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# Small bowel bacterial overgrowth and type 1 diabetes

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**Abstract. – *Background:*** **Gastrointestinal motility disorders are often present in diabetic patients (pts). Such motility dysfunctions have been attributed to autonomic neuropathy. Impaired intestinal motility is often associated with small-bowel bacterial overgrowth (SIBO) but only few studies evaluated the relationship between autonomic neuropathy and SIBO in diabetic pts.**

***Aim:*** **To compare the prevalence of SIBO between type 1 diabetic (T1D) pts with and without autonomic neuropathy.**

***Patients and Methods:*** **25 pts (13 males, 12 females; mean age 44.2±7) affected by type 1 diabetes with normal cardiovascular autonomic test (group A) and 25 type 1 diabetic pts with abnormal cardiovascular autonomic test (group B) were submitted to hydrogen lactulose breath test.**

***Results:*** **2 out of 25 (8%) showed SIBO among group A, while 11 out of 25 (44%) showed SIBO among group B ($p<0.01$). Interestingly, among group B, the daily insulin requirements was significantly higher in SIBO-positive pts compared to SIBO-negative: 0.66±0.3 vs. 0.59±0.1 UI/kg ($p<0.05$).**

***Conclusions:*** **Pts with autonomic neuropathy have a significantly higher prevalence of SIBO, that is also associated with a higher daily insulin requirements.**

*Key Words:*

Type 1 diabetes, Diabetic autonomic neuropathy, Small bowel bacterial overgrowth, Insulin requirement.

## Introduction

Type 1 diabetic patients (pts) are often affected by macro- and micro-vascular complications; among these, the most important are retinopathy, nephropathy and neuropathy[1,2]. Diabetic autonomic neuropathy (DAN) is a common (and often not diagnosed) diabetes complication observed in about 20% of all pts. For the diagnosis of DAN, besides the careful examination of the patient, a number of specific tests are available[1-3]. DAN may affect many organ systems (e.g., gastrointestinal (GI), genitourinary, and cardiovascular)[4-7]. GI disturbances (e.g., esophageal enteropathy, gastroparesis, constipation, diarrhea, and fecal incontinence) are common and any section of the GI tract may be affected[7,8]. Many studies reveal that both systemic and gastric symptoms of DAN, in the presence of abnormal autonomic function tests, carry a particularly poor patient's prognosis[9-13].

Delayed gastric emptying and intestinal motility disturbance, caused by DAN, may also lead to small bowel bacterial overgrowth (SIBO)[2,7]. SIBO is a clinical syndrome due to the presence of more than $10^6$ colony-forming units per milliliter of intestinal aspirate and/or colonic-type species[14]. The lumen of the proximal small intestine normally contains fewer than $10^4$ organisms per ml of fluid[15]. Many factors restrict bacterial cell growth in the small bowel such as the bacteriostatic role of the gastric acid, of the digestive enzymes, of the bile salts, of the peristalsis and of the secretory IgA. SIBO syndrome is characterized, in its florid form, by diarrhoea and weight loss due to a malabsorption of nutrients and some vitamins. The diagnosis of SIBO was originally defined by jejunal aspiration and culture of intestinal fluid. This technique is considered to be invasive, timeconsuming and expensive[16]. Nowadays, the breath testing technique is preferred, because it is not invasive, less expensive and more tolerated. The commonly used test is the lactulose breath test (LBT) characterized by higher sensitivity (68% versus 16.7%) but lower specificity (44% versus 70%)[17,18] than the jejunal aspiration technique. A positive test re-

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quires an elevated breath hydrogen ($H_2$) concentration within 90 min, two distinct peaks, and an increase >20 ppm over the $H_2$ basal value[19,20].

Only few studies evaluated the relationship between DAN, impaired intestinal motility and SIBO in diabetic pts. The aim of this study was to evaluate the prevalence of SIBO in type 1 diabetic pts with and without autonomic dysfunction and to investigate the possible relationship between SIBO and glycaemic control.

