

Prevalence of Small Intestinal Bacterial Overgrowth (SIBO) In Type 2 Diabetes Mellitus: A Systematic Review

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Abstract

Purpose: Gastrointestinal symptoms affect 50-70% of diabetic patients, resulting in a microbiota composition imbalance. Autonomic neuropathy is irreversible, resulting in diabetic enteropathy and sometimes even small intestine bacterial overgrowth (SIBO). SIBO can result in bile acid deconjugation, diarrhea, steatorrhea, vitamin and micronutrient malabsorption, weight loss, mucosal injury, bacterial translocation, and worsened intestinal motility. Carbohydrate malabsorption is related to the pathogenesis of diabetic macrovascular complications. The goal of this study is to find out how prevalent SIBO is in type 2 diabetes patients.

Methods: "Small intestinal bacterial overgrowth," "small bowel bacterial overgrowth," "SIBO," "type 2 diabetes mellitus," and "type 2 DM," are the keywords used. We searched Proquest, CINAHL, SCOPUS, ScienceDirect, PubMed/MEDLINE, and manual searches through world diabetes associations such as ADA, EASD, EFSD, IDF, FASEB, and PERKENI using the keywords. We use the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for bias risk assessment, and for data analysis, we use STATA 16.

Results: Six articles covered 1072 type 2 diabetes patients in clinics and hospitals. With a minimum score of 7.42% and a maximum value of 53.85%, 95% CI 9.97-38.86, and an I2 of 97.17%, the pooled prevalence was 24.39% SD 15.31. HbA1c levels were higher ($p=0.02$) in type 2 DM patients with SIBO, and blood insulin levels were lower ($p=0.001$) in type 2 DM patients with SIBO. Each study was pretty varied, and there was evidence of publication bias. Assessment of findings based on GRADE is moderate.

Conclusion: According to this study, SIBO is present in 24.39% of type 2 diabetes patients. SIBO conditions exacerbate the morbidity of patients with type 2 diabetes, as indicated by lower insulin levels and a higher HbA1c. In type 2 diabetes patients, a hydrogen breath test (HBT) is recommended to be performed regularly, especially in those who have had DM for more than 5 years.

Introduction

Diabetes mellitus shows a rising prevalence year after year. Diabetes affects 24.1 million people in the United States. Meanwhile, the National Health Survey in Singapore found that 9% of adults in Singapore have diabetes.[1] Diabetes mellitus (DM) is known as the century's epidemic, with an estimated 382 million DM patients worldwide in 2013 and an 8.3% prevalence rate. This number has been steadily rising, and by 2019, it had risen to 463 million people (9.3%). The number is expected to rise, with 578 million people worldwide diagnosed with diabetes by 2030 (10.2%). The prediction of the figure's increment over time is consistent with current trends. Indonesia is one of the top ten countries with the most diabetes patients globally, with 8.5 million people diagnosed in 2013 and a predicted 14.1 million by 2030.[2–5] According to blood glucose test results, the prevalence of diabetes patients in Indonesia had risen from 6.5% in 2013 to 8.5% in 2018.[6]

Gastrointestinal symptoms are common in diabetic patients (50-70%) and can affect patients' quality of life as well as diabetes morbidity. Anorexia, vomiting, abdominal pain, constipation, and diarrhea are among the symptoms. These symptoms are caused by gastrointestinal motility abnormalities, which are a symptom of irreversible autonomic neuropathy. Other research has linked these events to the duration of diabetes and the type of diabetes treatment. Acute changes in blood glucose concentration have been shown in other studies to have a significant impact on gastrointestinal motoric function in both healthy people and diabetic patients. These gastrointestinal symptoms are thought to be linked to diabetic patients' glycemic control.[7–9]

