Small Intestinal Bacterial Overgrowth and Coronary Artery Disease: What Is in the CARds?

Christopher Adkins¹ · Ali Rezaie¹

Published online: 6 January 2018
© Springer Science+Business Media, LLC, part of Springer Nature 2018

Small intestinal bacterial overgrowth (SIBO) manifests with a variety of gastrointestinal symptoms, including bloating, flatulence, abdominal pain, nausea, dyspepsia, fatigue, diarrhea, and constipation [1]. SIBO has been implicated as a cause of hepatic encephalopathy and of D-lactic acidosis in patients with short bowel syndrome [2, 3]. Moreover, SIBO is associated with a variety of conditions outside of the gastrointestinal system, including rosacea [4], restless legs syndrome [5], interstitial cystitis [6], and chronic prostatitis [7], and correlates with the level of somatic pain in fibromyalgia [8]. Along these lines, recent studies have reported a link between SIBO and cardiovascular disease.

Ponziani et al. [9] recently published data linking SIBO with subclinical atherosclerosis through the vitamin K-dependent activity of the matrix Gla-protein (MGP), which maintains arterial structure and function through prevention of calcification of vessel walls and the regulation of the extracellular matrix. MGP is carboxylated by the cofactor vitamin K2 to assume its active form. Increased expression of the inactive, uncarboxylated MGP is a marker of low vitamin K2 status, associated with signs of early vascular disease such as arterial stiffness and vascular calcifications, as well as cardiovascular morbidity and mortality. The bulk of vitamin K2 in humans is derived from gut bacterial biosynthesis, and prior studies showed low circulating levels of vitamin K2 in patients with SIBO [10].

In their prospective cohort study, 39 patients were included with SIBO suspected on the basis of gastrointestinal symptoms who also had low cardiovascular disease risk and no prior history of cardiovascular events. All patients underwent a glucose breath test, and 12 (39.0%) were diagnosed with SIBO. The median level of inactive MGP was

significantly increased among patients with SIBO compared to patients without SIBO (9.5 vs 4.2 µg/L, $p = 0.02$). Correspondingly, arterial pulse wave velocity, which increases when there is an increase in arterial stiffness, was increased among patients with SIBO compared to that observed in the group without SIBO (10.25 vs 7.68 m/s, $p = 0.002$). The authors concluded, then, that SIBO is associated with reduced MGP activation as well as arterial stiffening, regarded as important indicators of subclinical atherosclerosis [9].

In the current issue of *Digestive Diseases and Sciences*, Fialho et al. [11] expand upon this work by demonstrating a previously undescribed association between SIBO and coronary artery disease (CAD). In their study, they retrospectively reviewed medical records at a single tertiary care center in order to identify all patients who underwent a glucose hydrogen/methane breath test. Records were cross-referenced to identify 160 patients who had undergone left heart catheterization with coronary angiography at the same center. These records were reviewed to determine the presence and extent of CAD. Importantly, widely recognized risk factors for CAD such as age, smoking, diabetes, hypertension, obesity, dyslipidemia, and metabolic syndrome were identified and adjusted for in this study.

CAD was significantly more prevalent among patients with SIBO compared to those without SIBO (78.9 vs 38.6%, $p < 0.001$), a pattern that persisted even when the interval between breath testing and coronary angiography was narrowed to 6 months or 1 year. Intriguingly, there were also an increased number of vessels affected by CAD among patients with SIBO compared to those without. After adjusting for traditional risk factors for CAD, SIBO continued to be associated with CAD (OR 7.18; 95% CI 3.09–16.67; $p < 0.001$).

The currently accepted criteria suggest that a rise of ≥ 20 p.p.m. from baseline in hydrogen by 90 min should be considered a positive test for SIBO and that an absolute level of ≥ 10 p.p.m. should be considered positive for

✉ Ali Rezaie
ali.rezaie@cshs.org

¹ GI Motility Program, Division of Gastroenterology, Department of Medicine, Cedars-Sinai, 8730 Alden Drive, Thalians Bldg, #E226, Los Angeles, CA 90048, USA

methane [12]. In this study, the glucose breath test was considered positive for SIBO when there was either (1) an increase in hydrogen and/or methane by > 20 parts per million (p.p.m.) above basal value or (2) an increase in hydrogen and/or methane by > 12 p.p.m. between minimal and maximal values after glucose ingestion within three hours after the administration of glucose. These diagnostic criteria may have increased the number of patients testing positive for SIBO. We encourage researchers to use the currently accepted criteria to facilitate the reproducibility and comparability of studies related to SIBO.

