PREVALENCE AND DETERMINANTS OF SMALL INTESTINE BACTERIAL OVERGROWTH (SIBO) AND CARBOHYDRATE INTOLERANCE IN SYMPTOMATIC FUNCTIONAL BOWEL DISORDER (FBD)

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TABLE OF CONTENTS

LIST OF ABBREVIATIONS

BMI: Body Mass Index

CFU: Colony Forming Unit

CH_4: Methane

CI: Confidence Interval

CNS: Central Nervous System

FBD: Functional Bowel Disorder

FD: Functional Dyspepsia

FGID: Functional Gastrointestinal Disorder

GI: Gastrointestinal

GP: General Practitioner

H_2: Hydrogen

HUSM: Hospital Universiti Sains Malaysia

IBS: Irritable Bowel Syndrome

OR: Odd Ratio

PPI: Proton Pump Inhibitor

ppm: parts-per-million

SIBO: Small Intestinal Bacterial Overgrowth

WHO: World Health Organization

ABSTRAK

Pengenalan: *Functional Bowel Disorder* (FBD) bergejala adalah suatu keadaan yang lazim ditemui oleh pegawai kesihatan. Pesakit-pesakit ini selalunya mempunyai kondisi lain yang wujud sama, seperti *Small Intestinal Bowel Overgrowth* (SIBO) dan intolerensi karbohidrat. SIBO dan intolerensi karbohidrat akan memudaratkan lagi gejala FBD. Dengan adanya ujian nafas hidrogen sekarang, kondisi SIBO dan intolerensi karbohidrat boleh dikenalpasti dengan mudah. Tambahan lagi, ujian tersebut selamat dikendalikan. Ini membolehkan isu FBD refraktori diselesaikan dan menambahbaik gejala-gejala pesakit yang mengalami FBD.

Kaedah: Kajian keratan rentas retrospektif ini melibatkan subjek yang melebihi umur 12 tahun dan pernah melalui ujian nafas hidrogen di Hospital Universiti Sains Malaysia (HUSM) Kubang Kerian daripada 1 Januari 2015 sehingga 31 Julai 2019. Data telah diperolehi dari rekod subjek dan dianalisis untuk kewujudan SIBO dan intolerensi karbohidrat. Kajian juga telah menganalisis factor-faktor perkaitan dengan menggunakan ujian regresi logistik berganda and mudah.

Hasil kajian: Sejumlah 104 subjek telah dianalisis. Daripada jumlah subjek tersebut, 51.9% (n=54) adalah perempuan dan 48.1% (n=50) lelaki. Umur min kesemua peserta adalah 49.76 tahun. Kewujudan SIBO, intolerensi fruktosa /malabsorpsi, dan intolerensi laktosa /malabsorpsi adalah pada 20%, 39% dan 66% masing-masing. Terdapat perkaitan ketara antara umur ($p \leq 0.050$) dan *diabetes mellitus* ($p < 0.001$) dengan SIBO. Kajian tidak mengesan sebarang faktor perkaitan ketara untuk intolerensi karbohidrat.

Rumusan: Hasil kajian menunjukkan tahap intolerensi laktosa / malabsorpsi yang lebih tinggi di kalangan FBD berbanding dengan intolerensi fruktosa /malabsorpsi dan SIBO dalam kajian ini. Tidak banyak factor perkaitan ketara dikesan untuk tiga kondisi yang dikaji.

ABSTRACT

Background: Symptomatic functional bowel disorder (FBD) has been a quite common presentation to the healthcare personnel. These patients often have other conditions that co-exist, such as small intestinal bacterial overgrowth (SIBO) and carbohydrate intolerance. SIBO and carbohydrate intolerance tend to worsen the symptoms of FBD. With the hydrogen breath test readily available nowadays, we can easily diagnose SIBO and carbohydrate intolerance. The test is rather simple and safe. This allow us to tackle the issue of refractory FBDs and improving the symptoms of those who has FBDs.

Methods: This retrospective cross-sectional study involved all subjects who were more than 12 years old and had undergone hydrogen breath test at Hospital Universiti Sains Malaysia (HUSM) Kubang Kerian from 1st January until 1st July 2019. The data were obtained from the subject's medical record. We analysed the prevalence of SIBO and carbohydrate intolerance. We also analysed the associated factors using simple and multiple logistic regression.

