Examining the Root Cause of SIBO

Going Beyond the Bloat

Kiran Krishnan

MICROBIOME LABS

POWERED BY novozymes one HEALTH

IBS-(C and D) AND SIBO

Between 4% and 78% of irritable bowel syndrome (IBS) is caused by SIBO

Most common symptoms of IBS (C and D) are abdominal pain and/or discomfort, irregular stool form and passage, bloating and constipation (hard or lumpy stool) or diarrhea (loose and watery stool).

Most common symptoms of SIBO are abdominal pain or discomfort, bloating, flatulence, loose motion or constipation.

SIBO is defined as increase in bacteria equal to or greater than 10^5 colony forming unit per mL of upper gut aspirate

It is widely accepted that stasis is a feature of SIBO

- What is overgrowing?
- Are they dysbiotic or native microbes to the region?
- Where are they coming from?
- Why are they overgrowing?
- What is driving the stasis?
- What are our natural protections against these issues?

- **MUST BE MULTIFACTORIAL**
- **MUST BE DRIVEN BY COMMON BEHAVIORS**

"60% of diabetic patients yielded oral Enterococcus fecalis, and E. faecium, as opposed to only 6.6% in the controls."

Komiyama EY, et al PLoS One.

"A recent study found that SIBO was present in 43% of diabetic patients with chronic diarrhea, and 75% had a significant improvement in their symptoms after being treated with antibiotics."

Dukowicz AC, et al. Gastroenterol Hepatol (N Y). 2007

What is overgrowing?
Are they dysbiotic of native microbes to the region?

In studying conditions that have SIBO as an established complication, i.e. NAFLD, NASH and hepatic steatosis, the following is well understood:

- The predominant microbes in a healthy small intestine are gram-positive bacteria like Blautia, Rumminococcaceae
- Overgrowth is characterized by a taxa shift to gram-negative bacteria, such as Enterobacteriaceae sp.; Escherichia coli, Klebsiella pneumonia and Proteus mirabilis as well as other gram negatives like Pseudomonas aeruginosa.
- In some cases there can be gram-positives such as Staphylococcus species, Streptococcus species, Enterococcus faecalis, and Enterococcus faecium

Where are they coming from?

