive oil and monounsaturated fatty acids has shown preventive effects against MASLD progression [22]. Figures 1 and 2 summarize the potential role of aspirin in the pathogenesis of MASLD. As our understanding of the pathophysiology of MASLD deepens, aspirin's role may become increasingly critical in preventing disease progression.

Emerging evidence of aspirin's impact on metabolic-associated steatotic liver disease

Currently, the primary management of MASLD is through lifestyle management such as exercise, reducing weight, managing blood pressure, lipid levels, and diabetes. Until recently, no approved pharmaceutical intervention existed for MASLD. However, in March 2024, resmetirom (Rezdiffra, Madrigal Pharmaceuticals, West Conshohocken, Pennsylvania, USA) gained U.S. Food and Drug Administration (FDA) approval for treating metabolic dysfunction-associated steatohepatitis (MASH). The clinical trial conducted by Harrison *et al.* [23] showed that both doses of resmetirom (80 and 100 mg) were found superior to placebo in patients of MASH with fibrosis, in terms of improvement of MASH as well as improvement in fibrosis by at least one stage. In addition to this, studies have also been conducted recently to find the effectiveness of aspirin in patients with MASLD.

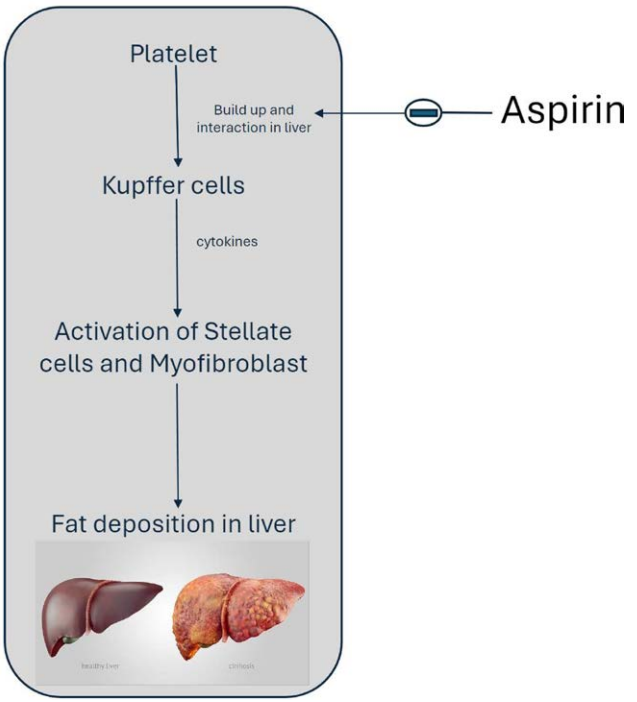

Fig. 1. Summarize the potential role of aspirin in the deposition of fat in liver.

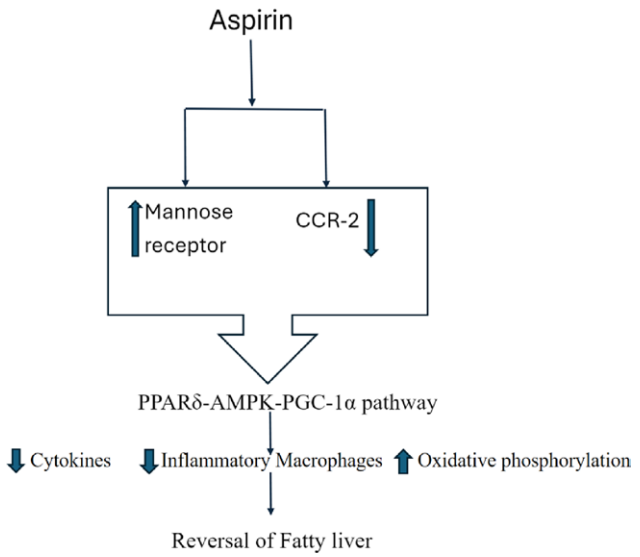

Fig. 2. Illustrates the role of aspirin in the pathogenesis in MASLD. CCR-2, C-C chemokine receptor type-2; MASLD, metabolic-associated steatotic liver disease.