Results: A total of 104 subjects were analysed. Among the 104 subjects, females were 51.9% (n=54), and males were 48.1% (n=50). The mean age of all the participants was 49.76 years old. The prevalence of SIBO, fructose intolerance /malabsorption, and lactose intolerance /malabsorption were 20%, 39% and 66% respectively. There were significant association between age ($p \leq 0.050$) and diabetes mellitus ($p < 0.001$) with SIBO. There were no significant association factors found for the carbohydrate intolerance.

Conclusion: It appears that lactose intolerance /malabsorption has higher prevalence in FBD compared to fructose intolerance /malabsorption and SIBO in this study. Not many significant associated factors for the three conditions that we studied were obtained.

CHAPTER 1: INTRODUCTION

The clinicians have been encountering various types of patients throughout their career. One of the common presentations of the patients to the doctors would be abdominal symptoms. These abdominal symptoms were described in many ways, such as belching, bloating, pain, flatus, indigestion, etc. However, not all persons with the abdominal symptoms, which were less than half of them, would seek medical advice. In the western world, it was estimated at 12% and 30% of all cases in the general practitioner (GP) clinics and gastroenterology clinics, respectively (Rosemore & Lacy, 2002). About half of these patients would be diagnosed to have functional bowel disorders (FBDs).

FBDs are a part of the bigger functional gastrointestinal disorders (FGIDs). FGIDs are disorders of gut-brain interaction, and by definition, is a group of disorders classified by GI symptoms related to any combination of the following: motility disturbance, visceral hypersensitivity, altered mucosal and immune function, altered gut microbiota, and altered central nervous system (CNS) processing (Drossman, 2016). FGIDs are further classified based on their anatomical region, i.e. esophageal, gastroduodenal, bowel, biliary, anorectal plus functional abdominal pain. FBDs are mainly confined to the middle or lower GI tract. These include irritable bowel syndrome (IBS), functional abdominal bloating, functional constipation, functional diarrhea, and unspecified functional bowel disorder (Longstreth et al., 2006; Thompson et al., 1999). The diagnosis of a FBD is made when the symptoms present for 12 weeks or more within the past 12 months; the 12 weeks need not be consecutive. It is always presumed a structural or biochemical explanation for the symptoms is absent (Thompson et al., 1999).

Hydrogen and methane breath tests are inexpensive, simple, and non-invasive tests that can be used for detection of excess bacteria in the small intestine and evaluation of carbohydrate maldigestion. Back in the 1970s, the breath test was used to estimate lactase

deficiency (Rana and Malik, 2014). In 1975, Newcomer and associates has used this test to study lactose malabsorption. In recent years, hydrogen breath test is gaining its popularity due to the simplicity and non-invasiveness. The uptake of the breath test in the Asian setting only started the past decade (Yao et al., 2018). The principle of this test is, when we ingest dietary carbohydrate, the intestinal bacteria will ferment the undigested carbohydrate, and produces various gases such as hydrogen and methane. Though some of the gas produced expelled as flatus or in making other molecules such as sulphides, acetate and short chain fatty acids but most of the gas is absorbed in the large intestine into blood stream. The hydrogen-containing blood travels to the lungs and is exchanged into the airways and breathed out. The breath sample can be obtained, and analysed by a breath-testing machine (Rao and Lee, 2015; Ghoshal, 2011; Lindberg, 2009; Rana and Malik, 2014).

Functional dyspepsia (FD) and IBS are the common FGIDs. FD causes postprandial fullness, early satiation, or epigastric pain or burning. Whereas IBS will have symptoms of abdominal pain or discomfort associated with bowel habit changes and disordered defecation (Choi and Chang, 2016). Generally, FD has prevalence of 20% to 30%, while IBS has the prevalence of 10% to 20% (Tack et al., 2006; Lee et al., 2012). Frequently, they may overlap. It is thought that small intestinal bacterial overgrowth (SIBO) and carbohydrate intolerance, particularly fructose and lactose, also play a role in causing abdominal symptoms in FGIDs. Small bowel aspiration for quantitative culture has traditionally been used for the diagnosis of SIBO. Although there is no standard definition of a positive culture with studies using from more than 103 CFU/mL to more than 107 CFU/mL to define SIBO, a bacterial count of 105 CFU/mL or more has been accepted for the diagnosis of SIBO. However, this test is not feasible as it is costly, invasive, potential for sample contamination, and missing bacterial overgrowth in the distal small

