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ORIGINAL ARTICLE

Investigating the relationship between small intestinal bacterial overgrowth and hemoglobin A1C level in patients with type 2 diabetes mellitus: An epidemiologic study in Ahvaz, Iran

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Abstract

Background Type 2 diabetes mellitus (T2DM) is one of the most prevalent metabolic disorders, characterized by insulin resistance and chronic hyperglycemia. Recent studies have suggested that small intestinal bacterial overgrowth (SIBO) may influence glycemic control and gastrointestinal complications in diabetic patients. However, the precise relationship between SIBO and hemoglobin A1C (HbA1c) levels remains inadequately explored.

Objective The study aims to fill research gaps in Ahvaz, Iran, on the relationship between glycemic control and factors in diabetes patients with small intestinal bacterial overgrowth (SIBO) syndrome.

Methods This epidemiologic study, applying a descriptive-analytical cross-sectional research design, was performed on type 2 diabetes mellitus (T2DM) patients recruited based on the inclusion criteria, including, suffering from T2DM as diagnosed by an endocrinologist, having a history of Gastrointestinal (GI) symptoms, and being at the age range of 18–65 years. Upon signing a written informed consent form, the patient's baseline characteristics were checked and then imported into the data collection tool. The patients were subsequently divided into two groups as specified by glycemic control and hemoglobin A1C (HbA1C) level, namely, Group I ($n = 40$) consisting of the T2DM patients with reasonable glycemic control (HbA1C$\leq$7.5) and Group II ($n = 40$) comprised of the T2DM patients with poor glycemic control (HbA1C>7.5). Ultimately, the prevalence rate of SIBO coupled with the role of various factors in the relationship between glycemic control and the given syndrome were compared in both study groups.

Results The study results revealed that the prevalence rate of the SIBO syndrome was higher (p-value = 0.025) in T2DM patients with poor glycemic control, but this relationship could vary based on some associated factors, such as age, gender, disease duration, and even smoking.

Conclusion The study explores the link between T2DM and SIBO, emphasizing the importance of glycemic control in preventing symptoms and improving patient quality of life, particularly considering SIBO syndrome.

Keywords Epidemiologic study · Hemoglobin A1C · Type 2 diabetes mellitus · Small intestinal bacterial overgrowth

Main points

- SIBO was more prevalent in T2DM patients with poor glycemic control than in those with reasonable control. However, factors such as age, gender, disease duration, and smoking may influence this relationship.
- Most T2DM patients in the study were women aged 56 to 65 with a body mass index (BMI) below 25. Most patients had received oral drug treatments, and most had less than 10 years of DM treatment.
- In terms of age, disease duration, and various laboratory indicators, no significant differences were found between patients with effective and poor glycemic control, except for Fasting Blood Sugar (FBS). Drug treatment types and dyslipidemia showed substantial differences.
- There was a significant correlation between HbA1C levels and SIBO in the study. Despite adjustment for age, gender, BMI, dyslipidemia, anemia, smoking, drug treatment, and gastrointestinal symptoms, this relationship remained significant. The findings emphasize the importance of glycemic control in preventing SIBO symptoms in patients with type 2 diabetes.

Extended author information available on the last page of the article

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Introduction

Diabetes mellitus, particularly T2DM, has been acknowledged as one of the most common metabolic disorders. It is characterized by diminished or inappropriate insulin secretion by the beta cells of the Langerhans islets, accompanied by various degrees of insulin resistance, which gives rise to hyperglycemia [1–3]. It is estimated that over 537 million people worldwide suffer from this condition, and aging and lifestyle changes have been identified as the most significant risk factors [4].

