Should *Helicobacter Pylori* be eradicated in cirrhotic patients with Peptic Ulcer Disease?

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Abstract. *Helicobacter pylori* is known for being the main cause of Peptic Ulcer Disease (PUD), knowing that a large percentage of cirrhotic patients develops PUD and that cirrhotic patients have shown to have a higher risk of *H. pylori* infection. Consequently, studies were made to contemplate if there was a relation between *H. pylori* infection in cirrhotic patients with the occurrence of PUD, meaning to find if the bacteria eradication could diminish or terminate the development of PUD in cirrhotic patients. Therefore, this narrative review aims to critically evaluate pre-existing studies on the topic, using a search database with no time restriction based on articles on PubMed, resulting in the inclusion of 10 relevant studies. The present narrative review acknowledges a consistent pattern of little to no relation of *H. pylori* infection being a cause for PUD in cirrhotic patients, believing an "ulcerogenic factor" in cirrhosis to be the cause. Studies which stated a positive weak correlation declared to have research limitations. However, some studies were still in favor of implementing *H. pylori* eradication treatment, even if proclaiming no direct relation, stating that the infection could be a cause for PUD complications. While further research is needed to elucidate the cause of PUD in cirrhotic patients and how beneficial *H. pylori* eradication treatment is for those patients, the existing evidence suggest that the therapy might not be that advantageous, with not enough evidence to prescribe nor reject the treatment.

Keywords. *Helicobacter pylori*, Liver cirrhosis, Peptic Ulcer Disease, treatment, eradication.

1. Introduction

Helicobacter pylori (*H. pylori*) is a Gram-negative bacillus, resistant to the activity of gastric juices that affect more than 50% of the human population [1,2]. The infection of this widespread human pathogen causes the increase of cytokines interleukin that leads to stimulation of local inflammatory reaction and aggravates other inflammatory reactions on the human body [2], being the most common cause of peptic ulcer disease (PUD), with 70% of gastric ulcers and 95% of duodenal ulcers associated with *H. pylori* infections [3].

Combining this knowledge, with the high probability of *H. pylori* infections being more frequent among patients with post inflammatory liver cirrhosis [4, 5, 6], and the prevalence of PUD being increased in cirrhotic patients [2, 4, 7], there have been studies on the relation of *H. pylori* eradication in liver cirrhosis on helping to reduce the incidence of PUD in cirrhotic patients [1, 5, 6, 7, 8, 9]. This review has the objective to analyse studies of different views and bring back the debate of the theme.

2. Methods

The present narrative review was based on PubMed articles, using the key words "*H. pylori*", "cirrhotic patients", "peptic ulcer disease", "infection", "therapy" and "eradication". Original observational studies, systematic reviews, and meta-analysis, in English, were inclusion criteria for article selection, with no time restriction. Studies that did not have the terms "cirrhosis" or "cirrhotic", or "*H. pylori*" or "*Helicobacter pylori*" in the title were exclusion criteria.

Under these conditions, 10 studies were found. From these, a descriptive only review was made, as statistical analysis was impractical and not the aim of this study. The review studies were not included in

the Results but were mentioned in the Discussion session.

3. Results

There is some variation between the selected studies in how much *Helicobacter pylori* influences the development of PUD in patients with cirrhosis.

Yang *et al*. found this correlation of *H. pylori* infection in cirrhotic patients with PUD (OR 15.1; 95% CI: 13.9-16.4), yet non-cirrhotic patients had much higher association (OR 48.8; 95% CI: 47.5-50.1). However, African Americans (OR 2.3, 95% CI: 1.5-3.6), Hispanics (OR 2.6, 95% CI: 1.7-4.0) and smokers (OR 1.5, 95% CI: 1.1-2.2) demonstrated stronger association among cirrhotic patients. Despite the correlation, the study used already hospitalised patients for samples, so these results may have a selection bias. [9]

Voulgaris *et al*. also found the presence of H. pylori not related to PUD and to esophageal varices, but to severe cases of cirrhosis (66%), as opposed to the control group (52%). [4]

Kim *et al*., however, reported that the bacterial infection was far more common between PUD in patients without cirrhosis (73,7%) than those with cirrhosis (35,1%). [8]

Chang *et al* stated that the prevalence of *H. pylori* in patients with cirrhosis and PUD is generally less than 60%, suggesting that the pathogenesis of ulcer disease in a substantial proportion of cirrhotic patients may not be related to *H. pylori* infection. However, the same authors in another study declared that early *H. pylori* eradication is associated with a lower risk of recurrent peptic ulcers in cirrhotic patients. [1]

4. Discussion

Peptic Ulcer Disease (PUD) has been frequently found in cirrhotic patients, mainly associated with liver cirrhosis [2, 4, 7]. The pathology of the correlation was unknown, and, although more is known now, it is still inconclusive. The discovery that cirrhotic patients are more susceptible to *Helicobacter pylori* infections [4, 5, 6], the most common cause of PUD, [3] brought the concept of a relation between *H. pylori* infection in cirrhotic patients with peptic ulcer. While some studies considered there may be a weak correlation between both [5, 10], however, most pondered the results as inconclusive or of no association [1, 7, 8, 9, 10].

The importance on discovering if there is a connection between *H. pylori* infection in cirrhotic patients with PUD lies on the fact that cirrhotic patients with PUD have higher risks of peptic ulcer bleeding (PUB), so if there is proof that *H. pylori* infection do cause PUD on cirrhotic patients, the eradication of *H. pylori* could prevent PUB in cirrhotic patients [5].