bowel. Furthermore, some the luminal bacteria may go uncultured (Choi and Chang, 2016). Factors that can fostered the occurrence of SIBO can be divided into anatomical (stenoses – strictures, blind loop, diverticulum, duplication), associated with disturbances to the function (diabetic autonomic neuropathy, intestinal pseudo-obstruction syndrome, systemic scleroderma, achlorhydria, slow gastrointestinal motility), and conditions predisposing to the development of bacteria (primary and secondary immunodeficiency, intestinal fistulas, achlorhydria, removal of the ileocecal valve) (Miazga et al., 2015). Jejunal aspirate cultures commonly grew gram negative bacilli and Enterobacter (Ghoshal et al., 2017). Proliferation of the bacteria leads to fermentation of disaccharides and short-chain fatty acid, which produces symptoms such as bloating and diarrhea. The excessive bacteria also cause deconjugation of bile salts, result in fat absorption disturbance. Thus, this will cause malabsorption.

Lactose is a disaccharide present in the mammalian milk. Lactose needs to be hydrolyzed into glucose and galactose for it to be absorbed. This is done by lactase at the intestinal brush border in the small intestine. Lactose intolerance tend to be more prevalent in Asian than the Caucasian (Sahi, 1994; Lomer et al., 2008). Majority of the all the 3 major ethnic group in Malaysia are lactose intolerant (Asmawi et al., 2006). Lactase reduction occurs with advancing age. Neither prolonged ingestion of lactose in humans nor exclusion of lactose from the diet influences the capacity of the small intestine to absorb lactose, which strongly suggests that the enzyme activity is not directly regulated by availability of substrate. Decrement of lactase expression may also due to small bowel bacterial overgrowth, infectious enteritis, or mucosal damage due to coeliac disease, inflammatory bowel disease, drugs, gastrointestinal surgery, short bowel syndrome, or radiation enteritis (Lomer et al., 2008; Misselwitz et al., 2019; Goh et al., 2018).

Fructose is a monosaccharide that is naturally present in food and vegetables. Its absorption process does not require any enzymatic system. It is slowly absorbed across the intestinal epithelium by carrier-mediated facilitated diffusion, which is an energy-independent process. Not all fructose will be absorbed completely, even in the healthy subjects. Reasons for the absorptive capacity of fructose varying widely within the population remain unknown.

CHAPTER 2: OBJECTIVES OF THE STUDY

2.1 General Objective

To determine the prevalence and factors of SIBO and carbohydrate intolerance via hydrogen breath test among patients with symptomatic FBD.

2.2 Specific Objectives

i) To determine the prevalence of SIBO via hydrogen breath test among patients with symptomatic FBD.

ii) To determine the prevalence of lactose intolerance via hydrogen breath test among patients with symptomatic FBD.

iii) To determine the prevalence of fructose intolerance via hydrogen breath test among patients with symptomatic FBD.

iv) To determine the factors associated with SIBO in symptomatic FBD.

v) To determine the factors associated with lactose intolerance in symptomatic FBD.

vi) To determine the factors associated with fructose intolerance in symptomatic FBD.

CHAPTER 3: MANUSCRIPT

Title Page

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ABSTRACT

Background: Symptomatic functional bowel disorder (FBD) has been a quite common presentation to the healthcare personnel. These patients often have other conditions that co-exist, such as small intestinal bacterial overgrowth (SIBO) and carbohydrate intolerance. SIBO and carbohydrate intolerance tend to worsen the symptoms of FBD. With the hydrogen breath test readily available nowadays, we can easily diagnose SIBO and carbohydrate intolerance. The test is rather simple and safe. This allow us to tackle the issue of refractory FBDs and improving the symptoms of those who has FBDs.

Methods: This retrospective cross-sectional study involved all subjects who were more than 12 years old and had undergone hydrogen breath test at Hospital Universiti Sains Malaysia (HUSM) Kubang Kerian from 1st January 2015 until 1st July 2019. The data were obtained from the subject's medical record. We analysed the prevalence of SIBO and carbohydrate intolerance. We also analysed the associated factors using simple and multiple logistic regression.

Results: A total of 104 subjects were analysed. Among the 104 subjects, females were 51.9% (n=54), and males were 48.1% (n=50). The mean age of all the participants was 49.76 years old. The prevalence of SIBO, fructose intolerance /malabsorption, and lactose intolerance /malabsorption were 20%, 39% and 66% respectively. There were significant association between age ($p=0.050$) and diabetes mellitus ($p<0.001$) with SIBO. There were no significant association factors found for the carbohydrate intolerance.