## Patients and Methods

We consecutively enrolled 50 pts with a diagnosis of type 1 diabetes mellitus according to American Diabetes Association guidelines, who were regularly followed at the Diabetic Care Unit of our Hospital: 25 pts (13 males and 12 females; mean age 44.2±7) affected by type 1 diabetes with normal cardiovascular autonomic tests (CAT) (group A) and 25 type 1 diabetic pts with abnormal CAT (group B).

All pts were submitted to CAT and LBT under standard conditions. For each pts, HbA1c mean values were obtained by higher performance liquid chromatography analysis performed on Diamat BioRad (BioRad, Milan, Italy). The HbA1c reference range for healthy subject was 4.3-5.9%.

### Exclusion Criteria

None of the pts had a history of use of laxative, PPI, ranitidine, probiotics, antibiotics, steroid for a period of at least one month before the investigation. Pts who had a previous history of partial gastrectomy or history of pancreatic surgery were also excluded from the study.

Other causes of SIBO (blind-loop syndrome, small intestinal bypass, incomplete stenosis of the small bowel, duodenal and massive duodenal-jejunal diverticulosis, chronic infection of main bile duct, scleroderma, achlorydria, hypogammaglobulinaemia, celiac disease, inflammatory bowel disease, and hypothyroidism) were considered exclusion criteria.

### Informed Consent

The study was performed in accordance with the Declaration of Helsinki, approved by the Ethic Committee of our University and all patients gave written informed consent to participate to the study after full explanations from the investigators.

### Statistical Analisys

All results were expressed as means ± SD. Statistical differences between patients groups were assessed by appropriate test (Student's t test for continuous data, Chi-square for categorical ones); a results difference with $p<0.05$ was considered to be significant.

### Lactulose $H_2$-Breath Test (Lbt)

To minimize basal hydrogen ($H_2$) excretion, subjects were asked to have a carbohydrate-restricted dinner on the day before the test and to be fasting for at least 12 hours.

The day of LBT pts had a mouthwash with clorhexidine 20 mL at 0.05%. After providing a baseline hydrogen ($H_2$) breath sample, subjects ingested 10 g of lactulose in 200 ml water. The subjects were instructed not to eat, drink, smoke, sleep, or exercise vigorously during the test. End alveolar breath samples were collected with a two-bags system immediately before the ingestion of water-lactulose solution; then breath samples were taken every 15 minutes for 4 hours. The two bags system includes a mouthpiece, a T valve and two bags, the first collects dead-space exhaled air, the latter takes alveolar air. The air samples were aspirated from the latter bag with a 30 mL plastic syringe and immediately analysed using a DP Quintron Gas-Chromatograph (Quintron Instrument Company, Milwaukee, WI, USA).

The criteria for a positive test were a rise in $H_2$ >20 ppm by 90 min or 180 min. Moreover, the revised criteria applied by Pimentel et al[16,17] in 2003 for a normal test were "no rise of breath hydrogen or methane concentration before 90 min of lactulose with a definitive rise never >20 ppm during 180 min of measurement".

### Cardiovascular Autonomic Tests

DAN was diagnosed according to a standardized procedure including four CAT: (1) heart response to Valsalva manoeuvre or Valsalva ratio which is the ratio of the longest R-R interval after the manoeuvre to the shortest R-R interval during the manoeuvre; (2) heart rate changes during deep breathing at a frequency of 6 breaths/min; (3) heart rate changes in response to standing up: ratio of the 30 to the 15 interval after changing from supine to upright posture; (4) blood pressure response to standing up. According to Ewing and Clarke[21], the autonomic cardiovascular score was computed by summing scores attributed to the four individual tests as follows: 0 if normal, 1 if

**Table I.** Diabetic autonomic neuropathy was diagnosed according to a standardized procedure including four cardiovascular autonomic tests. According to Ewing and Clarke[21], an autonomic cardiovascular score was computed by summing scores attributed to the four individual tests as follows: 0 if normal, 1 if borderline and 2 if abnormal.