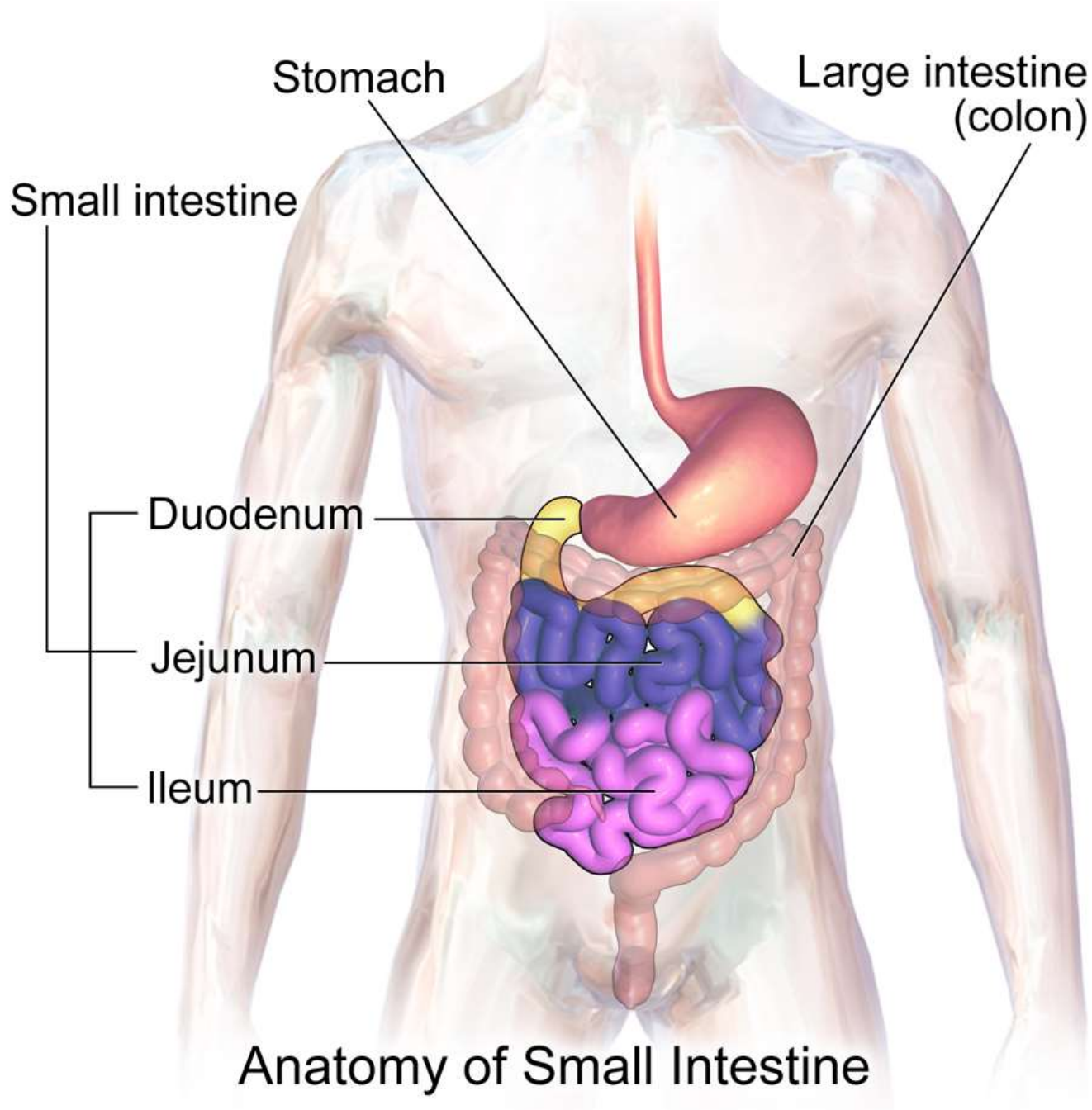
- A number of the SIBO bacteria are naturally found in the colon, but this may be a secondary route
- There is another source, which could be a primary route of these dysbiotic microbes…
- The Mouth!

WHY ARE THEY OVERGROWING?

Natural Protective Mechanisms Against SIBO

- Stomach Acid – gastric barrier
- Bile secretion and bile acid pool
- Bile activation of FXR nuclear receptor
- Peristalsis
- Migrating Motor Complex

https://en.wikipedia.org/wiki/Small_intestine



Anatomy of Small Intestine

Natural Protective Mechanisms Against SIBO

Stomach Acid/Gastric Barrier:

