International Journal of Current Advanced Research
ISSN: O: 2319-6475, ISSN: P: 2319-6505, Impact Factor: 6.614
Available Online at www.journalijcar.org
Volume 8; Issue 01(F); January 2019; Page No. 17064-17067
DOI: http://dx.doi.org/10.24327/ijcar.2019. 17067.3181

Research Article

TO STUDY THE PREVALENCE OF SMALL INTESTINAL BACTERIAL OVERGROWTH AMONG CHRONIC PANCREATITIS PATIENTS

Patil Chandrashekar., Chezhian A*., Venkateswaran A. R., Rajkumar Solomon T., Malarvizhi M and Murali R

Institute of Medical Gastroenterology, Madras Medical College, Chennai, Tamil Nadu, India

A R T I C L E I N F O

Article History:
Received 12th October, 2018
Received in revised form 23rd November, 2018
Accepted 7th December, 2018
Published online 28th January, 2019

Key words:
Chronic pancreatitis, SIBO, GHBT

A B S T R A C T

Background: Patients with chronic pancreatitis exhibit numerous risk factors for the development of small intestinal bacterial overgrowth (SIBO). It is to be considered a factor that worsens symptoms and nutritional status in patients with CP. Only a limited number of heterogeneous studies have evaluated the rate of SIBO in small groups of CP patients. ***Aim***: To assess the prevalence of small intestinal bacterial overgrowth (SIBO) in chronic pancreatitis (CP), and analyze factors related with SIBO in CP. ***Methods:*** It is a prospective study performed between June 2017 and February 2018 at Madras Medical College, Chennai.56 patients with chronic pancreatitis and 60 age and gender-matched healthy subjects (HS) were evaluated for SIBO using glucose hydrogen breath test (GHBT). Persistent rise in breath hydrogen 12 ppm above basal (at least two recordings) was diagnostic of SIBO. Results: SIBO was diagnosed more often among patients with chronic pancreatitis than controls (8/56[14.2%] vs. 1/60 controls [1.6%]; p (0.003). Of 56 patients, 40(71.4%) had alcoholic and 16 (28.5%) had idiopathic chronic pancreatitis. SIBO was as commonly detected among patients with alcoholic as idiopathic pancreatitis (6/40 [15%] vs. 2/16 [12.5%]. Age, gender, body mass index (BMI), steatorrhoea, pain, analgesic use, pancreatic calcifications, and use of pancreatic enzyme supplements had no relationship with the presence of SIBO. ***Conclusion:*** The prevalence of SIBO detected using GHBT was high among patients with CP both alcoholic and idiopathic than Controls.

INTRODUCTION

Small intestinal bacterial overgrowth (SIBO) is defined as the presence of >105 bacteria/mL in the small bowel, most of which are enterobacteria from the colonic flora [1].Such overgrowth can cause malabsorption and maldigestion, which subsequently leads to diarrhea, steatorrhea, bloating, chronic pain, and vitamin B12 deficiency [1]. Small intestinal bacterial overgrowth (SIBO) is known to occur in patients with chronic pancreatitis, particularly of alcoholic etiology. The reported frequency of SIBO among patients with chronic pancreatitis ranges from 0 to 92% [2-6]. Such wide variation in frequency of SIBO in patients with chronic pancreatitis might berelated to difference in methods of testing for SIBO and inclusion of patients with differing etiology. For example, highest frequency of SIBO of 92% was found when lactulose hydrogen breath test was used, a lower frequency was reported with glucose hydrogen breath test and an intermediate value was with jejunal aspirate culture, which is considered as the gold standard for diagnosis of SIBO. Pathogenesis of SIBO in patients with chronic pancreatitis is multi-factorial, which include small bowel stasis resulting from exaggerated ileal brake induced by action of malabsorbed fat passing through ileum[8], associated diabetic autonomic neuropathy, intake of opiate and non-steroidal analgesic, reduced gut defence due to a failure of conversion of prodefensin to defensin by trypsin [9-13], and alcohol consumption. Gastrointestinal symptoms and nutritional status are not reversed by the use of adequate doses of pancreatic enzyme preparations in up to 50% of CP patients. [14]In patients with insufficient response to PERT, the inhibition of gastric acid secretion with proton pump inhibitors (PPIs) should be attempted to improve the efficacy of therapy. Moreover, it has been suggested that the presence of small intestinal bacterial overgrowth (SIBO) should be considered in patients who do not respond to such treatments.[15-16] Only a limited number of heterogenous studies have evaluated the rate of SIBO in small groups of CP patients.Since alcohol itself can predispose to SIBO, the earlier studies that included only patients with alcoholic pancreatitis, may not give an exact estimate of frequency of SIBO occurring due to chronic pancreatitis independent to the effect of alcohol [17-18]. Hence, a study including patients with idiopathic pancreatitis would help to know the frequency of SIBO in patients with chronic pancreatitis independent of