| Tests | Normal | Borderline | Abnormal | Explored autonomic system |
|---|---|---|---|---|
| Heart rate response to Valsalva maneuver | >1.21 | 1.11-1.20 | <1.10 | Parasympathetic |
| Heart rate (R-R interval) variation during deep breathing, beats/min | >15 | 11-14 | <10 | Parasympathetic |
| Immediate heart rate response to standing (30:15 ratio) | >1.04 | 1.01-1.03 | <1.00 | Parasympathetic |
| BP response to standing, mm Hg | <10 | 11-29 | >30 | Sympathetic |

borderline and 2 if abnormal. Thus, the autonomic cardiovascular score can range between 0 and 8. Patients having at least one abnormal response or two borderline responses, with a cardiovascular score >2, were considered to have autonomic neuropathy (Table I).

## Results

All patients completed the study. Demographics and baseline characteristics of the studied population are reported in Table II.

### Lactulose Breath Test

Among Group A, 2 out of 25 (8%) pts showed SIBO, while 11 out of 25 (44%) showed SIBO among Group B pts. The difference between groups resulted to be statistically significant with a $p$ <0.01.

### Insulin Requirement

The insulin requirement was no different between Group A and Group B (0.60±0.2 vs 0.62±0.1 UI/kg; $p$=n.s.). Interestingly, among group B, the daily insulin requirements was significantly higher in pts with SIBO when compared with SIBO-negative pts: 0.67±0.2 vs 0.59±0.3 UI/kg ($p$<0.05).

## Discussion

The present study showed a significantly higher prevalence of SIBO in type 1 diabetic pts with abnormal CAT compared to those with normal CAT.

SIBO is a clinical condition characterized by a malabsorption syndrome due to an increase in microorganisms within the small intestine. The main mechanisms restricting bacterial colonization in the upper gut are the gastric acid barrier, mucosal and systemic immunity and intestinal clearance. When these mechanisms fail, bacterial overgrowth develops. Camilleri and Malagelada reported that small intestinal motility was abnormal in about 80% pts of long-standing diabetes with delayed gastric emptying. Both postprandial and fasting small intestinal dysmotility in their diabetic pts are altered[22].

So we hypothesized that the dysfunction of intestinal motility may predispose to SIBO in diabetic pts such as in other conditions (i.e. progressive systemic sclerosis). Furthermore, SIBO is responsible for sugar malabsorption such as glucose, fructose, lactose, sorbitol[23]. Intestinal bacteria, such as *Bacteriodes Thetaiotaomicron*[24], the most studied anaerobe bacteria colonizing the human colon, may provide a fermentation of these oligosaccharides and their malabsorption. In particular, in diabetics pts with SIBO a marked acute hyperglycemia, resulting from glucose malabsorption in small bowel, may require a major insulin dosage. In

**Table II.** Demographic characteristics of the type 1 diabetic pts with normal (Group A) and abnormal cardiovascular autonomics tests (Group B). CAT: Cardiovascular autonomic tests.

| | Normal CAT (Group A) | Abnormal CAT (Group B) |
|---|---|---|
| Gender | 13M/12F | 15M/10F |
| Mean age | 44.2±7 yrs | 52.4±6 yrs |
| Diabetes duration | 22.3±2 yrs | 29.8±3.6 yrs |

fact, in the absence of SIBO, ingested glucose is absorbed in the proximal part of the small bowel, and thus not fermented. All these aspects could explain the higher insulin requirement in SIBO-positive subjects.

Up to date our results are in accordance with several studies[25] demonstrating how transit disturbances can result in instable metabolic condition and in major insulin requirement. These findings could be of clinical relevance and need of further studies with a larger cohort of pts to confirm the findings.

Definitively, the dysfunction of gastrointestinal motility may contribute to maintain SIBO in diabetic pts with a round circle that automantains by itself.

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