Of the 90 patients who tested positive for SIBO in this study, 85 (94.4%) had elevated hydrogen levels and 77 (85.6%) had elevated methane levels, an unusually high rate of methane positivity. Excess methane production even among patients with ongoing GI symptoms is generally 10–20%. The largest study in this field studying 12,183 lactulose breath tests has reported a methane positivity rate of 19.5% [13]. The reasons for the unusually high rate of methane positivity in this study are not immediately evident. Further studies are needed to assess whether methanogenic microorganisms are specifically linked to CAD.

Lastly, as Fialho et al. [11] recognize, despite the association between SIBO and CAD demonstrated in this paper, no conclusions can be drawn about causality of the relationship. While the work by Ponziani et al. linking SIBO and atherosclerosis through the vitamin K-dependent action of MGP suggests a causal relationship, elucidation of an underlying mechanism linking SIBO and CAD is absent in the present study. While large, long-term, controlled prospective studies would be necessary to prove a causal relationship between SIBO and CAD, studies demonstrating possible molecular mechanisms by which SIBO may lead to the development of CAD may be more feasible. Moreover, given the multifactorial nature of CAD, substantial attention should be paid to control for known modifiable and non-modifiable risk factors of CAD.

The medical community are only beginning to understand the complex relationship between gut microbiota, its dysregulation as found in SIBO, and a host of other conditions. Studies such as the one by Fialho et al. should be commended for adding to the characterization of these

interactions. As physicians gain increased understanding of these relationships, the door is opened to the possibility of manipulating gastrointestinal conditions in order to affect the treatment of an ever-expanding number of potentially gut microbiome-associated diseases.

References

1. Rezaie A, Pimentel M, Rao SS. How to test and treat small intestinal bacterial overgrowth: an evidence-based approach. *Curr Gastroenterol Rep*. 2016;18:8.
2. Rai R, Saraswat VA, Dhiman RK. Gut microbiota: its role in hepatic encephalopathy. *J Clin Exp Hepatol*. 2015;5:S29–S36.
3. Bongaerts GP, Tolboom JJ, Naber AH, et al. Role of bacteria in the pathogenesis of short bowel syndrome-associated D-lactic acidemia. *Microb Pathog*. 1997;22:285–293.
4. Drago F, Ciccarese G, Parodi A. Effects of the treatment for small intestine bacterial overgrowth on rosacea. *J Dermatol*. 2017. <https://doi.org/10.1111/1346-8138.13985>.
5. Weinstock LB, Walters AS. Restless legs syndrome is associated with irritable bowel syndrome and small intestinal bacterial overgrowth. *Sleep Med*. 2011;12:610–613.
6. Weinstock LB, Klutke CG, Lin HC. Small intestinal bacterial overgrowth in patients with interstitial cystitis and gastrointestinal symptoms. *Dig Dis Sci*. 2008;53:1246–1251.
7. Weinstock LB, Geng B, Brandes SB. Chronic prostatitis and small intestinal bacterial overgrowth: effect of rifaximin. *Can J Urol*. 2011;18:5826–5830.
8. Pimentel M, Wallace D, Hallegua D, et al. A link between irritable bowel syndrome and fibromyalgia may be related to findings on lactulose breath testing. *Ann Rheum Dis*. 2004;63:450–452.
9. Ponziani FR, Pompili M, Di Stasio E, Zocco MA, Gasbarrini A, Flore R. Subclinical atherosclerosis is linked to small intestinal bacterial overgrowth via vitamin K2-dependent mechanisms. *World J Gastroenterol*. 2017;23:1241–1249.
10. Giuliano V, Bassotti G, Mourvaki E, et al. Small intestinal bacterial overgrowth and warfarin dose requirement variability. *Thromb Res*. 2010;126:12–17.
11. Fialho A, Fialho A, Gursimran K, et al. Association between small intestinal bacterial overgrowth by glucose breath test and coronary artery disease. *Dig Dis Sci*. (Epub ahead of print). <https://doi.org/10.1007/s10620-017-4828-z>.
12. Rezaie A, Buresi M, Lembo A, et al. Hydrogen and methane-based breath testing in gastrointestinal disorders: the North American consensus. *Am J Gastroenterol*. 2017;112:775–784.
13. Chang BW, Pimentel M, Chang C, et al. Prevalence of excessive intestinal methane production and its variability with age and gender: a large-scale database analysis. *Gastroenterology*. 2015;148:S729–S730.