Corresponding author:* **Chezhian A
Institute of Medical Gastroenterology, Madras Medical College, Chennai, Tamil Nadu, India

alcohol. Similarly, there is scanty data on factors associated with occurrence of SIBO in patients with chronic pancreatitis.

Aims

1. To study the frequency of SIBO in patients with chronic pancreatitis as compared to healthy controls using glucose hydrogen breath test, and
2. To study factors associated with occurrence of SIBO in patients with chronic pancreatitis.

METHODS

A prospective case-control study was performed between June 2017 and February 2018 at Madras Medical College, Chennai. The study population consisted of consecutive patients with CP attending the pancreatic disorders outpatients' clinic.

The inclusion criterion was a diagnosis of CP based on typical clinical and imaging features. Each patient underwent a detailed clinical evaluation to determine etiology and severity of CP, as well as assessment of symptoms throughout a standardized questionnaire.

Exclusion criteria were Patients with a history of gastric, intestinal, or pancreatic surgery (except appendectomy and cholecystectomy) as well as patients who Underwent antibiotic therapy in the past month were also excluded. Patients taking prokinetic agents, probiotics, or laxatives were asked to discontinue the medications at least seven days before the test.

Controls were consecutive subjects with nonspecific, without chronic gastrointestinal complaints seen at the outpatient's clinic for the first time, and willing to participate in the study protocol. The local Ethics Committee approved the study protocol, and all patients and controls provided informed consent.

Glucose Hydrogen Breath Test (GBT)

GHBT was performed using a breathanalyser (Bedfontgastrolyzer, BedfontScientific Ltd., UK) after an overnight fast. The subjects were asked to avoid slowly absorbed carbohydrates and fibre the previous night as these would cause delayed excretion of hydrogen in their breath. Cigarette smoking and exercise were avoided 2 h before and during the test, as hyperventilation can cause changes in breath hydrogen content. The subjects were asked to brush their teeth and rinse their mouth with antiseptic mouth wash and tap water before the test, to eliminate an early hydrogen peak due to the action of oral bacteria on test sugar. An average of three values was taken as the basal breath hydrogen level. Subjects were then asked to take 100 g glucose dissolved in 200 ml of water. Thereafter, breath hydrogen values were estimated every 15 min for the next 3 h. Persistent rise in breath hydrogen 12 ppm above basal (at least two readings) was considered diagnostic of SIBO. Patients with high basal breath hydrogen levels were re-tested on another day after ensuring repetition of all the above precautions.

Statistical analysis

Statistical analysis was performed using SPSS 15.0 (SPSS Inc., Chicago, IL, USA) software. Chi-square test was used for categorical data and Students' t test was used for continuous data.

