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ORIGINAL ARTICLE

Malabsorption, Orocecal Transit Time and Small Intestinal Bacterial Overgrowth in Type 2 Diabetic Patients: A Connection

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Abstract Type 2 diabetes mellitus consists of dysfunctions characterized by hyperglycemia and resulting from combination of resistance to insulin action and inadequate insulin secretion. Most of diabetic patients report significant gastrointestinal symptoms. Entire GI tract can be affected by diabetes from oral cavity to large bowel and anorectal region. Proteins, carbohydrates, fats, and most fluids are absorbed in small intestine. Malabsorption may occurs when proper absorption of nutrients does not take place due to bacterial overgrowth or altered gut motility. The present study was planned to measure various malabsorption parameters in type 2 diabetic patients. 175 patients and 175 age and sex matched healthy controls attending Endocrinology Clinic in PGI, Chandigarh were enrolled. Lactose intolerance was measured by using non-invasive lactose hydrogen breath test. Urinary D-xylose and fecal fat were estimated using standard methods. Orocecal transit time and small intestinal bacterial overgrowth were measured using non-invasive lactulose and glucose breath test respectively. Out of 175 diabetic patients enrolled, 87 were males while among 175 healthy subjects 88 were males. SIBO was observed in 14.8 % type 2 diabetic patients and in 2.8 % of controls. There was statistically significant increase ($p < 0.002$) in OCTT in type 2 diabetic patients compared with controls. OCTT was observed to be more delayed ($p < 0.003$) in patients who were found to have SIBO than in patients without SIBO. Lactose intolerance was observed in 60 % diabetic patients and 39.4 % in controls. Urinary D-xylose levels were also lower in case of diabetic patients but no significant difference was found in 72 h fecal fat excretion among diabetic patients and controls. Urinary D-xylose and lactose intolerance in SIBO positive type 2 diabetic patients was more severe as compared to SIBO negative diabetic patients. From this study we can conclude that delayed OCTT may have led to SIBO which may have instigated the process of malabsorption among type 2 diabetic patients.

Keywords Type 2 diabetic patients · Urinary D-xylose · Lactose intolerance · Small intestinal bacterial overgrowth · Orocecal transit time · Lactose intolerance

Introduction

Type 2 diabetes mellitus (T2DM) is a disease reaching a pandemic proportion in developed countries. It is a multifactorial disease that is typically linked to energy metabolism, particularly carbohydrate and fat management in the organism, however, most micronutrients are also involved in some way either as part of the cause or effect of this chronic pathology. Diabetes is fast gaining the status of a potential epidemic in India with more than 62 million diabetic individuals currently diagnosed with the disease [1, 2]. It is predicted that by 2030 diabetes mellitus may afflict up to 79.4 million individuals in India, while China (42.3 million) and the United States (30.3 million) will also see significant increases in those affected by the disease [3]. Preliminary results from a large community study conducted by the Indian Council of Medical research

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(ICMR) revealed that a lower proportion of the population is affected in states of Northern India (Chandigarh 0.12 million, Jharkhand 0.96 million) as compared to Maharashtra (9.2 million) and Tamil Nadu (4.8 million) [4].

It is characterized by impaired insulin secretion and variable degrees of peripheral insulin resistance leading to hyperglycemia. Studies have shown that marked hyperglycemia, which is characteristic of diabetes, decreases the motility index and propagation of duodenal and jejunal waves [5], reduces the cycle length of interdigestive motor activity in the fasted state [6], and slows small-intestinal transit [7, 8]. Elevation of the blood glucose to the upper end of the physiological range decreases duodenal compliance while increasing the stimulation of duodenal waves [9].

Small intestinal bacterial overgrowth (SIBO) is characterized by a variety of signs and symptoms. SIBO implies a quantitative assessment of bacteria present in the small intestine. Although a certain level of commensal bacteria is important, it is the presence of a particular species type in an atypical location of the bowel, in addition to an excess number, that results in the development of the classical clinical manifestations of this condition. SIBO is usually defined as the presence of $>10^5$ colony forming units (cfu)/mL of bacteria in the proximal small intestine [10]. A major pathophysiologic consequence of SIBO relates to the inflammatory epithelial changes that subsequently occur in the gut. These changes result in a reduction in the absolute or functional intestinal absorptive surface area and play a role in the subsequent development of the symptoms attributed to SIBO such as gas, bloating, abdominal cramping, diarrhea and steatorrhea leading to malabsorption.