Stress

Zinc deficiency

H.Pylori overgrowth

PPIs and Antacid

STOMACH HCL PRODUCTION

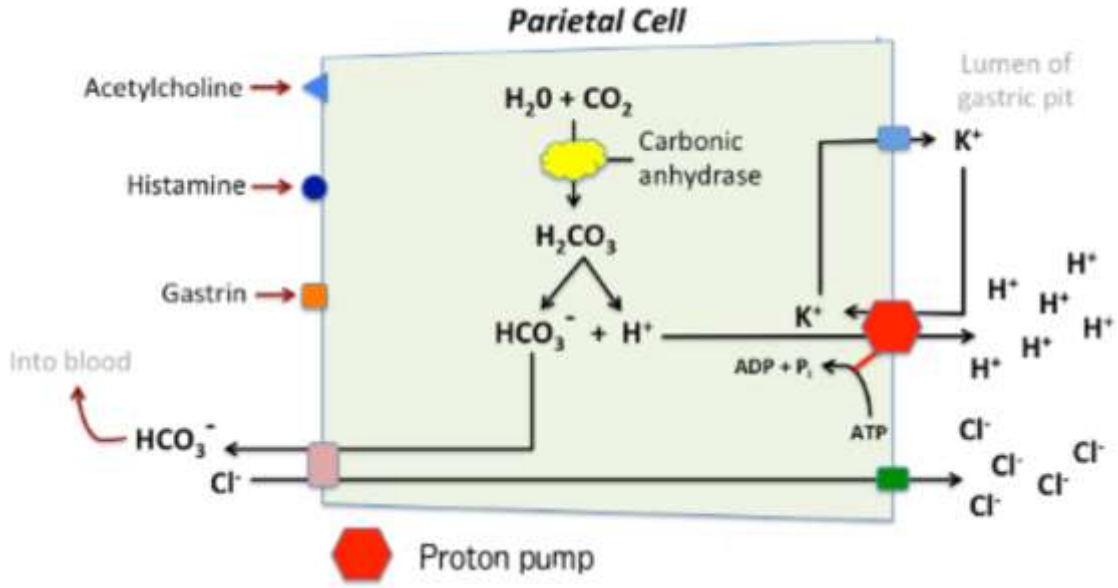
Magnesium Dependent →

STOMACH ACID:

- Potassium (K^+) and chloride (Cl^-) ions diffuse into the canaliculi
- Chloride ions come from recycling of bicarbonate buffering of HCL in the duodenum
- Hydrogen ions are pumped out of the cell into the canaliculi in exchange for the potassium ions – via the H+/K+ ATPase

REGULATION OF HCL SECRETION:

- Histamine, stimulates H2 histamine receptors (most significant contribution).
- Acetylcholine, from parasympathetic activity via the vagus nerve and enteric nervous system, stimulating M3 receptors.
- Gastrin, stimulating CCK2 receptors (least significant contribution, but also causes histamine secretion by local ECL cells)



http://www.vivo.colostate.edu/hbooks/pathphys/digestion/stomach/parietal.html

World Journal of Gastroenterology

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DOI: 10.3748/wjg.v21.i22.6817

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EDITORIAL

What are the effects of proton pump inhibitors on the small intestine?

Shunji Fujimori

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Author contributions: Fujimori S wrote the paper.

Conflict-of-interest: The author has no conflicts of interest to declare.

Several meta-analyses and systematic reviews have reported that patients treated with PPIs, as well as post-gastrectomy patients, have a higher frequency of small intestinal bacterial overgrowth (SIBO) compared to patients who lack the aforementioned conditions. Furthermore, there is insufficient evidence that these conditions induce *Clostridium difficile* infection. At this time, PPI-induced dysbiosis is considered a type of SIBO. It now seems likely that intestinal bacterial flora influence many diseases, such as inflammatory bowel disease, diabetes mellitus, obesity, non-alcoholic fatty liver disease, and autoimmune diseases. When attempting to control intestinal bacterial flora with probiotics, prebiotics, and fecal microbiota transplantation, *etc*., the influence of acid suppression therapy, especially PPIs, should not be overlooked.

"Several meta-analyses and systematic reviews have reported that patients treated with PPIs, as well as post-gastrectomy patients, have a higher frequency of small intestinal bacterial overgrowth (SIBO) compared to patients who lack the aforementioned conditions. "

"At this time, PPI-induced dysbiosis is considered a type of SIBO."

SIBO was detected in **50%** of patients using PPIs, 24.5% of patients with IBS, and 6% of healthy control subjects; there was a statistically significant difference **between** patients using PPIs and those with IBS or healthy control subjects (P .001).

CLINICAL GASTROENTEROLOGY AND HEPATOLOGY 2010;8:504–508

Increased Incidence of Small Intestinal Bacterial Overgrowth During Proton Pump Inhibitor Therapy

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See Editorial on page 480.

BACKGROUND & AIMS: Proton pump inhibitors (PPIs) can cause diarrhea, enteric infections, and alter the gastrointestinal bacterial population by suppressing the gastric acid barrier. Among patients that received long term PPI treatment, we evaluated the incidence of small intestinal bacterial overgrowth (SIBO; assessed by glucose hydrogen breath test [GHBT]), the risk factors for development of PPI-related SIBO and its clinical

when the proximal small intestine becomes colonized by a large number (>10^5/mL colony-forming units) of endogenous symbiotic bacterial flora normally restricted to the colon. Normally SIBO is prevented by the action of the intestinal immune system, gastric acid and pancreatic enzyme secretion, normal intestinal motility, and ileocecal valve function. Interestingly enough, recently it has been reported that as much as 84% of subjects with irritable bowel syndrome (IBS) have a positive lactulose breath test, suggesting the presence of SIBO.[4,5]