RESULTS

56 patients (48 males; mean age 35 ± 2yrs) and 60 healthy subjects (52 males; mean age 29 ± 3yrs) were evaluated for SIBO using glucose hydrogen breath test (GHBT). Cases and controls were comparable with regards to age (p = 0.1) and gender (p =0.001). Of 56 patients, 40 (71.4%) had alcoholic and 16 (28.5%) had idiopathicchronic pancreatitis. Mean BMI of patients with chronic pancreatitis was 19.7 ± 3.07 kg/m2. Pain, opioid use, steatorrhoea, diabetes, use of pancreatic enzymes and pancreatic calcifications was reported by 82.14%, 32.4%, 16.1%, 14.3%, 14.2% and 73.02% of the patients, respectively; frequency of these parameters was not significantly different between alcoholic and idiopathic chronic pancreatitis (Table 1).SIBO was diagnosed more often among patients with chronic pancreatitis than controls (8/56 [14.2%] vs. 1/60 controls [1.6%]; p =0.001). SIBO was as commonly detected among patients with alcoholic as idiopathic pancreatitis (6/40 [10.7%] vs. 2/16 [15.2%];p =0.809). Age, gender, body mass index (BMI), steatorrhoea, pain, pancreatic calcifications, use of opioid analgesics, NSAIDs and pancreatic enzyme supplements had no relationship with the presence of SIBO (Table 2). Diabetes mellitus tended to be commoner among patients with chronic pancreatitis with than without SIBO (6/8 [75%] vs. 2/8 [2.1%]; p = 0.0017).Out of 9 patients with pancreatic exocrine insufficiency, 2(22.2%) had persistent diarrhoea despite adequate enzyme replacement.2 out of these 9 (22.2%) patients not responding to pancreatic enzymes had SIBO on GHBT and underlying bacterial overgrowth may be a possible explanation for poor response to standard enzyme therapy. Only these two patients of the 9 with SIBO were treated with rifaximin (400 mg thrice daily for 2 weeks). Patients had improvement in diarrhoea on rifaximintreatment. Resolution of SIBO by repeat GHBT was not documented in these patients.

Table 1 Characteristics of patients with chronic pancreatitis based on etiology

Characteristic	Alcohol n=40	Idiopathic n=16	*p-Value*
Mean age (yrs)	35 ± 2	29 ± 3	NS
Male:Female	40:0	8:8	0.00
Mean BMI (kg/m2)	19.8	18.6	NS
Median duration of pain (yrs)	3.5 yrs	2.6 yrs	NS
Pain (n) (%)	32	14	NS
Opioid analgesics (n) (%)	22	10	NS
DM (n)(%)	6	2	NS
Exocrine insufficiency (n)(%)	6	3	NS
Pancreatic calcifications (n) (%)	32	9	NS
GHBT	6	2	NS

Table 2 Characteristics of patients with chronic pancreatitis with a positive and negative GHBT

Characteristic	GHBT Positive (n=8)	GHBT Negative (n=48)	*p-Value*
Mean age (yrs)	35.9 ± 4.6	34.4 ± 6	0.8
Male:Female	6:2	42:6	0.22
Mean BMI (kg/m2)	19.8 ± 2	19.8 ± 3	0.8
Median duration of pain (yrs)	1.8	2.2	0.3
Pain (n) (%)	6 (75%)	41(85.4)	0.458
Opioid analgesics (n) (%)	5 (62.5)	27(56.3)	0.74
DM (n)(%)	6(75%)	1(2.1%)	0.001
Exocrine insufficiency (n)(%)	3(37.5%)	6(12.5%)	0.075
Pancreatic calcifications (n) (%)	7(87.5%)	32(66.7%)	0.23
Characteristic	GHBT Positive (n=8)	GHBT Negative (n=48)	p-Value

Mean age (yrs)	35.9 ± 4.6	34.4 ± 6	0.8
Male:Female	6:2	42:6	0.22
Mean BMI (kg/m2)	19.8 ± 2	19.8 ± 3	0.8
Median duration of pain (yrs)	1.8	2.2	0.3
Pain (n) (%)	6 (75%)	41(85.4)	0.458
Opioid analgesics (n) (%)	5 (62.5)	27(56.3)	0.74
DM (n)(%)	6(75%)	1(2.1%)	0.001
Exocrine insufficiency (n)(%)	3(37.5%)	6(12.5%)	0.075
Pancreatic calcifications (n) (%)	7(87.5%)	32(66.7%)	0.23