Changes in the microbiota's composition could impact a variety of things, including the immune system, which is dependent on the microbiota for the production of cytokines and interleukins, as well as some diseases linked to changes in the microbiota's composition.[10] Differences in dietary patterns have been shown to affect the composition of the gut microbiota so that various factors can cause an imbalance in the microbiota composition.[11] SIBO (Small intestinal bacterial overgrowth) is one of the intestinal microbiota imbalances to be aware of.[12] SIBO can result from these changes in enteric myopathic neuropathy, which can cause bile acid deconjugation, diarrhea, steatorrhea, malabsorption of vitamins and micronutrients, weight loss, mucosal injury, bacterial translocation, and worsening intestinal motility. [8]

SIBO is defined as the finding of abnormal bacteria $>10^5$ colony forming unit per milliliter (CFU/mL) in proximal jejunal aspiration.[12, 13] SIBO is commonly found in immunocompromised patients and gastrointestinal disorders such as Irritable Bowel Syndrome (IBS), Chron's Disease, and other gastrointestinal disorders.[14] Diabetes, on the other hand, has been linked to an increased risk of SIBO. In diabetic patients, malabsorption and a longer transit time in the gastrointestinal tract increase the risk of SIBO. [15]

Materials And Methods

The literature search is conducted using the Patient-Intervention-Comparison-Outcome(PICO) method (P: adult population, I: diabetes mellitus type 2, C: non-diabetes mellitus type 2, O: small intestinal bacterial overgrowth). Observational studies were used. The 2009 Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) checklist for systematic reviews was used to adjust this study. Proquest, CINAHL, SCOPUS, ScienceDirect, and PubMed/MEDLINE databases were used as electronic data sources. Manual searches were also conducted on the websites of international diabetes organizations such as the ADA, EASD, EFSD, IDF, FASEB, and PERKENI. The operational definitions from the OGTT and/or HbA1c are used to diagnose DM. Hydrogen breath test (HBT) is used to diagnose SIBO.

The eligible study was based on the following inclusion criteria:

- Observational studies conducted within the last ten years.
- The study sample population was > 18 years old.

- The study sample population was associated with type 2 diabetes mellitus.
- The sample was examined for SIBO.
- There were prevalence outcomes.

Patients with gestational diabetes, type 1 diabetes, and other types of diabetes were excluded, as were animal studies and subjects with gastrointestinal surgery (intestinal resection, bariatric surgery, or RYGB). The Joanna Briggs Institute's Critical Appraisal in JBI Systematic Review for Prevalence (JBI) tool will be used to assess the quality and risk of bias. The distribution of bias risk is agreed upon with the provision that if the answer "Yes" to more than six questions is obtained, it is considered to have a low risk of bias, and if the answer "Yes" is obtained from 1-6 questions, it is considered to have a high risk of bias.

Data were analyzed in Stata 16 with results expressed as mean SD, I^2 was used to assess study heterogeneity, and data was presented in Forest plots and Funnel plots to assess the possibility of publication bias. Additional data is presented as a result of the systematic study's other findings.

Results

Six articles were eligible for analysis after searching databases and manuals, five of which were conducted in Asia and one in Europe. The study was conducted in clinics and hospitals with varying sample sizes between 2006-2020. Table 1 lists the characteristics of the studies. The duration of DM diagnosis in the sample was more than 5 years in 5 studies; only 1 study did not mention the duration of DM diagnosis. Each study was pretty varied, and there was evidence of publication bias.

Table 2 shows the results of the quality assessment and the risk of bias. JBI uses nine questions with the explanation of each question as follows:

1. A sample frame based on the target population

The study is declared "Yes" if the selected target population, in this case, Indonesian women with type 2 diabetes, matches the population represented. A study population is also considered to be of high quality if it includes nearly all target population members (e.g. in the census, register data). The sampling method is used to evaluate this question.

2. Recruiting study participants

If the study sample selection is done correctly and can represent the population being studied, and the research method explains the process, the study is declared as "Yes." The random probabilistic sampling technique was deemed appropriate for the majority of study methods. If the study employs a cluster sampling technique, the sampling procedure must be described in detail in the article. The convenience sampling method is deemed insufficient. The sample selection method is used to evaluate this question.

