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Proton pump inhibitor use and spontaneous bacterial peritonitis in cirrhosis: An undesirable association?

To the Editor:

It is well known that bacterial infections in cirrhotic patients are associated with significant morbidity and mortality, determining a poor short- and long-term prognosis and a low survival rate [1]. In a recent issue, Terg *et al.* [2] published their experience on the association between proton pump inhibitor (PPI) use and spontaneous bacterial peritonitis (SBP) in cirrhotic patients with ascites. They found that, among 770 hospitalized cirrhotic patients, SBP was diagnosed in 95 (24.7%) out of 394 patients with ascites and that there was no significant difference in the rate of PPI consumption between patients with SBP and those with ascites, but not with SBP (46% *vs.* 42%, $p > 0.05$). Moreover, a high percentage of cirrhotic patients were taking a PPI without any documented indication (42%).

When we evaluated the incidence of SBP in 1030 cirrhotic patients and its effect on survival [3], it was evident that SBP was a common complication in patients with cirrhosis and ascites (11.1%) and that it determined a poor prognosis (21.9% mortality rate). We are currently performing a prospective study assessing the incidence of SBP among cirrhotic outpatients using PPIs. Among 582 cirrhotic patients followed-up for a median time of 5 years, 258 patients developed ascites and were evaluated (Table 1). Among these, 151 were using PPIs (58.5%). SBP developed in 34 of the 151 patients who were using PPIs (22.5%) and in 23 of the 107 patients who were not using PPIs (21.5%, $p = 0.176$). In order to evaluate risk factors for the development of SBP, a multivariate analysis was performed and showed that only the Child-Turcotte-Pugh score was independently associated with the incidence of SBP in cirrhotic outpatients [odds ratio of 2.09, 95% confidence interval of 1.07–4.07; $p = 0.029$]. To the best of our knowledge, there is only one study that evaluated the incidence of SBP in a prospective cohort of cirrhotic outpatients using PPIs and did not find a difference between patients who used PPIs and those who did not [4]. Nevertheless, in that study, the incidence of SBP was evaluated in a small group with only 84 cirrhotic patients, of which 29 had ascites, and SBP was diagnosed in nine patients.

Even though most studies describe an association between the development of SBP and the use of PPIs, their results seem to be limited by their retrospective character. We share the understanding of Terg *et al.* [2], since, despite the indiscriminate use of PPIs in cirrhotic patients, our experience, prospectively evaluating cirrhotic outpatients, showed no significant difference in the incidence of SBP between the group of cirrhotics with ascites who used PPIs and the group who did not.

Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

Authors' contributions

AA Mattos and CV Tovo were responsible for the conception and design; JA John and SAS Miozzo collected and analyzed data; SAS Miozzo wrote the manuscript; AA Mattos and CV Tovo critically reviewed intellectual content; all authors reviewed the manuscript and approved its final version for publication.

Table 1. Characteristics of the 258 patients with cirrhosis and ascites.

	Using PPI (n = 151)	Not using PPI (n = 107)	*p* value
Age; years (mean ± SD)	54.7 ± 11.2	53.1 ± 11.3	0.26[a]
Male gender; n (%)	95 (63.3)	67 (62.6)	>0.99[b]
HCV-related etiology; n (%)	51 (34.5)	36 (34)	0.53[b]
CTP; n (%)			0.37[b]
A	64 (42.4)	39 (36.4)	
B	64 (42.2)	55 (51.4)	
C	23 (15.2)	13 (12.1)	
MELD (mean ± SD)	12.5 ± 3.9	12.7 ± 3.8	0.71[a]
SBP; n (%)	34 (22.5)	23 (21.5)	0.176

SD, standard deviation; n, number of patients; HCV, hepatitis C virus; CTP, Child-Turcotte-Pugh score; MELD, model for end stage liver disease.
[a]Student's t test, [b]Fisher's exact test.

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Evidence supporting a beneficial role of vitamin D in chronic hepatitis C

To the Editor:

We read with interest the recent meta-analysis by Kitson *et al.* [1]. The authors show that baseline vitamin D level is not associated with sustained virologic response (SVR) to pegylated interferon (PegIFN) plus ribavirin therapy in patients with chronic hepatitis C (CHC). Based on this finding, they question [1] the non-skeletal benefits of vitamin D supplements, an essential determinant in regulating bone metabolism in chronic liver disease [2], on CHC. However, as vitamin D deficiency has been identified as a main risk factor for CHC development, we believe that the non-skeletal benefits of this kind of vitamin on patients with CHC cannot be negligible and the conclusions of this meta-analysis [1] needs to be further discussed and researched.

First, the studies included in the meta-analysis by Kitson *et al.* [1] were performed in patients from America, Europe, Australia, or Israel, all of whom were predominantly white in skin color. Interestingly, a community-based cross-sectional study showed that, compared with white people, blacks had lower levels of vitamin D and vitamin D-binding protein [3]. In addition, potential differences were also observed between whites and blacks in relation to the influence of vitamin D status in the degree of hepatic fibrosis in CHC patients [4]. As a consequence, levels of vitamin D and its benefits may vary in individuals with different ethnicity, therefore the irrelevance between vitamin D and SVR, and the ineffectiveness of vitamin D in CHC shown in this study, needs to be also confirmed in other races.

Second, this meta-analysis only summarized eleven studies, seven of which, with 1951 patients, were published articles and the other four were conference abstracts with less convincing evidence. Among the eleven studies, the sole outlier, identified by funnel and forest plots, belonged to a conference abstract. Another coexisting meta-analysis with eleven full-text studies demonstrated that a lower level of vitamin D was significantly associated with a lower probability of SVR in CHC patients receiving Peg-IFNα/ribavirin therapy, especially when a cut-off value of 20 ng/ml for vitamin D deficiency was adopted [5]. Furthermore, a low vitamin D status was also found to be associated with a higher risk of advanced liver fibrosis in these patients [5]. Numerous clinical evidence also suggested that vitamin D supplementation might protect against disease progression and elevate the SVR rate following treatment for CHC [6,7]. Recurrence of hepatitis C after liver transplantation is universal worldwide [8]. In addition to its association with primary CHC, vitamin D insufficiency could also result in a low SVR in patients with recurrent hepatitis C following antiviral therapy while vitamin D supplementation significantly improves the probability of achieving a SVR [8].

Potential mechanisms that link vitamin D and CHC are complex and varied. Treatment with vitamin D reduces the extra- and intracellular levels of hepatitis C virus (HCV) core antigen in a dose-dependent manner [9] and produces calcitriol which could markably inhibit HCV productions [10], suggesting that vitamin D plays a natural antiviral role. In addition, the anti-inflammatory effects by reducing several pro-inflammatory factors like TNF-α, IFN-γ, and IL-17, as well as the anti-fibrotic role of vitamin D [7], might also partly explain the benefits of this vitamin supplementation in CHC.

As there is a global high prevalence of hypovitaminosis D among CHC patients, it is crucial to determine the association between vitamin D status/vitamin D supplementation and outcomes of CHC. Larger, random clinical trials are still required to confirm the important non-skeletal effects of vitamin D in patients with CHC.

Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.