Chart Showing GHBT Positive in Cases Compared To Controls Which is Statisticaly Significant

			GROUP		
			CASE	CONTROL	Total
GHBT	POSITIVE	Count	8	1	9
		% within GROUP	14.3%	1.7%	7.8%
	NEGATIVE	Count	48	59	107
		% within GROUP	85.7%	98.3%	92.2%
Total		Count	56	60	116
		% within GROUP	100.0%	100.0%	100.0%

Chart Comparing GHBT in Alcoholic Vs Nonalcoholic Which Is Statistically Nonsignificant

			ALCOHOLIC	IDIOPATHIC	
GHBT	POSITIVE	Count	6	2	8
		% within ETIOLOGY	15.0%	12.5%	14.3%
	NEGATIVE	Count	34	14	48
		% within ETIOLOGY	85.0%	87.5%	85.7%
Total		Count	40	16	56
		% within ETIOLOGY	100.0%	100.0%	100.0%

Chart Comparing GHBT in DM vs Non DM in Cp Patients Which Is Statistically Significant

			GHBT		
			POSITIVE	NEGATIVE	Total
DM	YES	Count	6	1	7
		% within GHBT	75.0%	2.1%	12.5%
	NO	Count	2	47	49
		% within GHBT	25.0%	97.9%	87.5%
Total		Count	8	48	56
		% within GHBT	100.0%	100.0%	100.0%

DISSCUSSION

The main finding of this study, conducted in the largest population examined with this aim, is that SIBO is a relatively common finding in CP patients without a previous history of surgery, being more common than in healthy subjects (14.3% vs. 1.6%), with a significant statistical difference between the 2 groups.

In previous studies, the rate of SIBO in populations of CP patients was highly variable, ranging from 0% to 92%.[20]Mancilla *et al*, who used a H2 lactulose

breath test, a method that is prone to a high rate of false positivity[24,25] reported the highest positivity rate (92%).Moreover, some of those studies included CP patients with a previous history of gastroduodenal surgery,[21-22] which is considered a cause of SIBO per se. Casellas *et al*reported a prevalence of SIBO of 40% in the CP group, but almost all CP patients (10/15) had gastroduodenal surgery, whereas 8 of 35 CP patients had a previous surgical treatment in the study of Trespi and Ferrieri,[21] which reported a prevalence of SIBO equal to 35% which reported high prevalence of SIBO in chronic pancreatitis patients.

Mechanism of bacterial overgrowth in chronic pancreatitis is multifactorial. First, pancreatic juice has antibacterial properties [27,28]. Thus, diminished secretion of pancreatic juice, as in pancreatic insufficiency, could allow excessive proliferation of the intestinal microflora. Second, it is known that impaired small bowel motility may be due to the use of narcotics or the effects of maldigestion associated with the increased release of peptide YY results in exaggerated ileal brake leads to development of bacterial overgrowth. Failure of conversion of prodefensin to defensin by trypsin, which is low in these patients one of the factors for SIBO.

Similar to the previous studies, SIBO was more frequent in our patients with chronic pancreatitis compared to healthy subjects. Frequency of 14.2% obtained in our study is lower than that in the previous studies carried out using GHBT (30-40%).

Our study further revealed that SIBO was equally frequent among patients with alcoholic and idiopathic pancreatitis, and though SIBO tended to be commoner among those with diabetes mellitus, there was no relationship with age, gender, BMI, steatorrhoea, pain, pancreatic calcifications, use of opioid analgesics, NSAIDs and pancreatic enzyme supplements. This is perhaps the first case-control study on frequency of SIBO among patients with chronic pancreatitis and also first study comparing the frequency of SIBO among patients with alcoholic and non alcoholic idiopathic pancreatitis. Our study showed comparable frequency of SIBO among patients with alcoholic and non-alcoholic pancreatitis.