3. A sufficient sample size

If a study has an adequate sample size, a narrow confidence interval, and a prevalence estimate, it is declared "Yes." A good article will explain how to calculate the sample size or if the study is large enough (e.g., a national survey) that the sample size is not necessary. If these conditions are not met, the authors can use the formula to calculate the number of samples (Naing et al. 2006 and Daniel, 1999).

4. Extensive description of subjects and settings

The study is declared "Yes" if the study subject and background are thoroughly explained so that other researchers can determine whether the study sample population corresponds to the population being studied. The background of the study and the essential characteristics of the sample are used to answer this question.

5. A sufficient amount of data was analyzed.

If there is no coverage bias in the study, it is declared "Yes." When the response rate of each subgroup in a single study is not the same, this bias occurs. This question is answered by examining the sample's essential characteristics in the research findings.

6. Reliable methods for identifying the condition

The study was declared "Yes" if the outcome was assessed using a clear and validated definition or diagnostic criteria. This question was evaluated by examining the study's inclusion and exclusion criteria, as well as its operational limitations. A doctor's diagnosis, a questionnaire, or an established medical diagnosis can all be used to define FSD.

7. Measurement of condition in a consistent and dependable manner

If the outcome measurements in the study are carried out correctly, the study is declared "Yes." The consistency of the measurement method and the quality of the researcher are critical in determining a good outcome. This question is answered by examining the research method in the form of the study's operational limitations.

8. Appropriate statistical analysis

If the numerator and denominator are described in detail and a confidence interval is provided, the study is declared "Yes." The study also describes the analysis technique and each of the variables studied in the method section. The research method is used to answer this question.

9. A sufficient response rate

If there is a reasonable response rate, the study is declared "Yes." A high number of dropouts, rejections, or incomplete data will lower the study's validity and response rate. Authors should include the sample's response rate and the reasons for non-response, as well as a comparison of the characteristics of the study group and the non-study group. The data in the research results can be used to answer this question.

The pooled prevalence of 24.39% SD 15.31 was calculated using Stata 16 on prevalence data from selected studies, with a minimum value of 7.42% and a maximum value of 53.85%, 95% CI 9.97-38.86. The deviation is quite large, which is most likely due to the heterogeneity of the studies.

Figure 3 depicts an overview of all selected studies' funnel plots. The description of the funnel plot shows that there is asymmetry, indicating the possibility of publication bias. Aside from the few published studies on SIBO in type 2 diabetes, there are very likely unpublished studies.

Table 1
Characteristics of the studies

No	Author	Year	Country	Study Design	Setting	Sample	Gender		Diagnosis Method			Outcome	
							Male	Female	T2DM	SIBO	T2DM Duration (year)	SIBO (n)	SIBO (%)
1	Rana SV, et al[15]	2016	India	Case-control	Clinic	350	175	175	TTGO, HbA1C	HBT	9.6	26	14.8
2	Malik A, et al[16]	2019	India	Cross-sectional	Clinic	300	142	158	TTGO, HbA1C	HBT	>5	43	14.4
3	Yan L, et al[17]	2020	China	Cross-sectional	Hospital	104	62	42	TTGO, HbA1C	HBT	8.5	56	53.85
4	Urita Y, et al[9]	2006	Japan	Cross-sectional	Hospital	82	40	42	HbA1C	HBT	-	7	8.5
5	Adamska A, et al[18]	2015	Polandia	Cross-sectional	hospital	109	71	38	HbA1C	HBT	>5	44	40
6	Rana SV, et al[19]	2011	India	Case-control	Clinic	127	51	33	TTGO, HbA1C	HBT	10.5	13	15.5