The gold standard for SIBO diagnosis is considered aspira-

Natural Protective Mechanisms Against SIBO

Bile secretion and bile acid pool. Bile activation of FXR nuclear receptor:

Gall bladder removal

Obstruction of bile ducts

Liver dysfunction

Dysbiosis

BILE

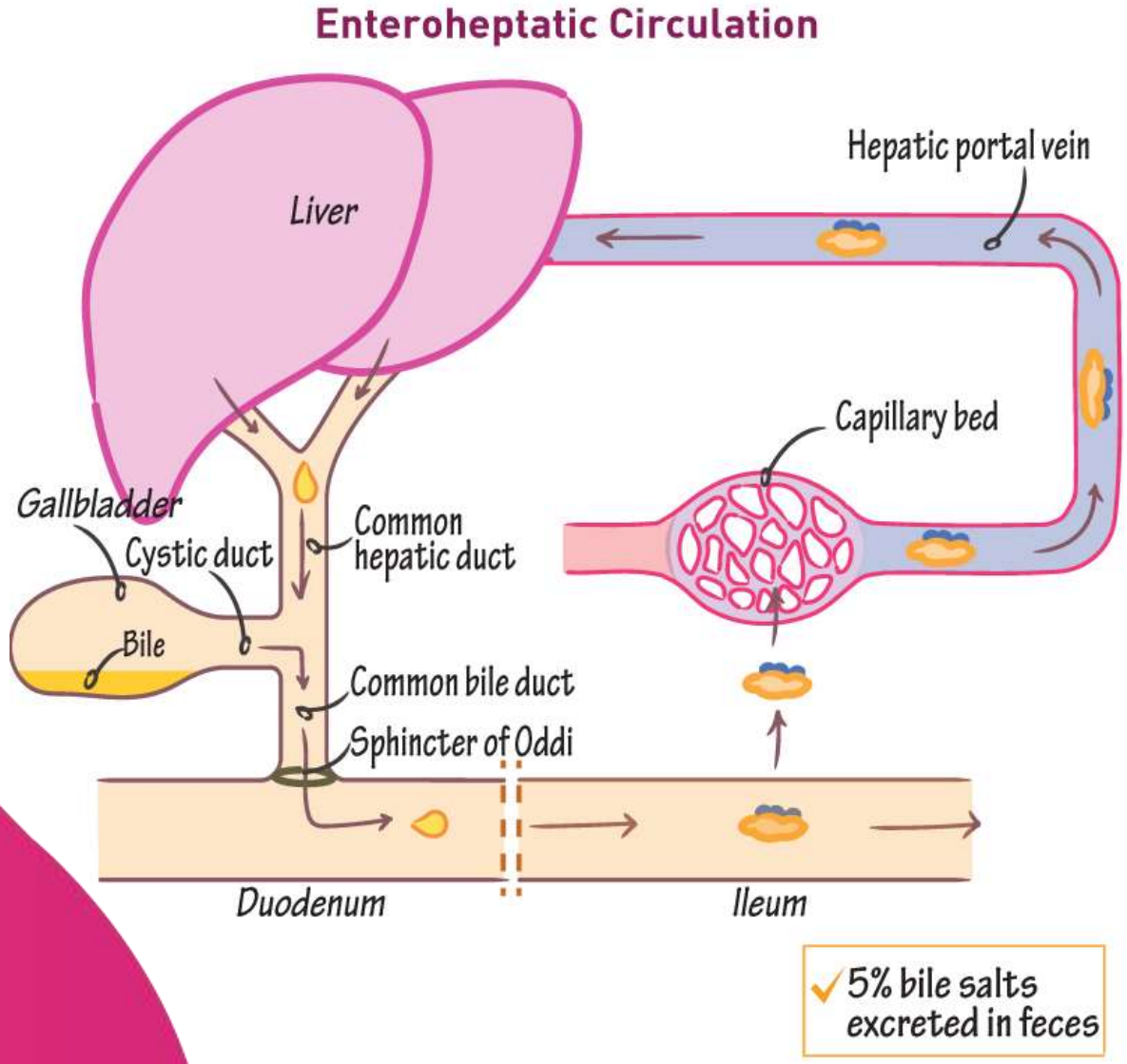
The composition of hepatic bile is 97% water, 0.7% bile salts, 0.2% bilirubin, 0.51% fats (cholesterol, fatty acids, and lecithin)

The facultative and anaerobic commensal bacteria in the small intestine metabolize bile salts through deconjugation and hydroxy group oxidation, resulting in the production of secondary bile salt compounds – NORMALYY 95% OF BILE IS REABSORBED AND ABOUT 5% IS COVERTED TO SECONDARY BILE SALTS.