However, there are some limitations to this study. Firstly, although GBT is considered the most accurate noninvasive examination for the diagnosis of SIBO, its accuracy is only equal to 71.7%[26] compared with jejunal aspiration and culture, which is considered the gold standard. However, because of the invasiveness of this method, which requires intubation of the small bowel, GBT must be considered the most accurate noninvasive test for diagnosis of SIBO in clinical practice. Furthermore, in this study, we did not evaluate the presence of methanogenic bacteria in the gut that might convert hydrogen into methane, and we cannot therefore rule out the presence of false-negative results because of the lack of measurement of both gases.

In this study, SIBO tended to be commoner among those with diabetes mellitus but there was no relationship with age, gender, BMI, steatorrhoea, pain, pancreatic calcifications and use of pancreatic enzyme supplements, hence questioning their role towards possible contribution to the development of SIBO. SIBO in diabetic patients with chronic pancreatitis could be attributed to small bowel motility disturbances secondary to the diabetic state and may not be due to the presence of chronic pancreatitis[29].

In conclusion, our findings suggest that SIBO is common in CP, even in a population of uncomplicated patients. SIBO in CP patients does not seem related to peculiar clinical features or medical treatment with PERT or PPIs, but it could affect nutritional status. Thus, it could be useful to exclude the presence of SIBO not only in CPpatients with PEI unresponsive to pancreatic enzymes, as but in every CP patient. Though presence of SIBO among patients with chronic

pancreatitis tended to be commoner among those with diabetes mellitus, there was no relationship with age, gender, BMI, steatorrhoea, pain, pancreatic calcifications and use of pancreatic enzyme supplements. Appropriate diagnosis and treatment for SIBO may alleviate symptoms and improve quality of life in these patients.