DM (including types 1 and 2) disrupts the digestive system's essential functions [5]. Thus, many patients undergoing this condition are burdened with GI symptoms, including nausea and vomiting, epigastric fullness, diarrhea, constipation, bowel incontinence, heartburn, abdominal bloating, and upper abdominal pain after eating. The prevalence rate of GI complaints is not the same in diverse racial categories [6], and GI symptoms mainly occur in 30–76% of DM patients [7]. Among the common digestive disorders in this respect is gastroparesis, also called gastric stasis. It occurs when high blood/or serum glucose levels for extended periods can permanently damage the nerve fibers of the stomach and intestines and impair the blood vessels feeding them. As another digestive disorder, some deviations also appear in the small and large intestines' movements, resulting in constipation or diarrhea. In such situations, the reduced motility of the intestines brings about intestinal bacteria overgrowth and accumulation, which cause diarrhea. Most GI complaints come from the lack of motions in the GI tract and the resulting bacterial overgrowth, formerly assumed as one of the manifestations of diabetic autonomic neuropathy (DAN) [8]. GI disorders caused by DAN can lead to small intestinal stasis, thereby augmenting the chance of SIBO [9]. The dysfunction of the vagus nerve and the internal gut autonomic ones may further intensify the GI-associated DAN [9]. Today, much more evidence shows that such complaints are multifactorial, and high blood/or serum glucose levels alone can be the root of movement disorders and bacterial overgrowth [10, 11]. SIBO syndrome has been described as the excessive colonization of aerobic and anaerobic Gram-negative bacteria in the proximal small intestine [12]. Recently, numerous studies have focused on a novel mechanism in which SIBO has been involved in T2DM development. Nearly all studies have demonstrated that the prevalence rate of the SIBO syndrome has been higher in DM patients, especially those suffering from T2DM and diabetic peripheral neuropathy [13, 14]. Previous research has similarly confirmed that GI symptoms in SIBO-positive T2DM patients with chronic abdominal pain or diarrhea and poor glycemic control have improved after the SIBO treatment [15, 16]. Given the high prevalence rate of DM as a significant public health concern in modern society in conjunction with the growing trend of GI complications and their annoying and even debilitating symptoms, as well as limited research on the relationship between glycemic control in DM patients with SIBO syndrome, the present study aimed to investigate the relationship between SIBO and hemoglobin A1C (HbA1C) level in the T2DM patients in Ahvaz, Iran, to fill such gaps.

Materials and methods

Study design

Eighty patients had T2DM, 40 with poor glycemic control and 40 with reasonable glycemic control, at the Endocrinology Clinic at Golestan Hospital in Ahvaz, Iran, in 2020. All the eligible patients were then selected in line with the inclusion and exclusion criteria and after providing some explanations regarding the research objectives and methods. Inclusion criteria were patients suffering from T2DM as diagnosed by an endocrinologist, having a history of GI symptoms, and being in the age range of 18–65. Patients with specific anatomical conditions, patients undergoing ileal resection, intestinal motility disorders, irritable bowel syndrome (IBS), and other small intestinal pathologies leading to SIBO were excluded from the study. Another exclusion criterion was patient death. After signing the written informed consent forms, the patients were included in the survey.

The patient's baseline characteristics were checked and imported into the data collection tool. It is worth noting that such information was collected by referring to the patient records, their history, and the laboratory test results.

Ethical approval and informed consent

This study was fulfilled based on observing the ethical principles of the Declaration of Helsinki (DoH) and upon receiving the approval of all the related protocols by the Research Council of Ahvaz Jundishapur University of Medical Sciences (AJUMS), Ahvaz, Iran, and obtaining the code of medical ethics (IR. AJUMS.REC.1399.032) from the Medical Ethics Committee of the respected university.

Outcome measure

This information also contained age, gender, disease duration, GI symptoms, smoking, height, weight, BMI, type of treatment (including oral drugs, insulin, or both), HbA1C level, complete blood count (CBC), thyroid stimulating hormone (TSH), lipid profile, and liver and kidney tests.