Bile acids in the ileum and returning to the liver trigger the FXR receptor to stimulate the production of antimicrobial compounds but the EIC

Primary bile acids have been shown to promote the germination of C. difficile spores, while secondary bile acids inhibit the germination of spores into vegetative bacteria

Decreasing levels of bile acids in the gut favor gram-negative members of the microbiome, some of which produce potent LPS, and include potential pathogens.



“Some studies reinforced the concept that small intestinal bacterial overgrowth (SIBO) plays an important role in the pathogenesis of NAFLD through endotoxin of bacteria and tumor necrosis factor (TNF) as effective mediators..”

DE GRUYTER
OPEN

Liver disease symptoms in non-alcoholic fatty liver disease and small intestinal bacterial overgrowth

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Introduction. It seems that there is a relationship between small intestinal bacterial overgrowth (SIBO) and non-alcoholic fatty liver disease (NAFLD). The main objective of this study was to evaluate the prevalence of SIBO among NAFLD patients.

Methods. In this descriptive-analytical cross-sectional study, 98 eligible NAFLD patients were evaluated for SIBO using hydrogen breath test (HBT). They were divided into SIBO-positive and SIBO-negative groups. Demographic, clinical, and laboratory data were obtained.

Results. Based on the HBT, 38 patients (39%) had bacteria overgrowth. There were no significant differences between SIBO-positive and SIBO-negative regarding demographic data and BMI classification ($P > 0.05$). Biochemical variables, the results of abdominal ultrasound, and liver elastography did not show any significant difference between SIBO-positive and SIBO-negative patients ($P > 0.05$). Patients with SIBO were found to have higher rates of bloating, while abdominal pain was more prevalent in SIBO-negative patients ($P < 0.001$).

Conclusions. SIBO is prevalent in NAFLD and associated with bloating in these patients. Further studies are necessary to elucidate if therapeutic manipulation of gut microbiota reduces the risk of NAFLD, fibrosis, and liver cirrhosis.

ORIGINAL PAPER

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Small Intestinal Bacterial Overgrowth Is Associated with Non-Alcoholic Fatty Liver Disease

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ABSTRACT

Background: Changes in gut bacteria play a role in type 2 diabetes mellitus (DM) and hepatic steatosis. There is a lack of studies evaluating the frequency and risk factors for non-alcoholic fatty liver disease (NAFLD) in patients tested for small intestinal bacterial overgrowth (SIBO). **Aim**: To evaluate the frequency of NAFLD and associated risk factors in patients tested for SIBO.

Methods: In this case-control study, 372 eligible patients submitted to glucose hydrogen/methane breath test for SIBO who also had an abdominal imaging study were included. Patients were divided into SIBO-positive and SIBO-negative groups. Clinical, demographic and laboratory variables were evaluated in addition to the presence of NAFLD on abdominal imaging.

Results: Of the 372 eligible patients, 141 (37.9%) were tested positive for SIBO (study group) and 231 (62.1%) were negative for it (control group). NAFLD occurred in 45.4% (64/141) of the study group compared to 17.3% (40/231) of the control group (p<0.001). Patients in the study group were found to have higher rates of elevated aspartate aminotransferase (AST) (20.6% vs. 11.3%; p=0.034) and alanine aminotransferase (ALT) levels (56.0% vs. 40.7%; p= 0.039), type 2 diabetes (23.4% vs. 13.9%; p=0.041), hypertension (54.6% vs. 40.3%; p=0.046) and metabolic syndrome (78.0% vs. 60.2%; p=0.020). In the multivariate analysis, SIBO (odds ratio [OR]: 1.95; 95% confidence interval [CI]: 1.14-3.31; p=0.014), type 2 DM (OR: 3.04; 95%CI: 1.57-5.90; p=0.001) and obesity (OR: 3.58; 95%CI: 1.70-7.54; p=0.001) remained associated with NAFLD.

