Proton pump inhibitors and the development of diabetes and its complications: a risk hidden in the shadows?

To the editor We really appreciated the very informative article by Castellana et al,[1] published in this issue of *Polish Archives of Internal Medicine* (*Pol Arch Intern Med*), providing an in-depth review on major adverse events observed with the long-term use of proton pump inhibitors (PPIs). We would like to add some information on the association between PPIs and the development of diabetes mellitus (DM) and its related complications.

In a recent prospective analysis of 3 cohorts from the United States in a total of 204 689 subjects without type 2 DM (T2DM) at baseline, it was shown that regular users of PPIs (treatment duration longer than 2 years) had a 26% increase in the risk of T2DM development compared with nonregular users (hazard ratio [HR], 1.26; 95% CI, 1.18–1.35).[2] Notably, the result was consistent across the 3 assessed cohorts. However, participants using PPIs up to 2 years did not experience a significantly increased risk compared to nonregular users.[2]

It is worth emphasizing that previously published observational studies enrolling patients with T2DM have demonstrated that PPIs do not increase the risk of albuminuria or its progression, have conflicting effect on worsening nephropathy, while they definitely increase overall risk of cardiovascular disease.[3,4] As Castellana et al[1] emphasize, PPIs increase overall cardiovascular disease burden and should be replaced in patients at increased cardiovascular risk. Since the major cause of death among patients with T2DM is cardiovascular disease and its components, it seems crucial for the physician to replace a medication that might accelerate disease progression in this patient population.

Of note, PPIs seem not to have a substantial effect on glycemic control, β-cell function, and insulin resistance, as documented in a recent relevant meta-analysis of observational studies in the T2DM population.[5] Therefore, other mechanisms seem to be implicated into the development of DM and related macrovascular complications among regular users. The alteration of gut microbiota might be a potential underlying mechanism, although this remains unclear.[2]

However, since relevant literature is limited, further prospective studies are required to shed more light on this interesting association with potentially major clinical implications.

ARTICLE INFORMATION

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Authors' reply We would like to thank Patoulias and colleagues for their observations, highlighting a possible association between proton pump inhibitors (PPIs) use and diabetes mellitus (DM). Besides the meta-analysis by Yuan et al,[1] including 3 cohorts of health professionals showing that regular PPIs use was likely to be associated with an increased risk of type 2 DM compared with controls, the evidence on such association appears contradictory and inconclusive to date.

Although similar changes in the microbiota phenotype have been reported between PPI users and patients affected by DM, suggesting that gut microbiota may mediate this association, the exact mechanisms have not yet been clarified. On the contrary, it has been suggested that PPIs could be effective as antidiabetic agents, since they increase serum gastrin concentrations, whereby affecting glucose metabolism through promoting β-cell regeneration and also enhancing insulin secretion.[2,3] Indeed, a meta-analysis on this topic found no significant effect on glucose metabolism and insulin resistance in patients with type 2 DM treated with PPIs[4] and population-based cohort studies demonstrated a decreased risk of DM in patients with upper gastrointestinal disease taking PPIs.[5]

Nevertheless, we agree with Patoulias and colleagues that clinicians should prescribe PPIs with caution to those affected by DM, as they represent patients at a high risk for developing cardiovascular complications and, as reported in our review, long-term PPIs use is associated with an increased risk of cardiovascular events.[6] Therefore, we also agree that further research is warranted to investigate the association, if any, between PPIs and DM, to clarify possible underlying mechanisms and their clinical implications.

ARTICLE INFORMATION

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