Editorial: proton pump inhibitor therapy and liver disease progression—more cause for concern?

The long-term consequences of proton pump inhibitor (PPI) therapy have been the subject of much concern. Previous studies have described an increased risk of pneumonia,\(^1\) *Clostridium difficile* colitis,\(^1\) spontaneous bacterial peritonitis\(^2\) and hepatic encephalopathy\(^2\) with PPI therapy but the literature base is heterogeneous and dominated by retrospective analyses.

Li et al explored the association between cumulative PPI dose and disease progression with regards to both development of cirrhosis and hepatocellular carcinoma (HCC) in a large-scale retrospective analysis of patients with pre-cirrhotic hepatitis C (HCV).\(^3\) They observed that PPI use was independently associated with a higher risk of hepatic decompensation in a dose-dependent manner; an observation not made with histamine 2 (H2) antagonist therapy. The implication is that PPI therapy most likely modulates the natural history of HCV via modulation of the gut microbiome, heightened bacterial translocation rates with excessive stimulation of profibrogenic and carcinogenic Toll-like Receptor 4 (TLR4) pathways. While this mechanism is unproven in this study, the evidence for TLR4 signalling in fibrogenesis and carcinogenesis in pre-clinical models is substantial.\(^4\) Furthermore, TLR4 expression by hepatic progenitor cells and biliary epithelial cells correlate positively with fibrosis and inflammation in HCV.\(^5\) The authors also observed that PPI use was associated with a significantly increased risk of HCC. Previous studies have demonstrated increased TLR4 expression in HCC.\(^6\) Lipopolysaccharide has been shown to promote angiogenesis in a murine model of HCC via TLR4 pathways\(^7\) and TLR4 deficiency or germ free conditions are protective against carcinogenesis.\(^8\)

That the effects of PPI therapy were independent of sustained viral response (SVR) is an important observation suggestive that PPI treatment independently influences the natural history of HCV in a manner synergistic with failure of SVR. PPIs also have the potential for drug-drug interactions with agents such as ledipasvir given insolubility at pH > 4. Indeed Tapper et al observed that twice daily PPI dosing was associated with a reduction in SVR12 rates.\(^9\)

The results of this study are interesting for several reasons. First, and most importantly they highlight the significant risk of long-term PPI therapy in this patient group. Second, they suggest that the microbiome plays a key role in modulating the natural history of HCV independently from SVR, implying that gut-specific targets could further prevent decompensation and HCC. The differential effect of PPIs vs H2 antagonist treatment is more likely to be a function of degree of acid suppression rather than non-gastric proton pump inhibition. While PPIs have pleiotropic effects, they are in general anti-inflammatory and anti-oncogenic and therefore do not mechanistically explain the accelerated disease progression observed in this study.

While the study is important and adds to the weight of evidence pointing to the deleterious effects of PPIs, the study is retrospective in nature and requires prospective validation. Nonetheless, the premise that PPIs promote bacterial translocation and accelerate disease progression is relevant and supports the conclusion that PPIs should be stopped or replaced by H2 antagonists where possible.

ACKNOWLEDGEMENTS

Declaration of personal interests: Prof Jalan was the Chief Investigator for a Sequana Medical sponsored trial of alfapump for refractory ascites. Rajiv Jalan has on-going research collaboration with Yaqrit and Ocera. He is also the founder of UCL spin-out company Yaqrit ltd. and Cyberliver ltd.

FUNDING INFORMATION

None.

ORCID

J. Macnaughtan \(\text{http://orcid.org/0000-0003-1211-9298}\)

LINKED CONTENT

This article is linked to Li et al paper. To view this article please visit https://doi.org/10.1111/apt.14391.

REFERENCES

1. Reimer C. Safety of long-term PPI therapy. Best Pract Res Clin Gastroenterol. 2013;27:443-454.
Editorial: non-alcoholic fatty liver disease—it is better to be slender after all

Non-alcoholic fatty liver disease (NAFLD) is one of the most common chronic liver diseases in the world. It is strongly associated with obesity, metabolic syndrome and cardiovascular risk factors. Interestingly to many physicians, a small but significant proportion of patients develop NAFLD despite having a relatively normal body mass index. Moreover, whether lean patients with NAFLD have better or worse histological disease severity and clinical prognosis compared with their overweight/obese counterparts is not well understood.

Sookoian and Pirola have performed commendable work in an effort to fill in our knowledge gaps. In their systematic review with meta-analysis, they compared the histological features of 493 lean and 2209 overweight/obese NAFLD patients pooled from eight hospital-based studies from Europe, Asia and South America. There are a few key findings. First, lean NAFLD patients had less severe liver histological manifestation than overweight/obese patients. Lean patients had significantly lower fibrosis scores. On average, fibrosis scores are 25% higher in the overweight/obese group. This is in keeping with previous studies using noninvasive tests of fibrosis. Lean patients also had lower NAFLD activity scores and steatosis grades. They were also less likely to have nonalcoholic steatohepatitis (NASH), with an odds-ratio of 0.58. Furthermore, a meta-regression analysis suggested that insulin resistance, but not age or waist circumference, explained the higher NAFLD activity score in overweight/obese patients. Although the authors reminded us to interpret this result with caution due to the limited information they had, it seems to correlate with our understanding of NAFLD’s close relationship with insulin resistance.

In summary, this remarkable systematic review furthers our understanding of NAFLD in lean and overweight/obese patients. It also highlights the scarcity of data in this area, and many important questions remain unanswered. Above all, it is unclear if lean NAFLD is part of the spectrum or a unique entity with distinct pathophysiologic mechanisms. There have also been few studies on the clinical outcomes of patients with lean NAFLD. In particular, the proportion of patients developing cardiovascular and liver events may differ in lean and obese patients. In addition, there are essentially no published data on the efficacy of lifestyle intervention and pharmacological treatment in lean NAFLD. For example, it is unclear if weight reduction is an important determinant of treatment response in lean patients. Clinicians do not even know whether they should recommend weight reduction in such patients in the first place. Lean patients are also underrepresented in clinical trials, rendering it difficult to predict the efficacy and safety of various drugs in this population.

The study by Sookoian and Pirola reassures us that the majority of lean patients have less severe NAFLD, and yet severe disease does occur. Until more data are available, the optimal treatment of this special group remains uncertain.

ACKNOWLEDGEMENTS

Declaration of personal interests: None.

FUNDING INFORMATION

None.

AUTHORSHIP

Guarantor of the article: Vincent Wong.

Author contributions: Both authors wrote and approved the final version of the article.