Of the 372 eligible patients, 141 (37.9%) were tested positive for SIBO (study group) and 231 (62.1%) were negative for it (control group). **NAFLD occurred in 45.4%** (64/141) of the study group compared to 17.3% (40/231) of the control group (p<0.001). Patients in the study group were found to have higher rates of elevated aspartate aminotransferase **(AST)** (20.6% vs. 11.3%; p=0.034) and alanine aminotransferase **(ALT)** levels (56.0% vs. 40.7%; p= 0.039), **type 2 diabetes** (23.4% vs. 13.9%; p=0.041), **hypertension** (54.6% vs. 40.3%; p=0.046) and metabolic syndrome (78.0% vs. 60.2%; p=0.020).

Natural Protective Mechanisms Against SIBO

Peristalsis/Migrating Motor Complex:

- Gastroparesis
- Celiac disease
- Enteropathy
- Diabetes
- Hypochlorhydria
- LPS!

PERISTALSIS AND MMC

"It is our hypothesis that the mechanism of SIBO development in the setting of unsanitary living conditions stems from repeated exposure to abnormal levels of lipopolysaccharide (LPS) via contaminated soil and drinking water, which abrogates the migrating motor complex leading to luminal stasis."

In animal models, Escherichia coli derived LPS has been shown to decrease both the frequency and strength of small intestinal contractions and to eliminate the migrating motor complex

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PMID: 25486880

Pediatric Small Intestinal Bacterial Overgrowth in Low-Income Countries

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Author information ▸ Copyright and License information Disclaimer

Abstract

Go to:

Small intestine bacterial overgrowth (SIBO) occurs when colonic quantities of commensal bacteria are present in the small bowel. SIBO is associated with conditions of disrupted GI motility leading to stasis of luminal contents. Recent data show that SIBO is also found in children living in unsanitary conditions that do not have access to clean water. SIBO leads to impaired micronutrient absorption and increased GI permeability, both of which may contribute to growth stunting in children. SIBO also disrupts mucosal immunity and has been implicated in oral vaccination underperformance and the development of celiac disease. SIBO in the setting of the impoverished human habitat may be an under recognized cause of pediatric morbidity and mortality in the developing world.

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PERISTALSIS AND MMC

Am J Physiol. 1999 Jan;276(1):R59-68. doi: 10.1152/ajpregu.1999.276.1.R59.

Induction of endogenous tumor necrosis factor-alpha: suppression of centrally stimulated gastric motility.

Hermann GE[1], Tovar CA, Rogers RC.

Author information

Abstract

Gastric stasis is frequently seen in conjunction with critical infectious illness, chronic inflammatory disorders, radiation sickness, and carcinogenesis. These conditions are associated with elevated circulating levels of the cytokine tumor necrosis factor-alpha (TNF-alpha). The present studies examined the relationship between endogenously produced TNF-alpha and the central neural mechanisms that augment gastric motility. Systemic lipopolysaccharide (LPS) was employed to induce TNF-alpha production in thiobutabarbital-anesthetized rats. Sixty minutes after intravenous LPS injection, gastric motility could not be stimulated by a potent centrally acting gastrokinetic stimulant, thyrotropin-releasing hormone (TRH). This failure to elicit gastric motility via central mechanisms coincided with high circulating levels of TNF-alpha. However, intravenous injections of bethanecol, a peripherally acting cholinergic agonist with direct gastrokinetic effects, were still able to elicit normal increases in gastric motility in the presence of TNF-alpha and LPS. Therefore, the inability to stimulate gastric motility via central TRH could not be attributed to the direct inhibitory effects of either LPS or TNF-alpha on the stomach. If the production of endogenous TNF-alpha was suppressed via the use of urethan as the anesthetic agent, then intravenous injections of LPS were no longer effective in suppressing gastric motility. Thus these effects on gastric motility are not directly attributable to LPS nor are they due to direct effects on the gastric smooth muscle. Our previous study demonstrated that microinjection of femtomole quantities of TNF-alpha in the brain stem dorsal vagal complex (DVC) can modulate gastric motility. This central TNF-alpha effect on gastric motility was dose dependent and required an intact vagal efferent pathway. The results from these two studies suggest that systemically produced TNF-alpha may gain access to the DVC to modulate gastric function.