Malabsorption is a failure to fully absorb nutrients from the gastrointestinal tract. There are many causes including abnormalities of the gut wall, failure to produce digestive enzymes and abnormalities of gut flora. D-xylose is normally easily absorbed by the small intestine. When problem with absorption occurs, D-xylose is not absorbed by the intestines, and its level in blood and urine is low. A 72-h fecal fat test measures the amount of fat excreted in stool. A positive qualitative fecal fat test or an increased amount of fat in a 72-h quantitative fecal fat test indicates that fat is likely not being absorbed normally and that the person may have impaired digestion or malabsorption. Lactose malabsorption is a common condition caused by reduced expression or activity of lactase in the small intestine. In such patients, lactose intolerance is characterized by abdominal symptoms (e.g. nausea, bloating, and abdominal pain) after ingestion of dairy products. Lactose malabsorption refers to inefficient digestion of lactose due to reduced expression or impaired activity of the enzyme lactase. After ingestion, lactose passes into the small intestine where it comes into contact with lactase at the intestinal brush border and hydrolysed into the monosaccharides: glucose and galactose, which can be readily absorbed [11].

Keeping the above things in mind it was hypothesized in the present study that hyperglycemia may lead to altered GI motility which may cause small intestinal bacterial overgrowth. This increased bacterial overgrowth may cause malabsorption in type 2 diabetic patients.

Materials and Methods

175 type 2 diabetic patients between the ages 24–70 years and attending Endocrinology Clinic in PGI, Chandigarh were enrolled for this study. Type 2 diabetes mellitus was diagnosed in all subjects according to World Health Organization criterion, which is any individual with two fasting plasma glucose levels of 126 mg/dL or greater. 175 healthy volunteers were also included in the study.

Orocecal Transit Time Measurement

Orocecal transit time (OCTT) was measured according to standard method [12] i.e. by analysis of end expiratory samples for hydrogen and methane concentrations in fasting state and at every 15 min interval for 4 h. Hydrogen and methane in breath were measured using a SC Microlyzer from Quintron, USA. 15 mL syrup containing 10 g lactulose was used as a substrate for this test. Orocecal transit time is defined as the time taken from ingesting of lactulose to the first sustained rise of hydrogen or methane or both in breath $\geq$12 ppm above the base line value. In patients with small intestinal bacterial overgrowth by glucose, orocecal transit time was measured by scintigraphy.

Small Intestinal Bacterial Overgrowth

All patients and controls underwent small bowel bacterial overgrowth study in fasting state after ingesting 70 g of glucose with 250 mL water. Patients were instructed not to eat high fiber diet 3 days prior to test. Analysis of end expiratory air was done at the onset of the test and every 15 min for 2 h. Rise of hydrogen or methane or both, $\geq$12 ppm over the baseline value within 2 h of ingesting glucose was taken as suggestive of bacterial overgrowth [13].

Lactose Intolerance

Lactose intolerance was measured by using non-invasive lactose hydrogen breath test [14]. 25 g lactose dissolved in 250 mL water was given to patients to drink after taking

Table 1 Demographic distribution of type 2 diabetes mellitus patients and controls

	Patients (n = 175)	Controls (n = 175)	*p* value
Males (%)	87 (49.7 %)	89 (50.8 %)	NS
Females (%)	88 (50.3 %)	86 (49.2 %)	NS
Weight (kg)	62.72 ± 10.1	59.9 ± 12.1	<0.05
Body mass index (kg/m^2)	26.8 ± 3.9	24.52 ± 2.7	<0.001
Hemoglobin A1c (%)	8.62 ± 2.3	5.34 ± 0.81	<0.001
Plasma glucose (mg %)	155.2 ± 9.3	98.7 ± 15.9	<0.001
Duration of diabetes (years)	9.6 ± 4.8	–	