Conclusion: It appears that lactose intolerance /malabsorption has higher prevalence in FBD compared to fructose intolerance /malabsorption and SIBO in this study. Not many significant associated factors for the three conditions that we studied were obtained.

Keywords: *functional bowel disorder, hydrogen breath test, SIBO, carbohydrate intolerance, prevalence, FGID*

INTRODUCTION

Functional bowel disorders (FBD) are a part of the bigger functional gastrointestinal disorders (FGIDs). FGIDs are disorders of gut-brain interaction, and by definition, is a group of disorders classified by gastrointestinal (GI) symptoms related to any combination of the following: motility disturbance, visceral hypersensitivity, altered mucosal and immune function, altered gut microbiota, and altered central nervous system (CNS) processing.[1] FGIDs are further classified based on their anatomical region, i.e. esophageal, gastroduodenal, bowel, biliary, anorectal plus functional abdominal pain.[2] FBDs are mainly confined to the middle or lower GI tract. These include irritable bowel syndrome (IBS), functional abdominal bloating, functional constipation, functional diarrhea, and unspecified functional bowel disorder.[3,4] Less than half of the persons with abdominal symptoms, such as belching, bloating, pain, flatus, indigestion, and etc., would seek medical advice.[5,6] In the western world, it was estimated at 12% and 30% of all cases in the general practitioner (GP) clinics and gastroenterology clinics, respectively.[7] About half of these patients would be diagnosed to have FBDs.[8] Two or more FGIDs often overlap each other.[2,9] The diagnosis of a FBD is made when the symptoms present for 12 weeks or more within the past 12 months; the 12 weeks need not be consecutive.[4] It is always presumed a structural or biochemical explanation for the symptoms is absent. It is thought that small intestine bacterial overgrowth (SIBO) and carbohydrate intolerance, particularly fructose and lactose, also play a role in causing abdominal symptoms in FGIDs.[10-12] Small bowel aspiration for quantitative culture has traditionally been used for the diagnosis of SIBO. However, this test is not feasible as it is costly, invasive, potential for sample contamination, and missing bacterial overgrowth in the distal small bowel.[9] Literature regarding SIBO in Asian region remain scarce. With the emergent of hydrogen breath test in the Asian setting, it is gaining its popularity due to its simplicity and non-

invasiveness.[13] Hydrogen and methane breath tests are inexpensive, simple, and non-invasive tests that can be used for detection of excess bacteria in the small intestine and evaluation of carbohydrate maldigestion.[14-16] In 1975, Newcomer and associates has used this test to study lactose malabsorption.[17] The principle of this hydrogen breath test is, when we ingest dietary carbohydrate, the intestinal bacteria will ferment the undigested carbohydrate, and produces various gases such as hydrogen and methane. Though some of the gas produced expelled as flatus or in making other molecules such as sulphides, acetate and short chain fatty acids but most of the gas is absorbed in the large intestine into blood stream. The hydrogen-containing blood travels to the lungs and is exchanged into the airways and breathed out. The breath sample can be obtained, and analysed by a breath-testing machine.[6,14-16] Malabsorption is defined as a rise in hydrogen (H_2) value ($\geqslant$20 ppm) or methane (CH_4) values ($\geqslant$10 ppm) above fasting base line value or a sustained rise in H_2 or CH_4 of 5 ppm over three consecutive breath samples. Intolerance is the presence of malabsorption with an increase of >2 over baseline using a symptom score index. SIBO is defined as fasting values of H_2 or CH_4 >40 ppm, or a rise in H_2 value ($\geqslant$20 ppm) or CH_4 values ($\geqslant$10 ppm) above fasting base line value or a sustained rise in H_2 or CH_4 of 5 ppm over three consecutive breath samples.[6]

The aim of this study is to determine the prevalence and factors of SIBO and carbohydrate intolerance via hydrogen breath test among patients with symptomatic FBD.

METHODOLOGY

This is a retrospective cross-sectional study conducted in Hospital Universiti Sains Malaysia (HUSM) Kubang Kerian. Data for patient that had undergone hydrogen breath test at the HUSM from 1st January 2015 untill 31st July 2019 were obtained from patient

medical record at the HUSM medical record unit. All patients with the age of more than 12 years old were included in this study. Data were prepared in Microsoft Excel file.

