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ORIGINAL RESEARCH

Association of Small Intestinal Bacterial Overgrowth in patients of Type II Diabetes Mellitus having central obesity

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Abstract
Type 2 Diabetes Mellitus (DM) involves an interplay between insulin resistance and inadequate insulin secretion manifesting as hyperglycemia resulting in various micro and macrovascular complications with the passage of time. Autonomic neuropathy is a common complication in diabetic patients, and it occurs throughout the whole gastrointestinal tract, affecting gastrointestinal motility .Gastrointestinal hypomotility due to diabetic autonomic neuropathy can result in small bowel stasis, thereby increasing the likelihood of SIBO. Similarly small intestinal bacterial overgrowth (SIBO) has been hypothesized to play an important role in NAFLD development and progression. Studies have indicated that NASH patients with SIBO have a higher prevalence of impaired glucose tolerance than those without SIBO.

Aim: Present study was conducted to assess Small Intestinal Bacterial Overgrowth in patients of Type II Diabetes Mellitus having central obesity.

Methods and result: A total of 54 diabetic patients falling in the domain of inclusion criteria were included in the study as Cases and similar number of normal healthy controls were included in the study as Controls. Difference in lipid levels (HDL, LDL, TGL and Total cholesterol) of Cases and Controls was statistically significant. Central obesity was present in all the cases (100.0%), 77.78% were hypertensive, 79.63% had raised triglycerides and 68.52% had low HDL levels. Metabolic syndrome and NAFLD were present in 94.44% and 50.0% of Cases and in 13.0% & 16.7% of controls. This difference was statistically significant. SIBO was significantly higher among Cases (33.33%) as compared to Controls (16.67%), this difference was statistically significant. The present study showed an increased prevalence of SIBO in obese type 2 diabetes mellitus patients as compared to an age- and gender- matched non-diabetic population, however, the study could not specify particular risk factors (except dyslipidemia) to be associated with this increased prevalence of SIBO in diabetic population. Further studies on a larger sample size after making provisions for adequate heterogeneity are recommended.

Keywords: SIBO, Small Intestinal Bacterial Overgrowth, gastrointestinal hypomotility, Small bowel stasis

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Introduction

Type 2 Diabetes Mellitus (DM) involves an interplay between insulin resistance and inadequate insulin secretion manifesting as hyperglycemia resulting in various micro and macrovascular complications with the passage of time. Along with the symptoms related to complications related to neuropathy, retinopathy, nephropathy many of the diabetic patients report gastrointestinal symptoms, including stomach ache, diarrhea, and constipation, which is known as diabetic enteropathy[1,2].

Clinical and experimental research has revealed that DM is characterized by intestinal hypomotility[3]; gut microbial dysbiosis[4,5] increased gut permeability[6,7]; microcirculation disorders[8]; dysfunction of intestinal stem cells(2), all of which may be linked to inflammation of intestinal mucosa. It decreases the motility index and propagation of duodenal and jejunal waves[9], reduces the cycle length of interdigestive motor activity in the fasted state[10] and slows small-intestinal transit[11,12].

The elevated blood glucose level effects the duodenal waves by increasing the stimulation and decreases the duodenal compliance[13].

With longstanding diabetes, there may ensue abnormal motility, secretion, absorption owing to enteric nerve supply being effected. Delayed emptying and stagnation of fluids in the small intestine may lead to bacterial overgrowth syndromes, resulting in diarrhoea, bloating and abdominal pain. The abnormal motility and secretion of fluid in the colon in a setting of long term diabetes can cause unexplained persistent diarrhoea and can also predispose to bacterial overgrowth. Other than this, anatomical abnormalities and disturbed gut immune function also increase the likelihood of developing SIBO. SIBO is usually defined as the presence of >105 colony-forming units (CFU)/ml in duodenal aspirate cultures[14].

As there is an embryonic connection between the liver and intestine; many emerging evidences have related the development and progress of non alcoholic fatty liver disease (NAFLD) in the background of altered mucosal permeability, intestinal dysbiosis and SIBO[15].Under normal conditions the intestinal bacterial products like the LPS (lipopolysaccharide) which permeate the intestinal barrier are detected by the receptors on the kupffer cells and they are eliminated by the liver by generating an immune response[16]. Ruiz *et al*[17] indicated that the serum levels of LBP were increased in obese patients with NASH compared to patients with simple steatosis ($P<0.05$), and the increased serum LBP level was correlated to an upregulated expression of TNF-α in the liver tissue.