Table 2 Age distribution of males and females of type 2 diabetic patients and controls

	Patients (n = 175)	Controls (n = 175)
Males		
Mean ± SD (years)	43.6 ± 13.2	42.1 ± 12.9
Age range (years)	(24–68)	(25–70)
Females		
Mean ± SD (years)	44.2 ± 11.9	43.1 ± 12.1
Age range (years)	(26–70)	(24–68)

fasting end expiratory breath. Breath samples were taken after every 30 min up to 4 h. Rise of hydrogen or methane or both, >20 ppm over the baseline value within 4 h of ingesting lactose was considered as lactose intolerance.

Urine D-Xylose Test

Urinary 5-g D-xylose test was done [15]. In brief, after emptying the bladder and discarding the urine, the patients were asked to ingest 5-g dose of D-xylose. To ensure adequate urine flow, patients were asked to drink 5–6 glasses of water during the test. Urine was collected for the next 5 h. D-xylose was estimated in urine. Values >1 g/5 h/5 g D-xylose (>20 % excretion) was taken as normal.

Fecal Fat

Stool sample was collected for 72 h. During this time patients were maintained on a high-fat diet for three days before beginning of the collection and continue during the 72-h collection period. Values ≤6 g of fat excretion/24 h was taken as normal.

Statistical Analysis

Results were expressed as mean ± SD and percentage. The Chi square test was used to analyze the presence of lactose intolerance in patients and controls; SIBO positive and negative patients. Student's unpaired "t" test was applied to compare malabsorption parameters between the study and control groups. All statistical analyses were performed by using SPSS version 16.0 for Windows (SPSS, Inc., Chicago, IL).

Results

Out of the 175 diabetic patients enrolled, 87 were males while among 175 healthy subjects 88 were males. Percentage of males and females in patients and controls were comparable. Body mass index of diabetic patients was more than controls but the difference was significant. Demographic distribution of type 2 diabetic patients and controls is given in Table 1. Mean ± SD and age range of patients and controls is given in Table 2.

There was a statistically significant increase ($p < 0.002$) in OCTT in type 2 diabetic patients compared with controls (Fig. 1).

SIBO was observed in 26 out of 175 (14.8 %) type 2 diabetic patients and in 5 out of 175 (2.8 %) of the control subjects (Table 3). The difference in SIBO between patients and controls was statistically significant ($p < 0.05$) (Table 3).

OCTT was observed to be more delayed ($p < 0.003$) in patients who were found to have small intestinal bacterial overgrowth than in patients without small intestinal bacterial overgrowth (Fig. 2).

Lactose intolerance was observed in 104 out of 175 (60 %) diabetic patients and 69 out of 175 (39.4 %) in controls. This study shows that lactose intolerance was significantly higher ($p < 0.0001$) in Type 2 diabetic patients as compared to healthy controls (Fig. 3).

Urinary D-xylose levels were also lower in case of diabetic patients but no significant difference was found in 72 h fecal fat excretion among diabetic patients and controls (Table 4).

Malabsorption in terms of Urinary D-xylose and lactose intolerance in SIBO positive type 2 diabetic patients was more severe as compared to SIBO negative diabetic patients (Table 5).

Discussion

Type 2 diabetes is the most common form of diabetes. In type 2 diabetes, either body does not produce enough insulin, or the cells in the body do not recognize the insulin that is present, resulting in high levels of glucose in blood. Hyperglycemia if left untreated can become severe and lead to serious complications affecting various parts of body.