Systemic LPS and induction of TNF-alpha stopped gastric motility, within 60 minutes of injecting LPS. It was **not possible** to elicit gastric motility via a potent centrally acting gastrokinetic stimulant (thyrotropin-releasing hormone). They showed that the effect of LPS and TNF-alpha **acted on brain stem dorsal vagal complex (DVC), causing centralized aberration of motility.**

PERISTALSIS AND MMC

Am J Physiol Gastrointest Liver Physiol. 2002 Sep;283(3):G634-9.

LPS-induced suppression of gastric motility relieved by TNFR:Fc construct in dorsal vagal complex.

Hermann GE[1], Tovar CA, Rogers RC.

Author information

Erratum in
Am J Physiol Gastrointest Liver Physiol 2002 Nov;283(5):following table of contents.

Abstract

Our previous studies suggested that the cytokine tumor necrosis factor-alpha (TNF-alpha) may act within the neural circuitry of the medullary dorsal vagal complex (DVC) to affect changes in gastric function, such as gastric stasis, loss of appetite, nausea, and vomiting. The definitive demonstration that endogenously generated TNF-alpha is capable of affecting gastric function via the DVC circuitry has been impeded by the lack of an antagonist for TNF-alpha. The present studies used localized central nervous system applications of the TNF-adsorbant construct (TNFR:Fc; TNF-receptor linked to the Fc portion of the human immunoglobulin IgG1) to attempt to neutralize the suppressive effects of endogenously produced TNF-alpha. Gastric motility of thiobutabarbital-anesthetized rats was monitored after systemic administration of lipopolysaccharide (LPS) to induce TNF-alpha production. Continuous perfusion of the floor of the fourth ventricle with TNFR:Fc reversed the potent gastroinhibition induced by LPS, i.e., central thyrotropin-releasing hormone-induced increases in motility were not inhibited. This disinhibition of gastric stasis was not seen after intravenous administration of similar doses of TNFR:Fc nor ventricular application of the Fc fragment of human immunoglobulin. These results validate our previous studies that suggest that circulating TNF-alpha may act directly within the DVC to affect gastric function in a variety of pathophysiological states.

In a follow up study, the authors again induced inhibition of gastric motility with systemic administration of LPS, which stimulated endogenous TNF-alpha production. An anti-TNF compound was able to restore central thyrotropin-releasing hormone increase in motility. Showing that endogenous TNF-alpha from LPS immune activation likely acts directly within the DVC leading to central motility aberration.

HOW COMMON IS LPS ENDOTOXEMIA?

WJGP World Journal of Gastrointestinal Pathophysiology

Submit a Manuscript: http://www.wjgnet.com World J Gastrointest Pathophysiol 2017 August 15; 8(3): 117-126

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ORIGINAL ARTICLE

Prospective Study

Oral spore-based probiotic supplementation was associated with reduced incidence of post-prandial dietary endotoxin, triglycerides, and disease risk biomarkers

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Author contributions: McFarlin BK designed the study, collected data, interrupted findings, and prepared manuscript; Henning AL, Bowman EM, Gary MM and Carbajal KM collected data, interrupted findings, and prepared manuscript.

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Manuscript source: Invited manuscript