Aspirin and metabolic-associated steatotic liver disease: preclinical studies

Few preclinical studies have shed light on aspirin's potential impact on MASLD. A study in mice fed a high-fat diet for 6 months found that aspirin significantly reduced liver weight ($P = 0.006$) and hepatic steatosis ($P = 0.01$) compared with the untreated group. While all NSAIDs tested (meclofenamate, mefenamate, flufenamate, and aspirin) reduced hepatic inflammation ($P = 0.000$), only aspirin showed significant reductions in liver weight and steatosis [24].

In another study using male rats on a choline-deficient, L-amino acid-defined diet, which induces liver fibrosis and inflammation, aspirin treatment for 16 weeks significantly reduced liver steatosis, inflammation, and fibrosis ($P < 0.05$ for all) compared with the control group without aspirin. This suggests aspirin's potential therapeutic benefit in mitigating the progression of liver disease in this model [25].

Conversely, a study on guinea pigs with hepatic steatosis found that the treatment with aspirin and pentoxifylline, either alone or in combination, for 8 weeks did not improve MASLD or hepatic fibrosis compared with the group receiving no drug. While liver weights were reduced by approximately 18 and 15% in all intervention groups compared with controls, the reductions were not statistically significant ($P = 0.1307$ and $P = 0.1440$, respectively). The study excluded animals without sufficient liver density reduction to mimic clinical fatty liver conditions, which limited the sample size and likely the statistical power [26].

Clinical evidence

Building open these, several clinical studies have also provided evidence towards this. Shen and colleagues conducted a pioneering study, employing a cross-sectional analysis of the American population ($n = 11\,416$). Data were derived from the Third National Health and Nutrition Examination Survey (NHANES III) spanning the years 1988–1994. It concluded that regular aspirin use (more than 15/month) is associated with a lower prevalence of MASLD ($P_{trend} = 0.04$) compared with nonregular use. Further stratification revealed the association to be only statistically significant in men ($P_{interaction} < 0.01$) as well as in older adults (more than 60 years of age) ($P_{interaction} < 0.01$). The study found no significant association between aspirin use and MASLD in females and younger population (less than 60 years) [27]. However, this study does not imply causation as well as does not show temporal association, calling for a need of a prospective or randomized clinical trial.

Conversely, a separate cross-sectional study conducted by Devaki *et al*. [28] on a US population ($n = 4658$), utilizing data collected from NHANES III spanning the years 1999–2012, found no discernible association between aspirin use and MASLD ($P = 0.19$).

A recent small-scale randomized, double-blinded clinical trial led by Simon *et al*. [21] revealed that daily low-dose aspirin (81 mg) effectively reduces hepatic fat content compared with placebo in MASLD patients without cirrhosis. Despite being conducted over 6 months on a modest scale with subjects primarily exhibiting moderate steatosis, there is a pressing need for larger scale investigations, including individuals with severe steatosis, to validate these findings (Table 1).

Nevertheless, one study found no impact of aspirin on overall mortality and cardiovascular mortality in MASLD patients. However, when conducting a stratified analysis by age, aspirin was linked to decreased all-cause mortality only among middle-aged individuals diagnosed with MASLD [29].

Impact of aspirin on fibrosis reduction

Aspirin's potential role in reducing fibrosis has been suggested by several studies. Jiang and colleagues conducted a cross-sectional analysis utilizing data from NHANES III, revealing a negative correlation between aspirin usage and reduced fibrosis index in patients diagnosed with MASH. This correlation remained consistent across all four fibrosis indices utilized to predict liver fibrosis, including fibrosis-4 score ($P = 0.07$), AST to platelet ratio index score ($P = 0.01$), Forns index ($P = 0.002$), and NAFLD fibrosis score ($P = 0.006$) [30]. This observational study does not take into consideration the duration and dose of aspirin required to achieve these effects.