Due to a strong interplay among obesity, Diabetes, gut permeability and relationship of the gut-liver axis we conducted a study to assess Small Intestinal Bacterial Overgrowth in patients of Type II Diabetes Mellitus having central obesity and also to find out co relation of presence of SIBO with NAFLD in patients of Type II Diabetes Mellitus having central obesity.

Aim and objectives

1. To perform breath Hydrogen Test For detection of Small Intestinal Bacterial Overgrowth in patients of Type II Diabetes Mellitus having central obesity.
2. To find out co-relation of presence of SIBO with NAFLD in patients of Type II Diabetes Mellitus having central obesity.

Materials and methods

The study was an observational case control study conducted in a teaching hospital in North India. We included all indoor and outdoor obese patients (n=54) of Type2 Diabetes Mellitus attending the Medicine OPD. The controls (n=54) were age, sex and BMI matched non-diabetic healthy individuals from November 2014- May 2016. Acutely ill patients, Type 1 DM, patients already diagnosed with inflammatory bowel disease, Patients who had a prior

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diagnosis of a liver disease due to causes other than NAFLD, patients who had significant alcohol intake defined as greater than 20g of alcohol/day and those on antibiotics 2 weeks prior to enrolment were excluded. The study was given clearance by the ethical committee of the institution.

Patient was diagnosed as the case of diabetes mellitus according to recent ADA Guidelines. Patient were categorised as centrally obese according to waist circumference as per the NCEP ATP III criteria for South Asian population i.e. women > 80cms, men >90 cms. A detailed history and anthroprometric examination of patients was done. Pulse rate, Blood Pressure (BP) and waist circumference (WC) were measured. WC was measured once at the midpoint between the costal margin and the iliac crest in the mid clavicular line preferably by the same person to avoid observer variability.

These patients were then subjected to following investigations. Fasting Blood Sugar (FBS) Postprandial blood sugar (PPBS), Triglyceride, High density Lipoprotein (HDL). High Blood Pressure was defined as BP ≥130/85 mm of Hg (JNC 6) with average of ≥ 2 readings obtained on ≥ occasions. If the two readings differed by more than 5 mm Hg diastolic and 10 mm Hg systolic then a third reading was taken. The mean value of the two closest reading was calculated. Metabolic Syndrome diagnosis included three or more of the following: TG ≥ 150 mg/dl, HDL Cholesterol <40 mg/dl in men and <50 mg/dl in women ,fasting glucose ≥ 100 mg/dl or previously diagnosed with type 2 diabetes mellitus, waist circumference ≥ 90 cm in men and ≥ 80 cm in women according to ethnic criteria for Asians. Those meeting the inclusion criteria were subjected to Breath Hydrogen test which was done by Gastro ELISA after overnight fast. Before the test, subjects were asked to brush their teeth and rinse mouth with antiseptic mouth wash and tap water, to eliminate an early hydrogen peak due to action of oral bacteria on test sugars. Subsequently, the subject ingested a fixed amount of the test sugar 70 g of glucose with 250 ml of water.All samples of breath were analyzed for hydrogen and methane every 15 minutes for 2 hours. These values were then noted. SIBO was diagnosed if there was a rise in breath hydrogen by 12 ppm above the basal.

Statistical tools employed

The statistical analysis was done using SPSS (Statistical Package for Social Sciences) Version 15.0 statistical Analysis Software. The values were represented in Number (%) and Mean±SD.

Result

	Patients	**control**	**total**	**P value**
Female	31 57.41%	21 38.89%	52 48.15%	0.054
Male	23 42.59%	33 61.11%	56 51.85%	p=0.054
HbA1C	7.84mean	5.69mean		<0.001
Raised Triglycerides	43/54, 79.63%	20/54 ,20.152%		<0.001
Central Obesity	54/54,100%	0		<0.001

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Comparison of Associated Illnesses among Study population

Associated Illnesses	Total (n=108)	Cases (n=54)		Controls (n=54)		Significance	
		No.	%	No.	%	Chi Square	'p'
NAFLD	40	27	50.00	9	16.7	13.50	<0.001
Metabolic Syndrome	67	51	94.44	7	13.0	72.10	<0.001