Table 2
Selected studies' JBI Critical Appraisal Checklist

No	Study	1. Was the sample frame appropriate to address the target population?	2. Were study participants sampled in an appropriate way?	3. Was the sample size adequate?	4. Were the study subjects and the setting described in detail?	5. Was the data analysis conducted with sufficient coverage of the identified sample?	6. Were valid methods used for the identification of the condition?	7. Was the condition measured in a standard, reliable way for all participants?	8. Was there appropriate statistical analysis?	8. Was there appropriate statistical analysis?	9. V resj ade if n low rate app
1	Rana SV, 2016[15]	Yes	?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2	Malik A, 2019[16]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3	Yan L, 2020[17]	Yes	Yes	(-)	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4	Urita Y, 2006[9]	Yes	Yes	?	Yes	?	Yes	Yes	Yes	Yes	Yes
5	Adamka A, 2015[18]	Yes	Yes	?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6	Rana SV, 2011[19]	Yes	?	?	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Discussion

The prevalence of SIBO in patients with T2DM was significantly varied in this systematic review of six studies. The combined prevalence was 24.39% SD 15.31, with a minimum of 7.42% and a maximum of 53.85%, 95% CI 9.97-38.86. HBT was used in all studies to diagnose SIBO in patients with type 2 diabetes based on the OGTT and/or HbA1c tests. The number of samples differed between studies, indicating that Rana et al.[15] and Malik et al.[16] had adequate sample sizes. A history of gastrointestinal surgery, long-term use of antibiotics and PPIs, liver cirrhosis, prokinetics, and intestinal obstruction are all factors that must be ruled out when investigating SIBO in patients may limit the number of samples in the studies.

The Forest plot (Figure 1 and Figure 2) shows that the study distribution is quite wide, with an I^2 of 97.17%, indicating the heterogeneity of the existing studies. However, even though the intersection is quite wide, the pooled prevalence can still be analyzed. Each study's weights were more or less similar, indicating that each study was of similar significance. The funnel plot shows that more research is needed to see if there are any unpublished studies or studies with a larger number of samples than the ones currently available.

HbA1c levels were higher in type 2 diabetes mellitus patients with SIBO than type 2 diabetes mellitus patients without SIBO, according to Urita et al.[9] and Yan et al.[17], and the difference was statistically significant ($p = 0.02$). Urita et al. also discovered that patients with SIBO had a higher HOMA index, which measures blood sugar and insulin homeostasis, though the difference was insignificant ($p = 0.22$). The findings of Yan et al.[17], who discovered significantly lower blood insulin levels in patients with SIBO compared to patients without SIBO ($p = 0.001$), which is another indicator of poor glycemic control in patients with type 2 diabetes mellitus and SIBO, back up this theory. The levels of mediators TNF, IL-6, and IL-10 were also significantly higher in type 2 DM patients with positive SIBO compared to those with negative SIBO in the same population, according to Malik et al.[16]

The findings of this systematic review were graded on a GRADE scale to determine their quality. There is a strong suspicion that publication bias has lowered the study's quality. The findings are shown in Table 3.

Table 3. GRADE-based evaluation of the quality of the findings

Outcome	Subjects total (study)	GRADE
SIBO prevalence	1072 (6 studies)	 (Moderate) Bias in the publications exist.

This is the first study in Indonesia to look into the relationship between SIBO and type 2 diabetes. The articles were retrieved through published databases and DM associations all over the world. There is a low risk of bias in all of the studies that were chosen. The study's outcome is based on GRADE, and the result is moderate.

Conclusions And Recommendations

Several conclusions were drawn from this systematic study, including:

1. The prevalence of SIBO in type 2 DM patients was 24.39% SD 15.31.
2. Blood insulin levels in type 2 DM patients with SIBO were lower than those in type 2 DM patients without SIBO ($p = 0.001$).
3. HbA1c levels were higher in type 2 DM patients with SIBO than type 2 DM patients without SIBO ($p=0.02$)
4. The quality of the findings is moderate, according to the GRADE scale.