Simon and colleagues' preliminary cross-sectional analysis further demonstrated lower odds of MASH [adjusted odds ratio [aOR], 0.68; 95% confidence interval (CI), 0.37–0.89] and fibrosis (aOR, 0.54; 95% CI, 0.31–0.82) with regular aspirin use compared with nonregular use in biopsy-confirmed MASLD patients. Moreover, their prospective cohort study on MASLD patients with early fibrosis (F0-2) highlighted a significantly reduced risk of advanced fibrosis development in daily aspirin users versus nonregular users [adjusted hazard ratio (aHR), 0.63; 95% CI, 0.43–0.85], with a duration-dependent effect. The use of daily aspirin for less than 2 years was found nonsignificant in reducing the risk of advanced fibrosis

Table 1. Various studies evaluating the effects of aspirin on metabolic dysfunction-associated steatotic liver disease and related conditions

References	Type of study/sample size (*n*)	Aspirin dose and frequency	Results (with 95% confidence interval)		Inference
Simon *et al*. [21]	Randomized, double-blind controlled trial *n* = 80	81 mg aspirin daily, for 6 months	Absolute difference, −10.2% (−27.7 to −2.6%)		Low-dose aspirin significantly decreased hepatic fat content in comparison with a placebo in MASLD patients without cirrhosis.
Vell *et al*. [32]	Longitudinal cohort *n* = 148 022	NA	HR, 0.882 (0.803–0.968)		Aspirin users demonstrate a diminished risk of MASLD compared with nonusers.
Lee *et al*. [10]	Retrospective cohort *n* = 89 027	Aspirin daily for consecutive 90 days	aHR, 0.48 (0.37–0.63)		Daily aspirin use for at least 90 days significantly lowered the 10-year cumulative incidence of HCC compared with nonregular users.
Simon *et al*. [31]	Cross-sectional *n* = 361	Daily usage	OR, 0.68 (0.37–0.89)		Daily aspirin use was associated with lower odds of MASH compared with nonregular aspirin use.
	Longitudinal cohort *n* = 317		Aspirin use duration (0 to <2 year)	HR, 0.90 (0.68–1.20	Daily aspirin users exhibit reduced risk for advanced fibrosis compared with nonaspirin users, with effect being duration-dependent.
			Aspirin use duration (2 to <4 years)	HR, 0.90 (0.68–1.20)	
			Aspirin use duration (≥4 years)	HR, 0.50 (0.35–0.73)	
Devaki *et al*. [28]	Cross-sectional *n* = 4658	NA	OR, 1.31 (0.88–1.97)		No significant association between the use of aspirin and prevalence of MASLD.
Shen *et al*. [27]	Cross-sectional *n* = 11 416	<14 times/month	Male	OR, 0.58 (0.46–0.74)	Association of aspirin use and lower odds of MASLD only significant in male and elderly people(>60 years).
			Female	OR, 1.22 (0.95–1.57)	
			Age ≤ 60 years	OR, 1.00 (0.79–1.25)	
			Age > 60 years	OR, 0.74 (0.56–0.99)	
		≥15 times/month	Male	OR, 0.32 (0.23–0.45)	
			Female	OR, 0.80 (0.56–1.14)	
			Age ≤ 60 years	OR, 1.16 (0.84–1.61)	
			Age > 60 years	OR, 0.21 (0.14–0.30)	

All results show 95% CI in parenthesis.
CI, confidence interval; HCC, hepatocellular carcinoma; HR, hazard ratio; MASLD, metabolic-associated steatotic liver disease; NA, not available; OR, odds ratio.

when compared with nonregular use (aHR, 0.90; 95% CI, 0.68–1.20). The duration of aspirin for more than 2 years was significantly found to decrease the risk for incident advanced fibrosis, with maximum benefit for a duration of more than 4 years (aHR, 0.50; 95% CI, 0.35–0.73) [31].