Comparison of Incidence of Small Intestinal Bacterial Groath among Study population

Small Intestinal bacterial overgrowth	Cases (n=54)		Controls (n=54)		Total (n=108)	
	No.	%	No.	%	No.	%
No SIBO	36	66.67	45	83.33	81	75.00
SIBO	18	33.33	9	16.67	27	25.00

chi square=4.000 (df=1); p=0.040

Human intestinal microbiota create a complex polymicrobial ecology. This is characterised by its high population density, wide diversity and complexity of interaction. The duodenum and proximal jejunum normally contain small numbers of bacteria, usually lactobacilli and enterococci, gram-positive aerobes or facultative anaerobes ($<10^4$ organisms per mL). Coliforms may be transiently present ($<10^3$ bacteria per mL) and anaerobic Bacteroides are not found in the jejunum in healthy people.

SIBO prevalence is also shown to be higher in patients with diabetes[18] Although, prevalence of SIBO has been reported to be higher in diabetic patients, however, there is missing link regarding the reason for this high prevalence.

Considering the fact that obesity is a recognized complication associated with type 2 diabetes mellitus. Most of the previous studies evaluating the prevalence of SIBO in diabetic patients have remained silent on the obesity aspect[19], and hence the present study was planned with an aim to evaluate the prevalence of SIBO in type 2 diabetes mellitus patients with central obesity as a probable risk factor to be explored.

In present study, glycemic control parameters, *viz.* Fasting and post-prandial blood sugar levels and HbA_{1c} levels were significantly higher in cases as compared to controls, a finding characteristic of diabetic status of patients. Similar to present study Adamska *et al.*[20] as well as Rana *et al.*[21] also observed a significant difference in glycemic parameters between cases and controls. Hyperglycemia is known to cause autonomic neuropathy, which in turn, leads to slow gatric emptying and decreased intestinal motility'. However, whether glycemic control has an impact on prevalence of SIBO remains to be evaluated. Both Adamska *et al.*[20] as well as Rana *et al.*[21] failed to find a significant association of glycemic parameters with SIBO prevalence. In present study too, we did not find a significant difference in fasting and postprandial blood sugar and HbA_{1c} levels when comparing SIBO positive and SIBO negative subjects in combined as well as diabetic and non-diabetic groups independently. These findings in turn suggest that the hyperglycaemic status alone does not have a detrimental effect on the prevalence of SIBO.

In present study, lipid levels showed a statistically significant difference between cases and controls. Dyslipidemia in diabetes is a common finding that is generally stated to be the reason behind diabetes associated increased cardiovascular risk owing to its potential to cause atherosclerosis. Adipose tissue is an active endocrine and immune organ'. Among the more clinically relevant adipocyte hormones applicable to lipid metabolism are those responsible for triglyceride (TG) storage and free fatty acid release[22]. Thus the increased lipid levels in

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diabetic group of patients could mainly be attributable to the adiposity owing to obesity. On evaluating the relationship of SIBO with lipid levels, in present study, we found mean HDL levels to be higher in SIBO patients as compared to those not having SIBO on combined assessment as well as diabetic and non-diabetic groups independently. On evaluated the literature reviewed by us, we found that only Adamska *et al.*[20] had evaluated this relationship but he failed to find out any significant association of lipid parameters with SIBO prevalence. However, their study did not necessarily include the obese diabetics as in case of our study. Thus, the relationship between lipid levels and SIBO could be temporal in view of the reported evidence that shows that obesity increases the risk of SIBO[23] and conversely obesity is associated with a higher risk of dyslipidemia. Interestingly, in present study the SIBO showed an association with HDL, which is considered to be good cholesterol and instead of dyslipidemia it could be considered as eulipidemia and hence whether this finding is incidental or not remains to be examined.

