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Editorials

Helicobacter pylori infection and nonalcoholic fatty liver disease: Are the four meta-analyses favoring an intriguing association pointing to the right direction?

1. Introduction

Nonalcoholic fatty liver disease (NAFLD) is closely associated with obesity, insulin resistance (IR) and the metabolic syndrome (MetS) and is a leading cause of cirrhosis [1,2]. Its global prevalence is 25% [3] and is increasing worldwide [4] accompanied by severe complications particularly in high-risk older obese patients [5]. Thiazolidinediones, statins and vitamin E have been proposed for the management of NAFLD [6,7] together with lifestyle modifications [8], but there is currently no specifically approved medication. *Helicobacter pylori* (*Hp*) infection (*Hp*-I) is also very common with estimated global prevalence of 58% [9]; partly due to immigration, its prevalence in western populations remains apparently high [10]. Although the rates of both entities increase with age, they largely vary in certain subpopulation and geographical regions.

Hp-I has been strongly associated with gastrointestinal diseases, including non-ulcer dyspepsia, gastric and duodenal ulcer, gastric adenocarcinoma, gastric mucosa–associated lymphoid tissue lymphoma (maltoma), colorectal cancer and even esophageal adenocarcinoma in certain subpopulations [11,12]. Likewise, *Hp*-I has been associated with extragastric diseases, such as idiopathic thrombocytopenic purpura, iron deficiency anemia or vitamin B12 deficiency [13]. Growing evidence is further linking *Hp*-I with MetS, IR, diabetes mellitus, neurodegenerative diseases, coronary artery disease and distinct miscellaneous disorders, although controversy still exists [13,14].

The role of gastrointestinal microbiota, including *Hp*, in the pathogenesis of NAFLD has also been gaining interest [15,16]. The first case linking *Hp*-I with NAFLD was published in 2008 and reported the presence of 16S recombinant RNA of *Hp* spp. in the liver of a patient with NASH [17]. In 2012, we reported for the first time higher rates of anti-*Hp* IgG serology in patients with NAFLD than controls, and higher rates of previous *Hp* eradication treatment in patients with nonalcoholic steatohepatitis (NASH) than patients with simple steatosis [18]. Since then, growing evidence, derived from observational studies, favors an association between *Hp*-I and NAFLD [19]. This association is intriguing, since it may offer preventive and therapeutic implications. Certainly, if *Hp*-I contributes to the pathogenesis of NAFLD, *Hp* eradication may play a role in the prevention and management of NAFLD, the latter remaining an unmet need [20], though it affects large part of the population [21].

2. Four recent meta-analyses on the association between *Hp* infection and NAFLD

Four meta-analyses have been recently addressed the potential association between *Hp*-I and NAFLD (Table 1) [22–25]. All meta-analyses consisted of observational studies (mainly cross-sectional) and indicated a positive association between *Hp*-I and NAFLD with odds ratios ranging from 1.14 to 1.36 (Table 1). Most included studies in these meta-analyses were performed in Asia, whereas only a minority of them in America or Europe [22–25]. The heterogeneity of the meta-analyses was moderate to high and publication bias was considered significant in one of them [24] (Table 1). Different methods of diagnosis of NAFLD and *Hp*-I may possibly add to the heterogeneity of the meta-analyses, though it was not shown in all of them.

The first meta-analysis (Wijarnpreecha et al.) consisting of six observational studies (three in the form of congress abstracts) showed higher rates of NAFLD in *Hp* infected than non-infected individuals [22]. Despite the limitations of this meta-analysis, as elsewhere discussed [26], it is acknowledged that this was the first meta-analysis on the topic and that the odds ratio provided was very similar to those of the next three meta-analyses [23–25], which have included more than double studies and participants (Table 1). The last three meta-analyses, published almost simultaneously within the first four months of 2019, have included similar but not identical studies. More specifically, Zhou et al. [23] have included three congress abstracts (two of them were included in the Wijarnpreecha et al. meta-analysis [22]), whereas Ning et al. [24] and Mantovani et al. [25] did not include congress abstracts in their meta-analyses. Although the inclusion of congress abstracts generally implies a more complete search in the grey literature, thus limiting the likelihood of publication bias, the inclusion of congress abstracts may reduce the overall quality of included studies. In any case, the inclusion of abstracts did not modify the results of Zhou et al. meta-analysis, since similar results were retrieved after the exclusion of congress abstracts in a sensitivity analysis [23]. Generally, the association between *Hp*-I and NAFLD remained robust in all forms of sensitivity analyses performed by Zhou et al. [23], Ning et al. [24] and Mantovani et al. [25]. It is also of interest that the association between *Hp*-I and NAFLD remained statistically significant in subgroup analyses regarding year of publication, estimated quality of studies and sample size [23–25]. Moreover, in meta-regression analysis, Mantovani et al.

Abbreviation: hBD, human β-defensin; *Hp*, *Helicobacter pylori*; *Hp*-I, *Helicobacter pylori* infection; IR, insulin resistance; MetS, metabolic syndrome; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; RCTs, randomized clinical trials.

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Table 1
Main characteristics and results of meta-analyses having evaluated the association between *Helicobacter pylori* infection and NAFLD.

