Exploration of Digestive Diseases

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Helicobacter pylori infection in the pathophysiology of metabolic dysfunction-associated steatotic liver disease and its complications

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Academic Editor: Jose Carlos Fernandez-Checa, Institute of Biomedical Research of Barcelona (IIBB-CSIC), Spain

Received: January 10, 2025 **Accepted:** March 10, 2025 **Published:** March 20, 2025

Cite this article: Kountouras J, Zavos C, Papanikolaou IS, Polyzos SA, Vardaka E, Chatzopoulos D, et al. *Helicobacter pylori* infection in the pathophysiology of metabolic dysfunction-associated steatotic liver disease and its complications. Explor Dig Dis. 2025;4:100567. https://doi.org/10.37349/edd.2025.100567

Keywords

Helicobacter pylori, metabolic syndrome, metabolic dysfunction-associated steatotic liver disease, pathogenesis, complications

To the Editor,

In their recent review on metabolic dysfunction-associated steatotic liver disease (MASLD), Habib and Johnson [1] provide an overview of the condition's risk factors and complex pathophysiological processes.

In this regard, *Helicobacter pylori* infection (*Hp*-I), affecting over 4.4 billion people worldwide is connected with the high global burden of metabolic syndrome (MetS). Both disorders contribute to the pathogenesis of MASLD by various mechanisms [2]. Clinical studies, using the histological diagnostic "gold standard" for active *Hp*-I and MASLD, confirmed that active *Hp*-I was independently connected with MASLD severity in morbidly obese patients undergoing bariatric surgery [3]. This connection was evident in patients with MetS-related components, including insulin resistance (IR), dyslipidemia, and arterial hypertension [3]. Robust comparable results were also reported by additional small- and large-scale clinical data, signifying that eradicating *Hp*-I may contribute to a reduction in metabolic indices and the risk of developing MASLD [4].

Several pathophysiological mechanisms appear to explain this connection between *Hp*-I and MASLD. One key pathway relates to the ability of *Hp*-I to promote IR. Chronic infection induces proinflammatory cytokines [interleukin (IL)-1, IL-6, tumor necrosis factor-alpha] and plasminogen activator inhibitor-1 (PAI-

1), all of which contribute to IR and its negative downstream consequences in the liver [5]. In this context, prolonged IR supports ectopic fat deposition, propagates oxidative stress, and promotes hepatic steatosis. Dyslipidemia triggered by *Hp*-related inflammatory cascades may further aggravate hepatic fat accumulation.

Research on the impact of *Hp*-I on adipokines and novel biomarkers adds another dimension to this setting. High leptin levels are linked with severe MAFLD, whereas MetS-related adiponectin improves liver histology in MAFLD [6]. In addition, studies have shown an association between *Hp*-I and elevated serum fetuin A, a glycoprotein involved in transporting free fatty acids. Increased fetuin A levels are connected not only with IR but also with the progression of MASLD, suggesting that fetuin A could be an underrecognized player in linking *Hp* to the metabolic dysfunction that characterizes MASLD. Likewise, the overexpression of galectin-3 associated with both *Hp*-I and MetS-related inflammation may amplify fibrogenic activity and worsen disease severity.

Systemic hypertension and hyperhomocysteinemia in the context of *Hp*-I and MetS have also been described, potentially indicating a broader atherogenic state that promotes hepatic injury, MASLD-related cardiovascular complications [6], and neurodegenerative diseases, such as Alzheimer's disease (AD) [7]. In this respect, hyperhomocysteinemia is an increased risk factor for MASLD [8], and MASLD is linked with cardiovascular disease (CVD) [9]. There is an association between *Hp*-I and MetS-related parameters and CVD. For instance, myocardial infarction (MI), a potentially lethal CVD event, is strongly associated with MetS, and *Hp* is a risk factor for acute coronary syndrome including MI [10]. There is a potential connection between *Hp*-related CagA and MI, with the likelihood of MI being twice as high in *Hp*-positive individuals. Similarly, MetS, a key risk factor for MI, more than doubles the risk of adverse CVD events, while recovery from MetS significantly reduces the risk of major cardiovascular events, including MI. Additionally, *Hp*-I is considered a risk factor for atrial fibrillation (AF) [11], and there is a bidirectional association between *Hp*-I and MetS-related AF and MI; the incidence of MI is approximately 50% higher in patients with AF.