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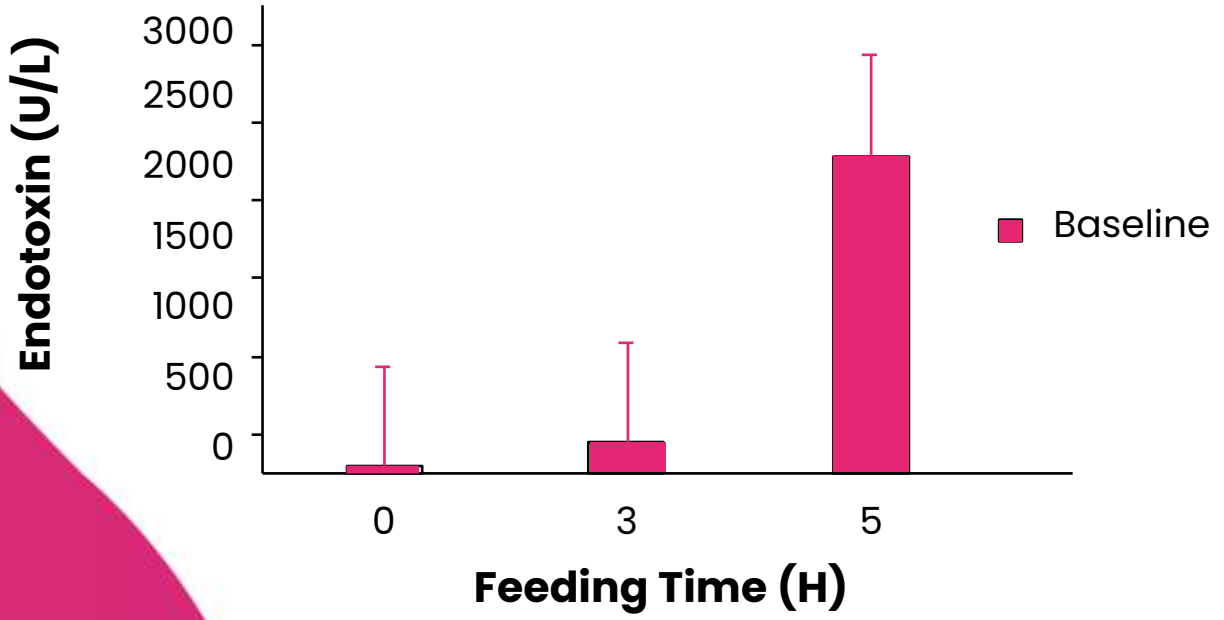
Received: January 26, 2017
Peer-review started: February 8, 2017

The effect of 30-days of probiotic supplementation on post-prandial responses to a high-fat meal
Principal Investigator: Brian K. McFarlin, PhD, FACSM, FTOS University of North Texas



INCREASED FAT INTAKE IN SIBO CAN MAKE THE CONDITION WORSE!

UNT UNIVERSITY OF NORTH TEXAS

Comprehensive SIBO Treatment

- In addition to targeting the over-growth with antibiotics and antimicrobials, it becomes important to address the underlying issue of stasis involving LPS mediated, systemic TNF-alpha upregulations and the central motility aberration that follows.
- Prokinetics won't help much if the DVC is compromised. To stop recurrence, LPS endotoxemia has to be addressed
- Low HCL and Gastroparesis must be addressed
- Liver support is critical
- To reduce the risk of comorbidities, mucosal damage and mucosal inflammation has to be addressed
- Colonic, saccharolytic bacteria have to be supported to prevent further pathology and secondary complications

SUPPLEMENT FACTS

Serving Size 1 Capsule
Servings Per Container 60

Amount Per Serving	% Daily Value
Artichoke leaf extract	320mg †
Gutgard® licorice flavonoids	75mg †
Ginger root extract (20% gingerols)	30mg †

† Daily values not established.

OTHER INGREDIENTS: Cellulose, vegetable capsule (cellulose and water).

GINGER ROOT EXTRACT (20%)

30 mg

Accelerates gastric emptying and soothes nausea

GUTGARD® LICORICE FLAVONOIDS

75 mg

Protects gastric mucosa and balances H. Pylori levels

ARTICHOKE LEAF EXTRACT

320 mg

Stimulates bile production and balances cholesterol levels

Recommended SIBO Protocol

If doing an antimicrobial phase, use MegaIgG and HU58 during the antimicrobial phase

Use FodMate + MegaGuard with Meals

Towards the end of the antimicrobial phase, start with MegaSporeBiotic and MegaMucosa

As typical symptoms are significantly reduced, add in MegaPre in small amounts. Enemas can be considered. Maintain MegaSporeBiotic and MegaMucosa.

THANK YOU


zenbiome
COPE
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Wheat
Rescue
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Dietary Supplement
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SKINCARE
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