In addition, the following suggestions are made:

1. In type 2 DM patients, an HBT examination to detect SIBO should be performed regularly, especially in those who have had DM for more than 5 years.
2. Patients with diabetes can consider taking probiotics.
3. The prevalence of SIBO in DM in the Indonesian population needs to be investigated.
4. With an adequate number of samples, further research is necessary to assess the relationship between SIBO and type 2 DM in Indonesia, and the factors thought to play a role in the incidence of SIBO in type 2 DM patients.

Abbreviations

SIBO: Small Intestinal Bacterial Overgrowth; HBT: Hydrogen Breath Test; DM: Diabetes Mellitus; IBS: Irritable Bowel Syndrome; OGTT: Oral Glucose Tolerance Test; PPIs: Proton-pump Inhibitors

Declarations

Consent for Publications

Not applicable

Ethics Approval and Consent to Participate

Not applicable

Authors' Contributions

Idea, study design: TJET, HC, IH, HS ; Data collection and analysis: TJET, HC, IH, HS ; Writing draft for publication: TJET, HC

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Competing Interest

All authors declare that there is no conflict of interest.

Availability of Data and Materials

The datasets used and/or analysed during the current study available from the corresponding author and co-author (TJET, HC) on reasonable request.

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Figures

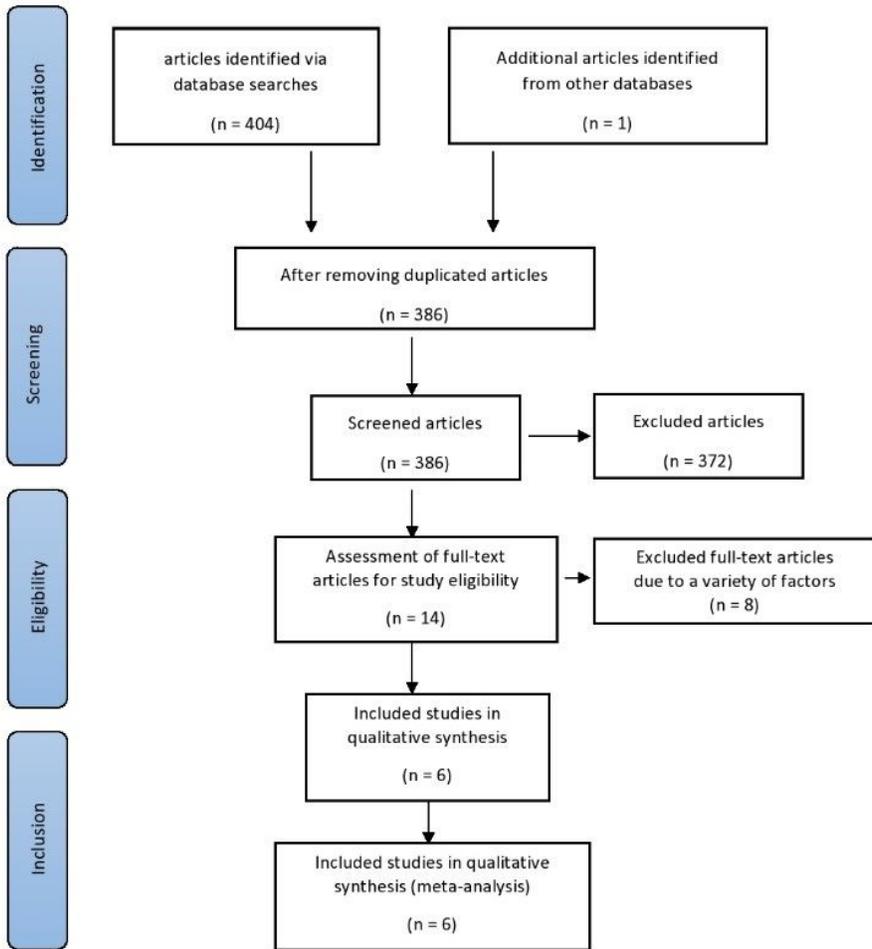


Figure 1
PRISMA Diagram Systematic Study

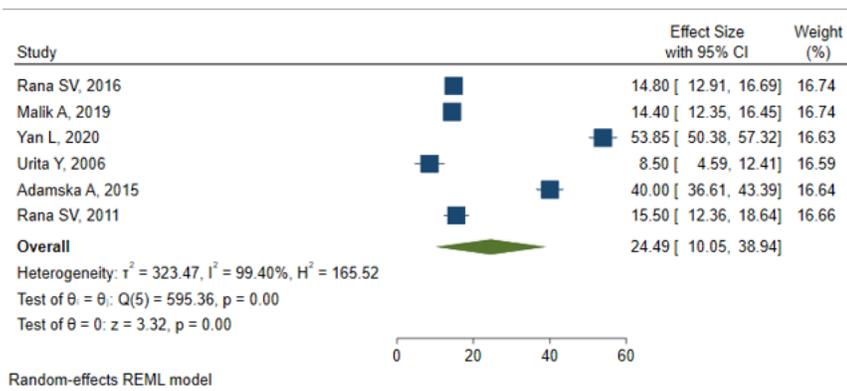


Figure 2
Forest plot of SIBO prevalence in T2DM

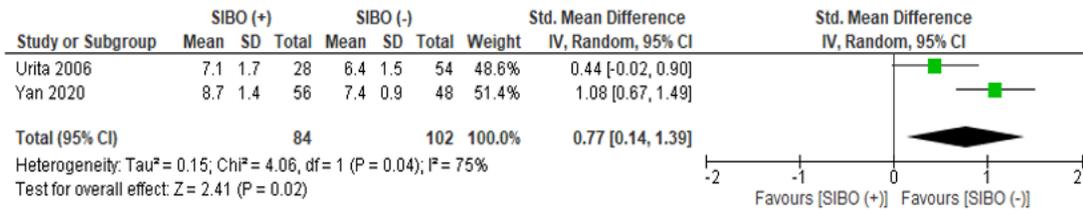


Figure 3

Forest plot of HbA1c levels from the study of Yan et al. and Urita et al.

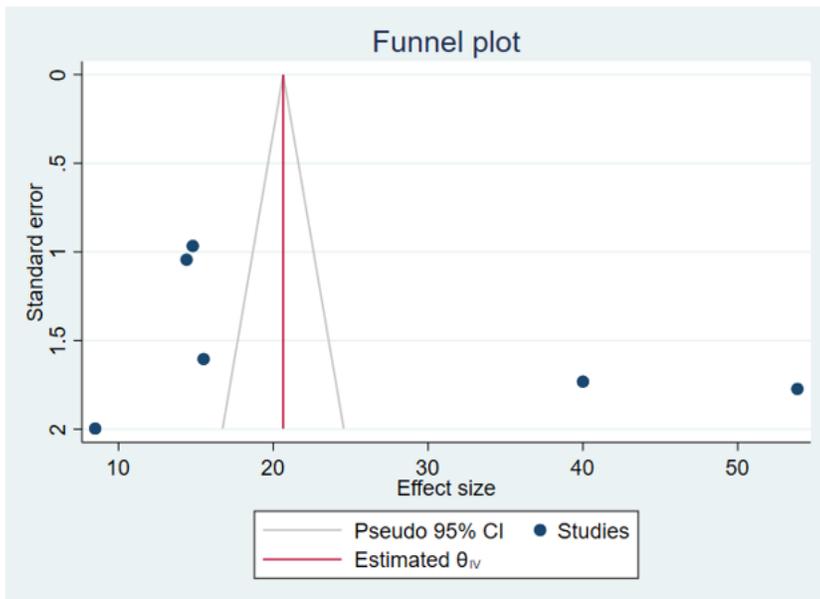


Figure 4

SIBO Funnel Plot in Type 2 Diabetes Mellitus

Supplementary Files

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