Hp-I and MetS-related galectin-3, and gut dysbiosis are also involved in the pathophysiology of CVD and its adverse outcomes [11]. Likewise, *Hp*-I and MetS are strongly connected with activation of mast cells (MC) [12], involved in the pathogenesis of CVD [13].

Moreover, MASLD is an independent risk factor for AD [14]. MASLD-related hyperhomocysteinemia plays a significant role in the pathophysiology of mild cognitive impairment, a strong predictor of AD progression [15]. This condition contributes to the AD pathway by triggering amyloid beta (Aβ) and tau pathologies, along with synaptic dysfunction, neuroinflammation, and memory decline, highlighting a potential therapeutic target for at-risk patients. There is a notable connection between *Hp-I* and AD-like Aβ and phospho-tau pathology, suggesting that *Hp* eradication may help prevent tauopathy. Additionally, *Hp* is an independent risk factor for long-term AF [11], which, beyond its association with MASLD [16], is also strongly linked to AD and cognitive decline. Thus, eliminating *Hp* may lower the risk of AF-related AD, warranting further investigation.

Hp is also associated with galectin-3, a key factor in the severity of MASLD [17] and a marker of memory loss and AD progression. Galectin-3 inhibitors suppress microglial activation, presenting a promising therapeutic target for neurodegenerative diseases, including AD.

Moreover, *Hp* induced gut dysbiosis contributes to the pathophysiology of MASLD [11, 18] and AD by driving neuroinflammation and disease progression. Therapeutic interventions including probiotics, prebiotics, synbiotics, and fecal microbiota transplantation display potential benefits in managing MASLD [19] and AD.

Hp eradication has a beneficial impact on patients with AD, potentially improving their long-term survival [20]. Furthermore, clinical evidence points to the role of the mentioned MC activation in the progression of MASLD, and heightened MC activity has been reported in both *Hp*-I and MetS. Inhibition of MC activation or *Hp* eradication could produce benefits for patients at increased risk of advanced liver disease and systemic disorders. These potential mechanisms illustrate the broad inflammatory and metabolic consequences of *Hp*-I and indicate that further research is warranted to clarify the precise

pathogenic interactions. Confirmatory large-scale and prospective studies are needed to determine whether eradicating *Hp*-I could serve as a practical adjunct strategy in preventing MASLD progression or its cardiovascular and neurodegenerative risks.

In conclusion, accumulating evidence suggests that *Hp*-I may amplify MetS components such as IR and dyslipidemia, both of which lie at the core of MASLD pathogenesis and its complications including CVD and neurodegeneration. Recognition of *Hp*-I as a contributing factor to MASLD underscores the necessity to explore targeted research on whether eradication of *Hp*—in appropriate clinical settings—may alter the disease's natural history. Enhanced understanding of these complex pathways could eventually guide strategies for risk stratification and management in MASLD and its systemic complications.

Abbreviations

AD: Alzheimer's disease

AF: atrial fibrillation

Aβ: amyloid beta

CVD: cardiovascular disease

Hp-I: *Helicobacter pylori* infection

IL: interleukin

IR: insulin resistance

MASLD: metabolic dysfunction-associated steatotic liver disease

MC: mast cells

MetS: metabolic syndrome

MI: myocardial infarction

Declarations

Author contributions

JK: Conceptualization, Supervision, Writing—review & editing. CZ, ISP, and SAP: Investigation, Writing—original draft. EV: Validation, Writing—original draft. DC: Visualization, Writing—original draft. MTC: Methodology, Writing—original draft.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical approval

Not applicable.

Consent to participate

Not applicable.

Consent to publication

Not applicable.

Availability of data and materials

Not applicable.

Funding

Not applicable.

Publisher's note

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