It has now been established that acute changes in blood glucose concentration—both hyper- and hypoglycemia have a marked, reversible, effect on gut motility [16]. Orocecal transit time (OCTT) is how long it takes for food to pass through intestine. It is important because the rate that food passes all the way through the intestinal tract influences how efficiently one's absorbed nutrients from food and influences fermentation associated with healthy gut flora. In the present study, delayed OCTT was observed in diabetic patients as compared to controls. Further, small-bowel bacterial overgrowth (SIBO) can result from alterations in intestinal anatomy or GI motility. This condition can lead to vitamin deficiencies, fat malabsorption, and under nutrition. In the present study, small intestinal bacterial overgrowth was found to be higher in diabetic patients. This is supported by another study [17] in which

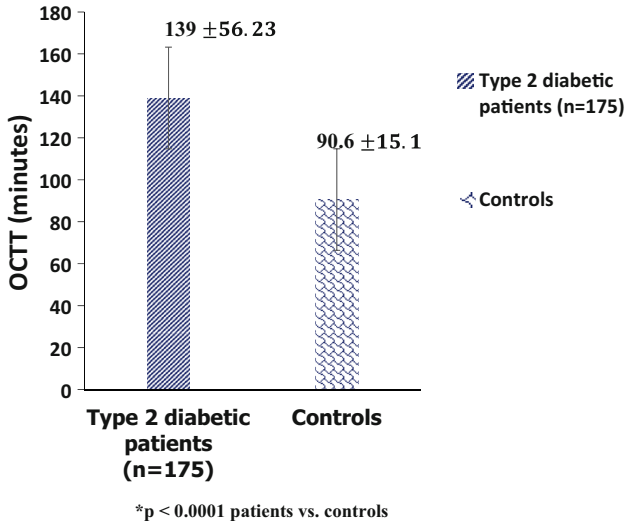

Fig. 1 OCTT (mean ± SD) in patients with type 2 diabetes mellitus and controls

Table 3 Small intestinal bacterial overgrowth in type 2 diabetic patients and controls

	Patients (n = 175)	Controls (n = 175)	*p* value
SIBO positive	26/175 (14.9 %)	5/175 (2.9 %)	<0.05
SIBO negative	149/175 (85.1 %)	170/175 (97.1 %)	

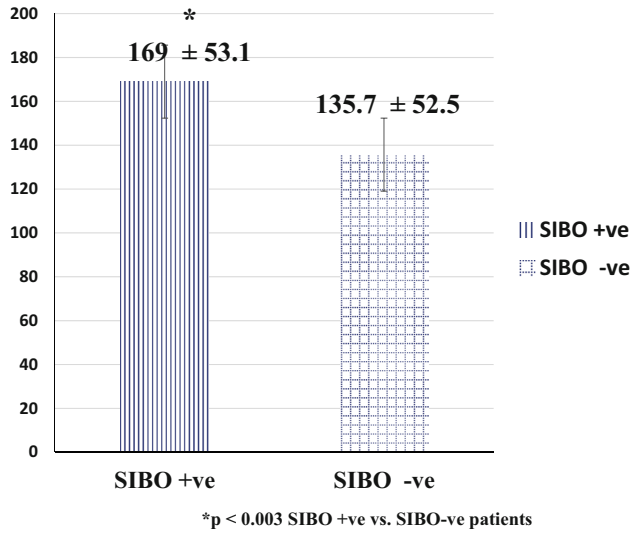

Fig. 2 OCTT in patients with and without SIBO

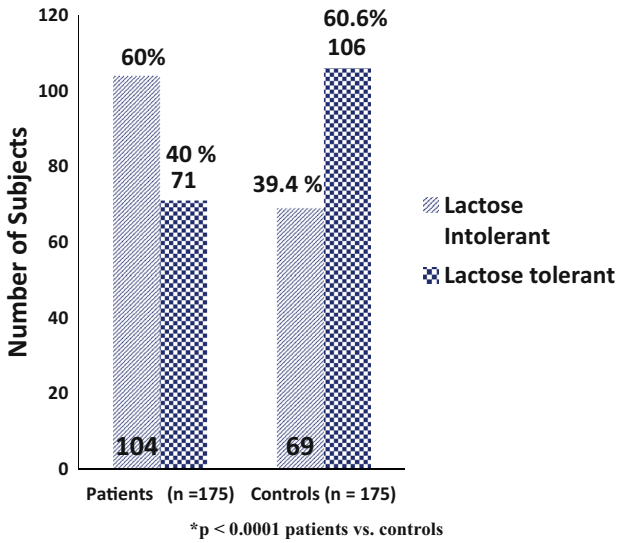

Fig. 3 Lactose intolerance among type 2 diabetic patients and controls

Table 4 Urinary D-xylose and fecal fat in type 2 diabetic patients and controls

	Patients (n = 175)	Controls (n = 175)	*p* value
Urine D-xylose (g/5 g D-xylose/5 h)	0.86 ± 0.33	1.78 ± 0.21	0.01
72 h fecal fat (g/24 h)	3.5 ± 2.15	2.9 ± 1.66	NS

