Letter to the Editor

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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 in patients chronically exposed to PPIs have been reported2 and might be responsible for structural/functional alterations of organ-specific barriers. Moreover, the proposed mechanism does not explain the link between PPIs exposure and risk of nongastrointestinal diseases.

Therefore, we would like to offer an alternative hypothesis to link the long-term PPIs administration with increased risk of chronic disease. The gut–vascular barrier, composed of enteral cells and pericytes that remain in close contact with intestinal vascular endothelial cells, controls the dissemination of bacteria into the bloodstream.3 Spadoni et al4 documented that Salmonella typhimurium disrupts the gut–vascular barrier, allowing the spread of bacteria into the systemic circulation. The process is initiated with a decrease of the wnt/β-catenin-inducible gene Axin2 (a marker of stem cell renewal) in gut endothelium. The wnt/β-catenin-conserved systems are also involved in regulation of blood–brain barrier. Of note, PPIs administration is associated with upregulation of mucosal genes responsible for increased pathogen invasion5 and an increased risk for Salmonella enteriditis infection.4 Because the pathogenesis of many chronic diseases revolves around microbiome alterations, the microbial manipulations of wnt/β-catenin pathways might be relevant. Changes in diet/lifestyle contribute to 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.5

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.6 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.7 Probiotics are capable of restoring the intestinal barriers,8 and therapeutic manipulation of microbiota led to decreased severity of myocardial infarction9 and fewer adverse cardiac events in patients with acute coronary syndrome in Roxis study.

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 of nonsteroidal anti-inflammatory drugs by inducing microbiome alterations. 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.

Wojciech Marlicz
Department of Gastroenterology
Pomeranian Medical University
Szczecin, Poland

Anastasios Koulaouzidis
Endoscopy Unit
The Royal Infirmary of Edinburgh
Edinburgh, United Kingdom

Igor Loniewski
Sanprobi Sp. z o.o.
Szczecin, Poland

George Koulaouzidis
Department of Cardiology
Royal Brompton Hospital
London, United Kingdom
References


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Wojciech Marlicz, Anastasios Koulaouzidis, Igor Loniewski and George Koulaouzidis

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