First author Year [Reference][a]	Included studies [type] (N)	Participants (N)	Heterogeneity (I^2)[b]	Publication bias	Main results	Risk assessment
Wijarnpreecha 2018 [22]	6 [1 case-control & 5 cross-sectional]	38,622	49%	Inconclusive (evaluated only by Funnel plot)	Higher rates of NAFLD in *Hp* infected individuals.	Odds ratio 1.21 (95% CI 1.07–1.37)
Zhou 2019 [23]	15 [2 cohort, 2 case-control & 11 cross-sectional]	97,228	66%	No	Higher rates of NAFLD in *Hp* infected individuals. The results remained robust in sensitivity analysis.	Odds ratio 1.19 (95% CI 1.11–1.29)
Ning 2019 [24]	12 [2 cohort, 2 case-control & 8 cross-sectional]	87,747	90%	Yes	Higher rates of NAFLD in *Hp* infected individuals. The results remained robust in sensitivity analysis.	Odds ratio 1.36 (95% CI 1.22–1.53)
Mantovani 2019 [25]	13 [2 cohort, 2 case-control & 9 cross-sectional]	81,162	59% (for case-control/ cross-sectional studies); 0% (for cohort studies)	No	Higher rates of NAFLD in *Hp* infected individuals. The results remained robust in sensitivity analysis.	Odds ratio 1.20 (95% CI 1.07–1.34) for case-control/cross-sectional studies Odds ratio 1.14 (95% CI 1.05–1.23) for cohort studies

Abbreviations: *Hp*, *Helicobacter pylori*; *Hp*-I, *Helicobacter pylori* infection; NAFLD, nonalcoholic fatty liver disease.
[a] References are presented in publication date order.
[b] Heterogeneity refers to the meta-analysis of the sum of studies.

also showed that age, sex and body mass index, all factors that affect NAFLD, did not significantly affect the association between *Hp*-I and NAFLD [25].

3. Closing remarks and future directions

Since recent meta-analyses of cross-sectional and case-control studies favor an association between *Hp*-I and NAFLD [22–25], more prospective cohort studies that provide the time sequence criterion of causality are needed for the hypothesis to be strengthened. Both conditions are so prevalent, which may have affected some cross-sectional studies supporting an association. Furthermore, although publication bias was not specifically shown in all meta-analyses (Table 1), the publication of original studies with positive results and subsequent meta-analyses of these original studies may have favored the demonstration of a possible association between *Hp*-I and NAFLD. Hopefully, in the future more studies in western populations, usually having lower rates of *Hp*-I, may prove consistency of this association [27]. To further fulfill the Bradford Hill criteria for causality, we would need to have studies proving biological mechanisms and biological gradient, i.e. greater exposure leading to greater incidence and severity of NAFLD. Further, plausibility, i.e. a logical explanation of underlying mechanisms, would be needed. Although some experimental data support the association between *Hp*-I and NAFLD, the molecular pathways have not as yet been fully mapped. As previously summarized [19], *Hp* invasion into gastric and intestinal mucosa increases their permeability, thus facilitating endotoxins passing via the portal vein to the liver; endotoxins and translocated bacteria are involved in NAFLD development and its progression to NASH. In this respect, human β-defensin (hBD)-1 may serve as a biomarker of bacterial translocation in chronic liver disease and *Hp*-I induces hBD-1 mRNA expression, thereby possibly contributing to *Hp*-related defensin-bacterial translocation sequence [28]. Furthermore, *Hp*-I: contributes to a low-grade inflammation by releasing proinflammatory and vasoactive mediators (cytokines and interleukins) and downregulating adiponectin [14]; increases oxidative stress and apoptosis [14]; and is positively associated with IR [29], all considered pathogenetic contributors to NAFLD. Coherence between epidemiological and laboratory findings is needed to support the likelihood of an effect being causal.

Despite accumulating data from observational studies favoring an association between *Hp*-I and NAFLD, studies evaluating the effect of *Hp* eradication on NAFLD are limited and their results are conflicting and inconclusive [30–33]. The lack of paired liver biopsies, the lack of placebo and the small sample size are some of the limitations of the existing interventional studies. The best to-date relevant evidence is provided by Abdel-Razik et al. that showed decrease in NAFLD rates after successful *Hp* eradication [33]; however, this study was also limited by the lack of paired liver biopsies and the lack of control group. Taking all the above under consideration, the initiation of physiology studies in humans, before a pilot proof of concept trial preceding and, if positive, setting the stage for larger randomized clinical trials (RCTs), with placebo arms and paired liver biopsies, evaluating the effect of *Hp* eradication treatment on patients with NAFLD would be reasonable to ponder at this point in time [19]. At this point, it remains unknown what the optimal duration and/or size of such trials would need to be for them to provide robust biological evidence on the potential effect of *Hp* eradication on hepatic steatosis and inflammation and fibrosis, the last considered as the main histological prognostic factor for advanced disease [34].

Summarizing, all recent meta-analyses of cross-sectional and case-control studies favor a positive association between *Hp*-I and NAFLD [22–25]. Moreover, there is a potential association between *Hp*-I and IR syndrome or MetS and associated morbidity. Based on these data, well-designed cohort studies, proof of concept studies and, if those are positive, then RCTs are warranted to show whether *Hp* eradication may have an effect on the prevention or treatment of NAFLD. Mechanistic studies are also warranted to show whether there are molecular pathways linking the two entities. Nonetheless, one needs to keep in mind that NAFLD is a multifactorial disease with many genetic, epigenetic, lifestyle and environmental factors ("hits") contributing to its pathogenesis [35,36]. Thus, even if the association between *Hp* and NAFLD is fully proven and even if *Hp* eradication is shown to be able to provide therapeutic benefit in some *Hp* infected patients [19], an integrated multi-targeted approach towards NAFLD prevention and treatment will still be the most rational [37].

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