References

1. R. S. Choung, K. C. Ruff, A.Malhotra *et al*., "Clinical predictors of small intestinal bacterial overgrowth by duodenal aspirate culture," *Alimentary Pharmacology and Therapeutics*, vol. 33, no.9, pp. 1059-1067, 2011.
2. Lembcke B, Kraus B, Lankisch PG. Small intestinal function in chronic relapsing pancreatitis. Hepatogastroenterology 1985; 32:149e51.
3. Casellas F, Guarner L, *et al*. Hydrogen breath test with glucose in exocrine pancreatic insufficiency. Pancreas 1998; 16:481e6.
4. TrespiErminio, FerrieriAntonella, *et al*. Intestinal bactErial overgrowth during chronic pancreatitis. Curr Med Research Opinion 1999; 15(1):47e52.
5. Madsen JL, *et al*. Bile acid malabsorption or disturbed intestinal permeability in patients treated with enzyme substitution for exocrine pancreatic insufficiency is not caused by bacterial overgrowth. Pancreas 2003; 26(2):130e3.
6. Mancilla Carla, María Ana, *et al*. Small intestine bacterial overgrowth in patients with chronic pancreatitis. Rev M_ed Chile 2008; 136:976e80.
7. Gubergrits Natalya B, *et al*. Morphological and functional alterations of small intestine in chronic pancreatitis. JOP 2012 Sep 10; 13(5):519e28.
8. Spiller RC, Trotman IF, *et al*. The ileal brake inhibition of jejunal motility after ileal fat perfusion in man. Gut 1984; 25:365e74.
9. Belvins CL, Porter Martin E. Defensins and innate host defence of the gastrointestinal tract. Gut 1999; 45:911e5.
10. Ganz Tomas. Gut defence. Nature 2003; 422:478e9.
11. Bos NA, Salzman N. How bugs and men live in harmony. Role of defensins in gut microbial composition and Th17 development. ImmunolLett; 2010.
12. Ishikawa C, Tanabe H, *et al*. Precursor processing of human defensin-5 is essential to the multiple functions in vitro and in vivo. J Innate Immun 2010; 2:66e76.
13. Ghosh D, Porter E, Shen B, Lee SK, Wilk D, Drazba J, *et al*. Paneth cell trypsin is the processing enzyme for human defensin-5. Nat Immunol 2002 Jun; 3(6): 583e90.
14. S. J. Lewis, S. Franco, G. Young, and S. J. D. O'Keefe, "Altered bowel function and duodenal bacterial overgrowth in patients treated with omeprazole," *Alimentary Pharmacology and Therapeutics*, vol. 10, no. 4, pp. 557-561, 1996.
15. S. M. Riordan, C. J. McIver, D. Wakefield, T. D. Bolin, V. M. Duncombe, and M. C. Thomas, "Small intestinal bacterial overgrowth in the symptomatic elderly," *The American Journal of Gastroenterology*, vol. 92, no. 1, pp. 47-51, 1997.
16. S. V. Rana and S. B. Bhardwaj, "Small intestinal bacterial overgrowth," *Scandinavian Journal of Gastroenterology*, vol. 43, no. 9, pp. 1030-1037, 2008.
17. Bode JC, *et al*. Jejunalmicroflora in patients with chronic alcohol abuse. Hepatogastroenterology 1984; 31:30e4.
18. Bode C, Kolepke R, *et al*. Breath hydrogen excretion in patients with alcoholic liver disease-evidence of small intestinal bacterial overgrowth. Z Gastroentrol 1993; 31:3e7.
19. Hauge T, Persson J, *et al*. Mucosal bacterial growth in the upper gastrointestinal tract in alcoholics (heavy drinkers). Digestion 1997; 58:591e5.
20. Mancilla AC, Madrid SAM, Hurtado HC, *et al*. Small intestine bacterial overgrowth in patients with chronic pancreatitis. Rev Med Chil. 2008; 136:976-980.
21. Trespi E, Ferrieri A. Intestinal bacterial overgrowth during chronic pancreatitis. Curr Med Res Opin. 1999; 15:47-52.
22. Casellas F, Guarner L, Vaquero E, *et al*. Hydrogen breath test with glucose in exocrine pancreatic insufficiency. Pancreas. 1998;16:481-486.
23. Madsen JL, Graff J, Philipsen EK, *et al*. Bile acid malabsorption or disturbed intestinal permeability in patients treated with enzyme substitution for exocrine pancreatic insufficiency is not caused by bacterial overgrowth. Pancreas. 2003;26: 130-133.
24. Kerlin P, Wong L. Breath hydrogen testing in bacterial overgrowth of the small intestine. Gastroenterology. 1988; 95:982-988.
25. Corazza GR, Menozzi MG, Strocchi A, *et al*. The diagnosis of small bowel bacterial overgrowth. Reliability of jejunal culture and inadequacy of breath hydrogen testing. Gastroenterology.1990;98:302-309.
26. Gasbarrini A, Corazza GR, Gasbarrini G, *et al*. Methodology and indications of H2-breath testing in gastrointestinal diseases: the Rome Consensus Conference. Aliment PharmacolTher. 2009;29:1-49.
27. Rubinstein E, Mark Z, Haspel J, *et al*. Antibacterial activity of the pancreatic fluid. Gastroenterology 1985; 88:927.
28. Simpson KW, Batt RM, Jones D, Morton DB. Effects of exocrine pancreatic insufficiency and replacement therapy on the bacterial flora of the duodenum in dogs. Am J Ver Res 1990;51:203e6
29. Monod M, Tielmans D, *et al*. Chronic diarrhoea and diabetes mellitus: prevalence of small intestinal bacterial overgrowth. Diabetes Metab 1998; 24:530.

How to cite this article:

Patil Chandrashekar *et al* (2019) 'To Study the Prevalence of Small Intestinal Bacterial Overgrowth Among Chronic Pancreatitis Patients', *International Journal of Current Advanced Research,* 08(01), pp. 17064-17067.
DOI: http://dx.doi.org/10.24327/ijcar.2019.17067.3181