4.1 Studies in favour of *H. pylori* eradication

Chang *et al.* believes that the treatment is plausible and important, not because of the belief that *H. pylori* infections in cirrhotic patients may be causing PUD, but because the eradication reduces the risk of recurrent complicated peptic ulcers [1]. With that in mind, they defend the usage of triple therapy for *H. pylori* eradication.

Wei *et al*. did a meta-analysis that included 14 studies, concluding that *H. pylori* infection might have a weak relation to PUD in cirrhotic patients. This article showed that, among the 14 analysed studies, 9 showed that there was no significant difference in the incidence of *H. pylori* infection in cirrhotic patients with or without PUD, while the other 5 studies showed that *H. pylori* infection was positively or weakly correlated with PUD in liver cirrhosis. The defence on the usage of eradication therapy relies on the belief that, although not directly involved, *H. pylori* infections might increase the risk of PUD. Therefore, the study believes that there must be an "ulcerogenic mechanism" specific to cirrhotic patients - which may be the true cause of PUD here - being *H. pylori* a possible aggravator. Wei *et al*. also mentions the work of Vergara *et al.,* whose meta-analysis suggested a direct correlation between *H. pylori* infection and PUD in cirrhotic patients, making sure to mention that this result must have occurred due to the diagnosis of *H. pylori* by serology, which is known to have a lower liability, affecting the sample size. [5]

Studies that defended the eradication of *H. pylori*, believing its infection might be the cause for PUD in cirrhotic patients, tended to have very high limitations, making the results controversial. A study made with patients from the largest United States population-based database found a slight prevalence of PUD in cirrhotic patients infected by *H. pylori*, showing contradictory results to previous studies. However, like it is stated in the article, this prevalence is more likely to be associated with complicated hospitalizations in the studied population. This study is stated as very limited, since it mainly relies on hospitalised patients, despite the large population sample. Therefore, the results are not applicable to the general outpatient population. [9]

4.2 Studies that don't believe that there are benefits in *H. pylori* eradication.

Kirchner *et al* concluded to be against a relevant role of *H. pylori* as the etiology of PUD in cirrhotic patients. Moreover, it showed that, despite the seroprevalence of *H. pylori* in cirrhotic patients being high, the gastric mucosal detection of *H. pylori* by Giemsa stain and the urease test results found a

considerably lower presence of the bacteria in those patients. The reason for this discrepancy, between the serological and histological *H. pylori* prevalence, is stated as unknown. Kirchner *et al*. also believes in the existence of "ulcerogenic factors" specific to cirrhotic patients which may be the cause of PUD and could additionally increase the ulcerogenic effects of *H. pylori* infection. The study results indicated that the eradication of *H. pylori* in patients with cirrhosis did not effectively reduce the recurrence of ulcers. Among the "ulcerogenic factors" suggested by the authors, the decrease in gastric prostaglandin E2 levels, hypergastrinemia, portosystemic shunting allowing the ulcerogenic factors to escape hepatic clearance, and the impairment of gastric mucosal defence secondary to portal hypertension and congestive gastropathy - which probably makes the mucosa more susceptible to damage from other agents or allows the reduction of its capacity to repair damage - were the most likely factors of PUD occurrence in cirrhotic patients. Therefore, the article defends that the pathogenic mechanisms of PUD in cirrhotic patients is a multifactorial event, being the role of the etiology of cirrhosis on the prevalence of *H. pylori* up to controversial. [6]

A study made in South Korea examined 288 patients with liver cirrhosis, 322 patients with non-ulcer dyspepsia, and 339 patients with peptic ulcer disease, using for *H. pylori* diagnosis the rapid urease test and Wright-Giemsa staining. They found that the prevalence of *H. pylori* infection did not differ depending on whether there was peptic ulcer or not in patients with liver cirrhosis. Other factors may contribute to the increased risk of peptic ulcer in cirrhotic patients. Kim *et al*. defends in this population study that factors such as reduced prostaglandins, decreased gastric acid secretion, elevated serum gastrin concentration, impaired mucus secretion, reduction in potential difference of the gastric mucosa, and portal hypertensive gastropathy may all play a role in the pathogenesis of peptic ulcer disease in cirrhotic patients, being *H. pylori* infection possibly not that relevant for the pathology. It is important to state that the results found lower prevalence of *H. pylori* infection on cirrhotic patients compared to other studies, stating that racial differences must be considered. [8]

5. Conclusion

The pathogenic pathways for the occurrence of peptic ulcer disease in cirrhotic patients still needs to be further clarified. There is not enough evidence to attribute *Helicobacter pylori* as the main cause for PUD. On the contrary, all studies reviewed agreed that the development of PUD in cirrhotic patients most probably has a multifactorial cause, in which *H. pylori* is not the main factor. Although some of those studies defended *H. pylori* eradication treatment to reduce the risks of complications or recurrence of peptic ulcers in cirrhotic patients, the ones who stated their belief in *H. pylori* infection having a weak correlation between PUD in cirrhotic patients admitted having limitations for their results, being the diagnostic methods used or the sample selection, requiring further studies to confirm their findings. Most studies, however, agreed there is little to no association of *H. pylori* to the occurrence of PUD in patients with cirrhosis, as the prevalence of the bacteria does not significantly vary between patients with and without PUD. In addition, one study even concludes that eradication treatment was not effective in preventing peptic ulcer recurrence. Therefore, there is not yet enough evidence to recommend *Helicobacter pylori* eradication treatment as a way to prevent PUD or its complications in patients with cirrhosis.

Randomised controlled trials comparing treated and non-treated cirrhotic patients with PUD are necessary to clarify this issue. So far there is no high-level evidence to support the treatment.

6. References

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