Table 5 Urinary D-xylose and lactose Intolerance in SIBO positive and negative type 2 diabetic patients and controls

	SIBO positive (n = 26) a	SIBO negative (n = 149) b	Controls c	*p* value a versus b	*p* value b versus c	*p* value a versus c
Urine D-xylose (g/5 g D-xylose/ 5 h)	0.71 ± 0.26	1.49 ± 0.38	1.78 ± 0.21	<0.001	<0.001	<0.001
Lactose intolerant	20/26 (76.9 %)	32/149 (21.4 %)	69/175 (39.4 %)	<0.01	<0.001	<0.001

34 % diabetic patients had SIBO. However, the percentage of SIBO is less in our study as compared to Zietz et al. 2000. The reason may be that our diabetic patients were not having auto neuropathy.

As already mentioned that SIBO can lead to various deficiencies and malabsorption. Therefore, in present study, malabsorption function tests like urinary D-xylose, fecal fat and lactose intolerance were estimated among patients and controls. The urinary D-xylose absorption test measures the level of D-xylose, a type of sugar, in a urine sample. This test is done to diagnose problems that prevent the small intestine from absorbing nutrients in food. D-xylose is normally easily absorbed by the intestine. When problems with absorption occur, D-xylose is not absorbed by the intestine, and its level in urine is low. In this study also, the levels of urinary D-xylose was significantly low in diabetic patients than controls.

The fecal fat test can help to estimate the amount of fat in the stool. This can help estimate the percentage of dietary fat that the body does not absorb. In the duodenum, dietary fat (primarily triglycerides) is digested by enzymes into smaller molecules of 1,2-diacylglycerols and free fatty acids which can be absorbed through the wall of the jejenum of the small intestine [18] and enter the circulation for metabolism and storage. As fat is a valuable nutrient, human feces normally contain very little undigested fat. However, a number of diseases of the pancreas and gastrointestinal tract are characterized by fat malabsorption. In this study, no significant difference was observed among diabetic patients and controls. Similar results were observed by Hardt et al. [19]. They observed that the fat excretion did not correlate with diabetes type, duration, or clinical symptoms.

Lactose is a sugar found in milk and milk products. The small intestine contains an enzyme called lactase. It breaks down lactose into two simpler forms of sugar: glucose and galactose. The body then absorbs these simpler sugars into the bloodstream. Lactose intolerance is a condition in which people have digestive symptoms—such as bloating, diarrhea, and gas—after eating or drinking milk or milk products. In this study, lactose intolerance was significantly higher among diabetic patients. However, no study is available to compare our results in terms of lactose intolerance in type 2 diabetic patients.

Moreover, urinary D-xylose levels was lower and lactose intolerance higher among diabetic patients with small intestinal bacterial overgrowth. This shows that small intestinal bacterial overgrowth exaggerates malabsorption leading to various gastrointestinal symptoms among diabetic patients and thus hampering their quality of life and causing GI symptoms.

Thus, we can conclude that delayed OCTT would have caused SIBO among diabetic patients. This SIBO can further instigate malabsorption in these patients which leads to low urinary D-xylose levels and increased lactose intolerance among type 2 diabetic patients.

Thus, it can be advised to these patients for using diet rich in curd/yogurt and small amount of milk and milk products at times in the management of functional gastrointestinal symptoms where lactose intolerance is suspected. This will increase dietary variety and ensure nutritional adequacy.

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Compliance with Ethical Standards

Conflict of interest None.

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