This study divided the patients into two groups based on glycemic control and HbA1C level. That is Group I consisted of the T2DM patients ($n = 40$) with good glycemic control (HbA1C≤7.5) [17–19] and Group II comprised the T2DM patients ($n = 40$) with poor glycemic control (HbA1C>7.5). Poor glycemic control was defined as an average glycated hemoglobin level of >7.5 based on ISPAD clinical practice consensus guidelines. Ultimately, the SIBO evaluation results were compared between both groups. The patients' GI symptoms were then examined by the Gastrointestinal Symptom Inventory (GISI), completed by the physician or the operator. Subsequently, four cc of blood samples were taken from all patients after 8–10 h of fasting to measure FBS and HbA1C levels at the laboratory of Golestan Hospital in Ahvaz, Iran. The patients were further referred to the Endoscopy Unit of this hospital to perform the hydrogen breath test to assess the SIBO syndrome using the LactoFAN2 device (V. 1.16–1.20, Germany). The given test was conducted as follows. At first, the patients in both groups were given 10 g of lactulose dissolved in 150 ml of water. Breath sampling was done before taking the solution and 30, 60, 120, and 150 min after giving it. Then, working with the hydrogen breath test device was done so the patient completely inserted one's lips into its mouthpiece, the start button was pressed, and the desired settings were selected (namely, the lactulose solution option on the device monitor). At the next step, the operator asked the patient to take a deep breath and hold it until the countdown on the device monitor was finished. Holding the device's mouthpiece tightly, the patient slowly blew into it for about 20 s. Afterward, the test results appeared on the device monitor. Accordingly, the SIBO-positive was defined as a growth of over 20 ppm in the hydrogen amount in the patient's breath by the LactoFAN2 device instructions.

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Science (SPSS v26.0.1, Chicago, IL, USA). The chi-square test counts the frequency of specific observations in both groups, poor glycemic control, and reasonable glycemic control. Clinical and demographic variables measured between two groups and data are presented as the mean ± SD. p values < 0.05 were considered to indicate statistically significant differences.

Results

The patient's demographic characteristics and the measurement of the study indicators demonstrated that most cases were women (55%) aged 56–65 (40%). Most patients also had a BMI of not more than 25 (43.75%). On the other hand, nearly all had received treatments in the form of oral drugs (metformin, sitagliptin, and empagliflozin) alone (62.5%). The DM duration in most cases was less than or equal to 10 years (60%). Besides, most patients (85%) had no history of smoking. Also, abdominal bloating, constipation, and diarrhea were the most frequent GI complaints (95%). Among 80 T2DM patients, SIBO was registered for 36 cases (45%) (Table 1).

Examining the laboratory test results in both study groups, with good (HbA1C≤7.5) and poor (HbA1C>7.5) glycemic control, further exhibited no statistically significant difference in patient's age, disease duration, and laboratory test indicators, such as the kidney, liver, TSH, vitamin D3, uric acid function test profile (p-value > 0.05). Still, there was a significant difference in the case of FBS (p-value < 0.014) (Table 2).

Besides, a statistically significant difference was detected between Group I (HbA1C≤7.5) and Group II (HbA1C>7.5) regarding the type of drug treatment (p-value < 0.001). The study included 50 patients (62.5%) taking oral tablets (metformin, sitagliptin, and empagliflozin) to control their blood sugar, while the rest were on combination therapy with tablets and insulin or insulin alone. A statistically significant relationship did not exist between SIBO in different treatment groups regarding the relationship between hemoglobin A1C level and incidence. Concerning BMI, there was no significant difference between smoking and GI symptoms (p-value > 0.05). Investigating dyslipidemia correspondingly revealed a statistically significant difference between both study groups (p-value = 0.025), but there was a difference in terms of anemia, which was not statistically significant (p-value > 0.05) (Table 3).

Table 4 illustrates the relationship between HbA1C and SIBO. The raw research model presents the association between the HbA1C level and the SIBO syndrome. Accordingly, there is a significant relationship between SIBO and HbA1C (p-value = 0.026, odds ratio (OR) = 2.81, 95% confidence interval (CI) = 1.13–6.99). The adjusted model 1 also included the review of the raw model with controlled age and gender, denoting that the relationship was investigated in the patients with the same gender and age in both study groups with good and poor glycemic control, and it was significant (p-value = 0.016, OR = 3.26, 95% CI = 1.24–8.55). The adjusted model 2 further contained the review of the adjusted model 1 with much control on BMI, dyslipidemia, anemia, smoking, type of drug treatment, and GI symptoms (p-value = 0.037, OR = 5.60, 95% CI = 1.11–28.30). There was also a significant relationship in both adjusted models 1 and 2.