Hydrogen Breath Test

Hydrogen breath test is an outpatient test which requires patient well-prepared prior to the test. The test takes about 3-4 hours to complete. For non-diabetic patients, carbohydrate that is utilized are lactose, fructose, and glucose; whereas in diabetic patients, only lactose and fructose are used. Prior to the test, patients are required to fill up the pre-evaluation breath test questionnaire. During the test, patients are needed to fill up the symptom scale index every 30-60mins until termination of test. The breath of patients is collected in a syringe/bag every 30-60mins. Then, it is introduced into the Quintron BreathTracker Analyzer to quantify the amount of H_2 and CH_4.

Statistical Analysis

Data were entered and analysed using SPSS version 22. Numerical data were presented as mean (SD) or median (IQR) based on their normality distribution. Categorical data were presented as frequency (percentage). Descriptive analysis was used to analyse the prevalence of SIBO, lactose and fructose intolerance /malabsorption. Simple Logistic Regression test was used to examine the association between each socio demographic with the outcomes (status of SIBO, lactose intolerance and fructose intolerance). Then, it was proceeded with multiple logistic regression to examine the association between related variables with the outcomes when adjusted for other variables.

Ethical Approval

The study was conducted according to the principles outlined in the Declaration of Helsinki. Ethical approval was obtained from the Human Research and Ethics Committee, Universiti Sains Malaysia

RESULT

A total of 104 participants were recruited for this study. The participants' demographic data was tabulated in Table 1. The result of the data showed that the mean age of all the participants is 49.76 years old, and the standard deviation is 15.99. Meanwhile, more than half were female (n=54, 51.9%). The majority was Malay (n=81, 77.9%). Majority of the participants presented with the symptoms of belching (n=85, 81.7%), abdominal distension (n=98, 94.2%), and flatulence (n=100, 96.2%).

The prevalence of SIBO, fructose intolerance /malabsorption, and lactose intolerance /malabsorption, as tabulated in Table 2, were 20%, 39% and 66% respectively.

Based on Table 3, there were significant association between age ($p \leq 0.050$) and diabetes mellitus ($p < 0.001$) with SIBO when adjusted for other variables. For people with age of more than 65 years old, there were 3.220 times odds to experience SIBO compared to people who aged 65 years old and less. For patient with history of diabetes mellitus, there were 6.037 times odd to experience SIBO compared to patient without history of diabetes mellitus.

Based on Table 4, there was no significant association between all the listed variables towards fructose intolerance /malabsorption when adjusted for other variables.

Based on Table 5, there was no significant association between all the listed variables with lactose intolerance /malabsorption when adjusted for other variables.

DISCUSSION

IBS is somewhat more common in the Western continent than the Asian continent. It was noted that about 3%-22% of the general Western population had IBS, while only less than 5% was reported from the Asian.[18,19] Study among the Malays, which are the major ethnic group in Malaysia, showed prevalence of IBS is between 12.4% and

15.8%.[20,21] SIBO has been thought to have a role in the pathophysiology of IBS.[22,23] The overall prevalence of SIBO in the general population is not well known.[24] A meta-analysis done by Ghoshal and associates showed wide variation in the prevalence of SIBO in IBS, ranging from 4.3% to 83.7%.[25] This study recorded prevalence of SIBO in FBD about 20%, which appears to be lower. The variations in prevalence is due to difference in geographical origin of studied population, different criteria for diagnosis of IBS, and heterogeneity in the diagnostic test for SIBO.[26] At present, we can either use jejunal aspirate culture or hydrogen breath test to diagnose SIBO. As we mentioned earlier, jejunal aspirate culture is the gold standard, but is seldom used due to the invasiveness of the procedure. One study showed that breath test detects SIBO less than the culture, which is 27% and 47% respectively.[27] Whereas one systemic review showed SIBO has pooled prevalence of 40% and 19%, using breath test and culture, respectively. In the review, a more stringent criterion of bacterial count $>10^5$ CFU/mL as a positive test was used. Furthermore, jejunal aspirate culture only evaluates proximal rather than the entire small intestinal bacteria burden, and there may be presence of non-culturable bacteria species. Thus, this may limit the test sensitivity.[28] Substrates that are commonly used in breath test for SIBO are glucose and lactulose. Glucose hydrogen breath test was first used for the detection of SIBO in 1976, while first usage of lactulose breath test was reported in 1979.[29,30] Glucose is a monosaccharide that is completely absorbed in the proximal small intestine under normal circumstances. If the proximal small intestine has bacterial overgrowth, it will ferment the glucose and produces gas that is causing the symptoms. Glucose breath test has difficulty in detecting distal small intestine bacterial overgrowth as most glucose will be absorbed before reaching the distal small intestine. Lactulose is a synthetic, non-absorbable disaccharide consisting of fructose and galactose, which is commonly used as an osmotic laxative. It passes from the small intestine to the cecum