Aspirin's chemoprotective role in hepatocellular carcinoma

Recent research has begun to bridge the gap in understanding aspirin's chemopreventive role in HCC specifically for patients with MASLD, a population previously understudied compared with those with viral hepatitis. A retrospective analysis of over 88 000 MASLD patients using Taiwan's National Health Insurance Research Database found that daily aspirin use for at least 90 days significantly lowered the 10-year cumulative incidence of HCC compared with patients not receiving aspirin therapy (0.25% vs. 0.67%; $P < 0.001$). Aspirin therapy was associated with a reduced HCC risk (aHR, 0.48; 95% CI, 0.37–0.63; $P < 0.001$), especially in high-risk patients (age ≥55 years and elevated serum alanine aminotransferase) with an aHR of 0.63 (95% CI, 0.53–0.76; $P < 0.001$).

Moreover, the study demonstrated a duration-dependent effect, with long-term aspirin use (≥3 years) offering more pronounced HCC risk reduction (aHR, 0.64; 95% CI, 0.44–0.91; $P = 0.013$), compared with short-term use (<1 year). This highlights the potential benefit of sustained aspirin therapy in lowering HCC risk among MASLD patients [10].

Genetic implications for aspirin use in metabolic-associated steatotic liver disease

Genetic predispositions may influence aspirin's efficacy in MASLD patients. Vell and colleagues conducted a prospective cohort study using data from the UK Biobank and Penn Medicine Biobank. The study found a reduced MASLD risk among aspirin users [hazard ratio (HR) = 0.882, $P = 0.008$), with a particularly strong effect in males (HR = 0.806, $P = 6.9 \times 10^{-4}$). Notably, individuals carrying protective gene variants, such as HSD17B13 rs72613567 and mitochondrial amidoxime-reducing component 1 rs2642438 alleles, experienced enhanced benefits from aspirin use. Homozygous carriers of the HSD17B13 variant had a nearly three-fold increased aspirin effect compared with the general population, suggesting a potential synergistic action of aspirin in this subgroup [32].

Considerations and risks of aspirin use in metabolic-associated steatotic liver disease

Despite promising evidence, aspirin administration warrants cautious consideration due to associated risks, notably bleeding. Even at low doses, aspirin poses a 33% increased risk of hemorrhagic stroke and a 59% increased risk of major gastrointestinal bleeding. These risks are amplified in high-risk patients, including those with bleeding disorders, ulcerations, or prior aspirin-related complications [8]. Therefore, when prescribing aspirin to MASLD patients, one must carefully weigh its benefits against risks, considering factors like age, bleeding risk, 10-year cardiovascular disease risk, and life expectancy.

Conclusion

MASLD is a spectrum of hepatic disorders with a global prevalence of around 25–30% consisting of benign NAFL to the more severe NASH characterized by steatosis, hepatocellular ballooning, lobular inflammation, which in extreme cases may lead to cirrhosis and HCC. MASLD involves a 'two-hit' concept with insulin resistance as the first hit and associated with oxidative stress, lipid peroxidation, and proinflammatory cytokines release, ultimately promoting hepatic inflammation and fibrosis, leading to NASH (MASLD) as the second hit. Currently, the management of MASLD involves lifestyle modifications and treating coexisting conditions such as obesity, hyperlipidemia, insulin resistance, and T2DM. However, apart from resmetirom, which is a newly approved drug, there are no effective drugs available to prevent or treat MASLD. Cyclooxygenase inhibitor, aspirin, through its antiplatelet and anti-inflammatory action, has been linked to modulating immune cell response and impacting oxidative stress, vascular inflammation, and insulin sensitivity. Studies have shown that regular aspirin use is associated with lower prevalence of MASLD especially in men and older adults, and it has also been linked to decrease all-cause mortality only among middle-aged individuals diagnosed with MASLD. However, other studies found no discernible association between aspirin use and MASLD. Age, risk of cardiovascular disease, hemorrhagic stroke, and gastrointestinal bleeding are also one of the factors we need to consider when deciding the optimal dose and duration of aspirin therapy. To determine the most effective strategies to use aspirin as an adjuvant medicine in the treatment of MASLD, more extensive clinical studies are required.

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Conflicts of interest

There are no conflicts of interest.

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