The chi-square test outcomes showed a statistically significant difference in the HbA1C level in the study groups with and without SIBO (p-value = 0.026) (Table 5). Furthermore,

Table 1 Demographic characteristics of T2DM patients

Variable	Ranges	Prevalence	Percentage
Age (years)	18–40	18	22.5
	41–55	30	37.5
	55–65	32	40
Sex	Male	36	45
	Female	44	55
Type of medicine	Oral agent	50	62.5
	Insulin	34	30
	Oral agent + Insulin	6	7.5
BMI (Kg/m^2)	<18	3	3.75
	18.01–25	35	40
	25.01–30	25	31.25
	30.01–35	11	13.75
	35<	9	11.25
Duration of diabetes (years)	≤10	48	60
	>10	32	40
HbA1C	≤7.5	40	50
	>7.5	40	50
SIBO	Negative	44	55
	Positive	36	45
Smoking cigarette	Yes	12	15
	No	68	85
Gastrointestinal symptoms	Dyspepsia (EPS, PDS)	38	47.5
	Constipation, obstipation, flatulence	38	47.5
	Diarrhea	4	5

Abbreviations: *HbA1C* hemoglobin A1C, *SIBO* small intestinal bacterial overgrowth, *BMI* body mass index, *EPS* epigastric pain syndrome, *PDS* postprandial distress syndrome

Table 2 Laboratory test indicators in T2DM patients in study groups based on HbA1C

Data	HbA1C ≤ 7.5 Average (standard deviation)	HbA1C > 7.5 Average (standard deviation)	*p*-value
Age (years)	50.9 (11.21)	46.75 (13.83)	0.14
Duration of diabetes (years)	8.82 (5.96)	9.52 (7.06)	0.63
AST	29.19 (17.41)	34.26 (25.94)	0.36
ALT	32.94 (22.43)	35.03 (25.98)	0.73
Total bilirubin	0.93 (0.32)	0.81 (0.28)	0.31
Uric acid	4.9 (0.96)	5.1 (0.14)	0.79
Vitamin D3	25.44 (11.39)	23.62 (7.94)	0.57
TSH	1.61 (0.47)	2.92 (3.84)	0.14
FBS	131.46 (47.53)	206.74 (74.57)	<0.001
Cr	0.94 (0.33)	1.23 (1.21)	0.13

Abbreviations: *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *TSH* thyroid stimulating hormone, *FBS* fasting blood sugar, *Cr* creatinine

the statistical analysis of each group age indicated that the observed difference in the HbA1C level in the study groups was significant only in the age group of less than 40 (p-value = 0.001) and that was not so in other age groups (p-value > 0.05). Likewise, the statistical analysis by gender revealed that the HbA1C level in the groups with and without SIBO was significant only in women (p-value = 0.033) but not in men having HbA1C levels with and without SIBO (p-value = 0.204). SIBO was found in 13 patients (32.5%) in the group with HbA1C≤7.5 and 23 cases in the group with HbA1C>7.5 (57.5%) (Table 5).

