Letter by Marlicz et al Regarding Article, “Proton Pump Inhibitors Accelerate Endothelial Senescence”

We read with great interest the study by Yepuri et al1 on the effects of proton pump inhibitors (PPIs) on endothelial cells. The investigators exposed human microvascular endothelial cells to PPIs and observed reduced cell proliferation, a decrease in NO, and impaired proteostasis. Moreover, numerous genes involved in cell senescence expression changes and attrition of telomere length were reported, which constituted the hallmark of endothelial dysfunction. Hence, the authors proposed an explanation to link chronic exposure to PPIs with increased risk of chronic disease. The epidemiological reports linking chronic PPIs administration with increased prevalence of myocardial infarction, renal failure, and dementia make this hypothesis plausible. However, the study by Yepuri et al has limitations. It is an in vitro study, which does not reflect the real-life clinical scenario. Besides the effect of drug–cell interaction, the influence of PPIs on the microbiome has not been taken into consideration. Microbiome alterations, the microbial manipulations of the gut microbial ecosystem alterations, knocking down old evolutionary door-keeping mechanisms, which maintain the integrity of intestinal barriers. Subtle mucosal changes, initially subclinical, are responsible for long-term/time-delayed side effects. Prospective data from the Bruneck study provided the first evidence linking the risk of atherosclerosis with bacterial endotoxemia.3

Furthermore, the use of nonsteroidal anti-inflammatory drugs has been associated with increased rates of myocardial infarction, cardiovascular death, and stroke. Capsule endoscopy studies revealed that adding PPIs to nonsteroidal anti-inflammatory drugs resulted in increased frequency of mucosal lesions in the small intestine. PPIs augment the toxic effect of nonsteroidal anti-inflammatory drugs by inducing microbiome alterations.4 Nonsteroidal anti-inflammatory drugs and PPIs affect the gut–vascular permeability. Gut microbiota–derived compounds—trimethylamine and trimethylamine N-oxide—contribute to the development of renal insufficiency and mortality risk in chronic kidney and cardiovascular diseases.5 Probiotics are capable of microbiome alteration. Dietary compounds for gut microbiota–derived compounds—trimethylamine and serum trimethylamine N-oxide—contribute to the development of atherosclerosis.6 Gut microbiota–derived compounds—trimethylamine and serum trimethylamine N-oxide—contribute to the development of cardiovascular diseases.7

Therefore, any minor/subclinical injury to the gut barrier results in significant, albeit delayed, metabolic consequences for the individual. This risk of such injury extends beyond the gastrointestinal tract and influences the condition of any organ associated with vascular system. The PPIs story fits the puzzle and illustrates the following scenario: a minor change in the microenvironment balance (drug–mucosal interplay) can have a large impact on clinical outcomes (cardiovascular disease). These phenomena could be illustrated with theoretical speculation that the flapping of the wings of a distant butterfly could be responsible for forming a hurricane several weeks later, a theory known as the butterfly effect. Validating the risk of chronic PPIs use and vascular morbidity in future prospective trials is a daunting task. The patients should be stratified for medications capable of microbiome alteration. Dietary compounds for gut microbiome manipulation of microbiome alteration. Dietary compounds for gut trimethylamine and serum trimethylamine N-oxide should be identified. Obviously, the study by Yepuri et al and other works into the drug–cell and drug–microbiome interactions make us more vigilant and aware of previously unexpected phenomena and clinical associations.

Disclosures

None.

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