intact, then it is metabolized by the colonic bacteria. Theoretically, it produces a "double-peak" pattern in SIBO. However, this is not always true. Glucose breath test has sensitivity of 20% – 93% and specificity of 30% – 86%, whereas lactulose breath test has sensitivity of 17% – 68% and specificity of 44% – 86%.[31] A meta-analysis done by Losurdo and associates concluded that glucose breath test has high values of diagnostic yield, more than lactulose breath test.[32] At the moment, the Rome Consensus Conference Expert Group recommended the usage of glucose hydrogen breath test in the diagnosis of SIBO.[33]

In this study, we tested the association of few factors for SIBO in IBS (age, gender, obesity, proton pump inhibitor (PPI), prokinetic usage, previous abdominal surgery, and diabetes mellitus). We found that there is an association between elderly and diabetes mellitus with SIBO. A study conducted by MacMahon and associates found that SIBO is prevalent in the elderly.[34] Few other review also suggested old age was associated with SIBO.[27,35-38] It was presumed that the elderly age group was more likely to have risk factors for SIBO, such as a reduction in intestinal motility, small bowel diverticulosis, intestinal surgery and achlorhydria as well as higher medication use.[34-36,38] Diabetes mellitus is a non-communicable disease that is known to cause target organ damage, including the gastrointestinal system. About 50% - 70% of diabetic patients would be presenting with gastrointestinal symptoms.[24] Virally-Monod and associates reported the presence of SIBO in 43% of diabetic patients.[39] Diabetes mellitus often causing gastroparesis and intestinal dysmotility. The orocecal transit time is delayed.[40] This would enable bacterial stasis and subsequent overgrowth. The subjects with history of PPI and prokinetic usage were less than half of the total study subjects. Many studies have demonstrated that PPI usage is a risk factor for SIBO.[41-46] Hypothetically, PPI induces achlorhydria state, which provide a favourable environment for bacterial proliferation.[47]

Our current study showed a contrasted result to this. Study by Thorens and associates showed that higher incidence of duodenal bacterial overgrowth in those treated with omeprazole compared to those treated with cimetidine.[44] Lewis and associates also demonstrated that PPI usage is associated with SIBO.[42] However, there were some studies that showed no association between SIBO and PPI usage. Giamarellos-Bourboulis and associates found that association between IBS and SIBO was completely independent from PPI intake.[48] A single centre study by Mujeeb and associates was observed that SIBO was not associated with duration/ dose/ type of PPI usage.[49] Thus, PPI usage as an associated factor for SIBO is still debatable. Previous abdominal surgery is often been listed as risk factor for SIBO. This study did not find any significant finding for this. There was less than half of the total study subjects had previous history of abdominal surgery. Most of the subjects did not mention type of abdominal surgery that was performed. We did not perform analysis on the type of previous abdominal surgery. Petrone and associates did not find history of abdominal and pelvic surgery associated with SIBO, but the prevalence of SIBO was higher in this group of patient.[50] Rao and associates demonstrated a significantly higher prevalence of SIBO in a cohort of patients with colectomy and chronic unexplained gastrointestinal symptoms.[51] Another study by Kim and associates concluded that SIBO in patients with abdominal surgery was common, particularly more common in the gastrectomy group.[52] Thus, GI-related abdominal surgery is more prone to develop SIBO compared to non-GI-related abdominal surgery. Our current study also did not show any significant association between obesity and SIBO. Obesity in this context is defined as BMI of 27.5 kg/m^2 and above, which is lower than the WHO classification, based on the Malaysian Clinical Practice Guidelines on Management of Obesity 2004.[53] Few reviews had showed obesity played a major role in SIBO.[54-56] Obesity reduces the diversity of gut microbiome. It causes dysbiosis in the gut.