The statistical analysis in terms of the different BMI values and treatment types suggested that the observed difference in the HbA1C level in the groups with and without SIBO based on BMI and types of treatment was not significant. Moreover, the statistical analysis of the DM duration denoted that the HbA1C level in different groups with SIBO was significant merely in the group with the DM duration of not more than 10 years (p-value = 0.01) but that was not so in the group with the DM duration of more than 10 (p-value = 0.618). The observed difference concerning smoking was statistically significant (p-value

Table 3 Frequency of indicators in T2DM patients in study groups based on HbA1C

Data	Ranges	HbA1C ≤ 7.5 Number (percentage)	HbA1C > 7.5 Number (percentage)	*p*-value
BMI (Kg/m^2)	<18	0	3 (7.5%)	0.184
	18.01–25	13 (32.5%)	19 (47.5%)	
	25.01–30	15 (37.5%)	10 (25%)	
	30.01–35	6 (15%)	5 (12.5%)	
	35<	6 (15%)	3 (7.5%)	
Type of medicine	Oral agent	31 (77.5%)	19 (47.4%)	<0.001
	Insulin	4 (10%)	20 (50%)	
	Oral agent + Insulin	5 (12.5%)	1 (2.5%)	
Smoking cigarette	Yes	8 (20%)	4 (10%)	0.35
	No	32 (80%)	36 (90%)	
Gastrointestinal symptoms	Dyspepsia (EPS, PDS)	19 (47.5%)	19 (47.5%)	1.00
	Constipation, Obstipation, flatulence	19 (47.5%)	19 (47.5%)	
	Diarrhea	2 (5%)	2 (5%)	
Dyslipidemia*	Negative	23 (69.7%)	12 (41.38%)	0.025
	Positive	10 (30.3%)	17 (58.62%)	
Anemia**	Negative	30 (86%)	22 (63%)	0.054
	Positive	5 (14%)	13 (37%)	

Abbreviations: *BMI* body mass index, *EPS* epigastric pain syndrome, *PDS* postprandial distress syndrome

*One or more of the following: Total Chol>240, LDL>160, TG>200, HDL<40

**Anemia as a level of Hb below 13.0 g/dL in male adults, below 12.0 g/dL in female adults

Table 4 Relationship between HbA1C and SIBO

	Odds ratio	*p*-value	95% CI
Crude model	2.81	0.026	1.13–6.99
Adjusted model 1	3.26	0.016	1.24–8.55
Adjusted model 2	5.60	0.037	1.11–28.30

Table 5 Frequency of HbA1C level based on SIBO in T2DM patients

HbA1C	SIBO based on number of patients (percentage)			*p*-value
	SIBO –	SIBO +	Total	
HbA1C ≤ 7.5	27 (67.5%)	13 (32.5%)	40 (100%)	0.026
HbA1C > 7.5	17 (42.5%)	23 (57.5%)	40 (100%)	

Abbreviations: *HbA1C* hemoglobin A1C, *SIBO* small intestinal bacterial overgrowth.

= 0.014), but the HbA1C level was unimportant in the non-smoking groups with and without SIBO (*p*-value = 0.127). The statistical analysis of the GI symptoms further showed that the difference observed in the HbA1C level in different SIBO groups was statistically significant only in the patients with GI complaints (*p*-value = 0.03) (Table 6).

Discussion

The pathophysiological mechanism of SIBO has not been fully explained. Few studies reflect on the relationship between beta-cell function in T2DM and SIBO. In this manner, Rana et al. observed SIBO in 14.8% and 2.8% of the 175 T2DM patients and the 175 healthy controls, respectively. They similarly reported higher BMI in the T2DM patients than the controls, with a significant difference. As well, Zietz et al. [20] illustrated the prevalence rate of SIBO in 34% of DM patients. In this study, 50 diabetic outpatients with previously unknown diabetes-related gastrointestinal disorders (20 type 1 and 30 type 2 diabetic patients, mean age 47.3 ± 2.2 years, duration of diabetes 14.4 ± 1.3 years, HbA1c 8.4 ± 0.3%) were enrolled. The patients with SIBO-positive symptoms presented more GI symptoms than the SIBO-negative ones, which included diarrhea and abdominal bloating.