In present study, all the diabetic cases had central obesity as compared none of the non-diabetic cases, thus showing a significant difference between two groups, however, on evaluating the association of obesity with SIBO, it was found to be significant statistically only on combined assessment and not in independent assessment in diabetic and control groups. One of the limitations of present study was that we did not have non-obese diabetic patients or obese control patients, hence we could not assess the impact of obesity in diabetic patients separately while at the same time it is difficult to state whether higher prevalence of SIBO in diabetic group is attributable to obesity or it was entirely dependent on diabetic status. As such the previous studies have shown a variable impact of obesity on SIBO prevalence. However, Adamska *et al.*[20] in their study among type 1 diabetic patients failed to find out any significant difference between SIBO positive and SIBO negative groups for both BMI as well as waist circumference. In a study by Sabaté *et al.*[24] among morbidly obese patients (mean BMI 46.1±6.4 kg/m^2) with liver lesions the prevalence of SIBO was found to be significantly higher as compared to healthy controls. On the other hand in present study, among healthy controls too majority were obese whereas among diabetic group all the patients were obese and hence this relationship could not be illustrated. In their study, Jung *et al.*[25] showed that obesity has an inverse relationship with SIBO in non-constipation irritable bowel syndrome patients whereas Roland *et al.*[49] found the prevalence of SIBO to be positively associated with obesity. In present study, we did not assess the constipation status of the patients hence we are not in a position to comment over this aspect.

As far as prevalence of SIBO was concerned, in present study it was found to be 33.33% in cases and 16.67% in controls thus showing a significant difference between two groups. In their study among diabetic patients with chronic diarrhoea Virally-Monod *et al.*[26] reported the prevalence of SIBO to be as high as 43%. However, Cuoco *et al.*[27] in their study reported this prevalence to be only 4.1%. Rana *et al.*[51] in their study reported this prevalence to be 12.3% in patients with type 2 diabetes mellitus with hypertension and 11.1% in patients with type 2 diabetes mellitus only. Ojetti *et al.*[18]on the other hand showed SIBO in 8% type 1 diabetic patients without autonomic neuropathy and 44% among type 1 diabetic patients with autonomic neuropathy. Rana *et al.*[21] on the other hand reported this prevalence to be 15.5% in type 2 diabetes mellitus cases as compared to only 2.2% of controls. Compared to this in present study we had 16.67% controls showing prevalence of SIBO whereas in cases it was 33.3%. The reason for this difference could be high prevalence of obesity in diabetic patients. Interestingly, Adamska *et al.* in their study reported SIBO prevalence in 37.8% of type 1 diabetes cases as compared to 73% of healthy controls, thus showing an upside down picture of the relationship between diabetes and SIBO prevalence. These findings thus show that the relationship of diabetes and obesity with SIBO is not as simple as summing two plus two and

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this relationship is multifactorial which cannot be assessed without a comprehensive assessment of the patient.

The fact that the concept of higher prevalence of SIBO revolves around intestinal motility and constipation. It is considered that among diabetic patients owing to hyperglycemia induced autonomic neuropathy the intestinal motility is affected which in turn could be responsible for constipation as well as bacterial overgrowth in small intestine[28] .Despite this conceptual basis, most of the studies, including ours, focussed only on the presence or absence of diabetes and ruled out autonomic neuropathy for evaluation and hence it must be an integral part of assessment. Moreover, given the conflicting reports showing role of obesity, especially in context with its changed relationship in patients without constipation as observed by Jung *et al.*[25] shows that the relationship needs to be assessed in varying context. Unfortunately, in present study we did not assess either the constipation as well as the autonomic neuropathy status of the patients. With respect to NAFLD, recent studies suggest that the characteristics of the gut microbiota are altered in NAFLD, and also, that small intestinal bacterial overgrowth (SIBO) contributes to the pathogenesis of this condition, thus as such the direction of this relationship is not well established and still needs further study. With respect to metabolic syndrome, in present study owing to prevalence of obesity as well as hypertension in both cases as well as controls, metabolic syndrome, like obesity was so dominant that it overshadowed a causal relationship, if any. Interestingly, in present study, there were substantial number of cases of metabolic syndrome in non-diabetic subjects too.

Conclusion

The present study was conducted to assess Small Intestinal Bacterial Overgrowth in patients of Type II Diabetes Mellitus having central obesity. A total of 54 diabetic patients falling in the domain of inclusion criteria were included in the study as Cases and similar number of normal healthy controls were included in the study as Controls. Difference in lipid levels (HDL, LDL, TGL and Total cholesterol) of Cases and Controls was statistically significant. Central obesity was present in all the cases (100.0%), 77.78% were hypertensive, 79.63% had raised triglycerides and 68.52% had low HDL levels. Metabolic syndrome and NAFLD were present in 94.44% and 50.0% of Cases and in 13.0% & 16.7% of controls. This difference was statistically significant.

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