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LETTER TO THE EDITOR

Impact of *Helicobacter pylori*- and *Porphyromonas gingivalis*-associated metabolic syndrome on local and systemic disorders

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To the Editor,

In their review, Straka *et al.* (2026) discussed the role of *Helicobacter pylori* infection (*Hp*-I) in gastric and oral pathologies and highlighted the benefits of *Hp* eradication at both gastric and oral sites when combined with concomitant periodontal therapy (Straka *et al.* 2026). In this context, it is worth further emphasizing the broader impact of *Hp* and *Porphyromonas gingivalis* (*Pg*) in metabolic syndrome (MetS) and in bacteria-driven local and systemic disorders.

Hp-I remains highly prevalent worldwide, affecting more than 4.4 billion individuals (Kountouras 2025). As a Group I carcinogen, *Hp* plays a central role in gastric carcinogenesis through Correa's cascade, namely the progression from chronic gastritis to atrophy, intestinal

metaplasia, dysplasia, and ultimately gastric cancer (Kountouras *et al.* 2008). In addition, *Pg* and its virulence factors, particularly gingipains, have also been implicated in this carcinogenic sequence (Salazar *et al.* 2013).

Beyond its primary colonization of the gastric mucosa, *Hp* may also inhabit the oral cavity, including dental plaque, saliva, periodontal pockets, and especially dental pulp, thereby acting as an important extragastric reservoir (Momtaz *et al.* 2012). This oral–gastric axis may contribute to persistent infection, reinfection after eradication, and enhanced transmission (Momtaz *et al.* 2012). Likewise, the oral cavity is a major reservoir for *Pg*, which can disseminate systemically through the bloodstream and influence distant organs (Farrugia *et al.* 2021).

Hp-I, together with alterations in the oral–gut microbiota, may disturb the microecological balance of this axis. Both *Hp* and *Pg* are strongly associated with oral diseases, particularly periodontitis, a dysbiosis-driven inflammatory disorder. Periodontitis itself has been linked to the initiation and progression of malignancies, especially oral cancers (Farhad *et al.* 2024).

Although *Hp* and *Pg* colonize different anatomical niches, they appear to share important pathogenic mechanisms (Doulberis *et al.* 2021). A major determinant of *Pg* virulence is the gingipain family, a group of cysteine proteases involved in tissue destruction, immune evasion, and bacterial invasion. Emerging evidence also suggests that *Hp* may express functionally similar proteolytic enzymes, indicating overlapping or complementary pathogenic strategies (Doulberis *et al.* 2021). Notably, co-incubation of *Hp* and *Pg* has been reported to enhance *Pg* virulence, supporting a synergistic interaction that may aggravate both local and systemic disorders (Doulberis *et al.* 2021). These shared features underline the potential value of targeting both pathogens in antimicrobial strategies.

Increasing evidence also links *Hp* and *Pg* to metabolic dysfunction-associated steatotic liver disease (MASLD), the hepatic manifestation of MetS (Doulberis *et al.* 2021; Nakahara *et al.* 2018). Both pathogens have been implicated in metabolic dysregulation, supporting the concept that they may act as shared contributors to MASLD pathogenesis (Kountouras *et al.* 2021; Watanabe *et al.* 2021). Therefore, therapeutic approaches aimed at controlling *Hp* and *Pg* may also be relevant in MASLD management.

Moreover, *Hp*- and *Pg*-associated MetS appears to be relevant to cardiovascular disease (CVD), mainly through chronic inflammation, atherogenesis, and endothelial dysfunction (Kountouras *et al.* 2022; Leonov *et al.* 2025). *Hp*-I has been associated with increased risk of atherosclerotic events, including myocardial infarction and cerebrovascular disease (Wang *et al.* 2020), whereas *Pg* is increasingly recognized as a contributor to CVD pathogenesis (Leonov *et al.* 2025). Further studies are needed to clarify the molecular pathways connecting these pathogens with cardiovascular outcomes and to identify more specific interventional targets.

The pathogenic overlap between *Hp* and *Pg* may also extend to neurodegeneration. *Hp* may promote neuronal injury through systemic inflammation and blood–brain barrier (BBB) disruption, thereby facilitating the entry of bacteria, bacterial components, or neurotoxic mediators into the brain (Kountouras *et al.* 2017; Gravina *et al.* 2018). Similarly, *Pg*-derived gingipains have been implicated in BBB disruption, supporting a direct contribution to neurodegenerative processes (Shawkatova *et al.* 2025).

Chronic inflammation induced by these pathogens may also favor the accumulation of amyloid-β (Aβ), a hallmark of Alzheimer's disease (Gravina *et al.* 2018; Antequera *et al.* 2026). Both *Hp* and *Pg* have been associated with cognitive decline, potentially through shared neuroinflammatory pathways and Aβ deposition (Gravina *et al.* 2018; Antequera *et al.* 2026). In parallel, MetS-related galectin-3 may further amplify this process through effects on microglial activation and immune modulation, and it has been linked to both *Hp*- and *Pg*-associated neuroinflammation (Boziki *et al.* 2020; Zavala-Medina *et al.* 2026).

Besides inflammatory mechanisms, metabolic pathways may also contribute to these effects. *Hp*-associated MetS has been linked to gut dysbiosis, which may disturb metabolic homeostasis and promote both systemic and neuroinflammation (Kountouras *et al.* 2024). Similarly, *Pg* may contribute to metabolic dysfunction and thereby further increase the risk of neurodegenerative disorders (Gan *et al.* 2026; Kwon *et al.* 2026; Zhang *et al.* 2026).

Taken together, the interplay between *Hp*-, *Pg*-, and MetS-related pathways deserves closer attention because these factors converge on chronic inflammation, immune dysregulation, and metabolic disturbance implicated in both local and systemic disorders. Further investigation is warranted to better define these interactions and to develop targeted oral and gastric eradication strategies, particularly when combined with concomitant periodontal therapy, in order to mitigate bacteria-driven local and systemic pathologies.

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COMPETING INTERESTS

None declared.

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AUTHOR CONTRIBUTION

Prof. Jannis Kountouras: (1) conception and design of the study, acquisition and interpretation of data; (2) investigation, methodology, supervision, validation; (3) drafting of the article and critical revision for important intellectual content; (4) final approval of the version to be submitted.

All other coauthors: (1) interpretation of data; (2) critical revision for important intellectual content; (3) final approval of the version to be submitted.

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