In the meta-analysis by Tarigan et al. [21], 1072 T2DM patients were also examined in six studies at different clinics and hospitals, indicating that the HbA1C level in the T2DM patients with SIBO was higher (*p*-value = 0.02), and blood insulin levels were lower (*p*-value = 0.001). According to this study, SIBO was present in 24.39% of the T2DM patients, and it exasperated the complications in such cases, characterized by lower insulin and higher HbA1C levels. As stated in Urita et al. [22], between 82

Table 6 Frequency (percentage) of HbA1C level and SIBO based on GI symptoms in T2DM patients

HbA1C	Gastrointestinal symptoms based on number of patients (percentage)					
	Dyspepsia (EPS, PDS)		Constipation, obstipation, flatulence		Diarrhea	
	SIBO −	SIBO +	SIBO −	SIBO +	SIBO −	SIBO +
HbA1C ≤ 7.5	15 (78.9%)	4 (21.1%)	12 (63.2%)	7 (36.8%)	0	2 (100%)
HbA1C > 7.5	6 (31.6%)	13 (68.4%)	11 (57.9%)	8 (42.1%)	0	2 (100%)
p-value	0.003		0.741		-	

Abbreviations: *HbA1C* hemoglobin A1C, *EPS* epigastric pain syndrome, *PDS* postprandial distress syndrome

diet-controlled diabetic patients (42 women and 40 men; age range 30–84 years, average 62 years), the patients with carbohydrate malabsorption were older and had poor glycemic control, as compared with those who did not have carbohydrate malabsorption. Besides, Yan et al. [12] considered the relationship between beta-cell function and SIBO in 104 patients who had an oral glucose tolerance test (OGTT) before or after the glucose H2/CH4 breath test, wherein the given syndrome was associated with lower insulin production and poor glycemic control. Still, no difference was observed between both groups. Moreover, there were no statistically significant differences in terms of age, gender, and disease duration. In this line, Malik et al. [23], in an analytical observational study in India on 300 T2DM patients with a disease duration of over 5 years referred to a diabetes clinic, observed that SIBO had been significantly higher (p-value < 0.001) in such patients than the controls. Similarly, the oxidative and inflammatory stress markers in the T2DM and SIBO-positive patients were substantially higher (p-value < 0.001) than those in the control group with SIBO-negative. The HbA1c levels were also significantly higher in the T2DM patients (p-value < 0.05) than the controls. Another study from Martin et al. [24] aimed to determine the prevalence of small intestine bacterial overgrowth in 200 patients of both sexes without age limitation associated with digestive symptoms. This study accordingly reported that GI symptoms were higher in women, which was somehow related to the higher prevalence rate of SIBO in female patients with higher HbA1C levels and the possible effect of gender on this relationship, consistent with the results in the present study. Jung et al. [25] found that patients with SIBO had significantly lower BMI and waist circumference than those without this condition.

Limitations of the study

Among the limitations of this study was its completion during the coronavirus disease 2019 (COVID-19) pandemic, which made it more demanding to recruit T2DM patients about the inclusion criteria. Moreover, no healthy control group was considered for comparison because all people might suspect Coronavirus, and a healthy control group was not used in the study. The lack of studies on the role of smoking in SIBO occurrence and its relationship with glycemic control in DM patients to make use of previous experiences was the other limitation of the present study.

Conclusion

The high prevalence rate of SIBO and indigestion as a clinical symptom with a significant role in SIBO and glycemic control in T2DM patients might be accordingly related to the genetic background or the diet in the statistical population. In addition, the role of proper glycemic control in SIBO could become dimmer after more than 10 years with T2DM and the increase in the patient's age. The present study could thus provide new insights into the role of smoking and the female gender in SIBO, and poor glycemic control was additionally among other results in this study, calling for more investigations in the future. More comprehensive studies, such as the simultaneous examination of beta-cell function or the utilization of the latest advanced techniques, would ultimately provide broader perspectives in this field.

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Data availability The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate The approval of our work was issued by the ethics committee for research at the Ahvaz Jundis-

hapur University of Medical Sciences (AJUMS) with the code of ethics of IR.AJUMS.REC.1399.032.. All participants signed informed written consent, and this study followed the Second Statement of Helsinki.

Consent for publication Not applicable.

Competing interests The authors declare no competing interests.

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