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Firmicutes/Bacteroidetes Ratio of Gut Microbiota and Its Relationships with Clinical Parameters of Type 2 Diabetes Mellitus: A Systematic Review

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Abstract

BACKGROUND: Type 2 diabetes mellitus (T2DM) is a global health problem with multifactorial etiopathogenesis. Recent studies show gut microbiota dysbiosis that plays a crucial role in pathogenesis and complications of T2DM. *Firmicutes* and *Bacteroidetes* phylum ratio (F/B ratio) is one of the markers for gut microbiota dysbiosis which remains to be investigated in recent decades.

AIM: The present study summarized the correlation between B/F ratio with some clinical parameters of T2DM.

METHODS: A systematic review of the literature for clinical studies was performed on PubMed, ProQuest, and Google Scholar. Studies were assessed for risk of bias using Newcastle–Ottawa scale. All observational cross-sectional, case–control, and cohort studies that studied F/B or B/F ratio in T2DM were included. Key evidence was analyzed and qualitatively synthesized.

RESULT: Seven relevant studies were included. Five studies were high-quality and two studies were medium-quality. The F/B ratio of the gut microbiota varies in different types of T2DM and is associated with different clinical parameters. The F/B ratio decreased inT2DM and had significant negative correlation with OGTT blood glucose but had unsignificant correlation with fasting fasting blood glucose, postprandial blood glucose, and HbA1C. The F/B ratio might increase in T2DM and was positively correlated with lean tissue index and associated with the wider left atrial size.

CONCLUSION: Current systematic review demonstrated that intestinal microbiota dysbiosis played a key role in the pathogenesis of T2DM. The gut microbiota F/B ratio was varied and was associated with various clinical parameters in T2DM.

Introduction

Diabetes mellitus (DM) is a group of progressive chronic metabolic diseases characterized by hyperglycemia caused by diverse etiologies that include defects in insulin secretion, defects in insulin action, or both [1]. DM is a key global health issue in cause of its continuous increment trend of prevalence. According to IDF Atlas on 2017, there were 425 million people worldwide that was diagnosed with diabetes and this number is expected to rise to 629 million by 2045 [2]. Indonesian Basic Health Research, in 2018, reported the prevalence of DM in people aged more than 15 is 10.9%, increased from 8.5% in 2013 [3], [4].

Type 2 DM (T2DM), reaching more than 90% DM cases, is characterized by two main defects, namely, insulin resistance and insulin secretion defects. The insulin secretory defect can be caused by reduced mass and/or dysfunction of β-cells which influenced by genetic predisposition and environmental factors [5], [6]. Genetic factors can directly affect the reduced mass and function of -cells or indirectly through insulin resistance pathways (especially in the individuals with overweight), modulation of the immune system, and inflammation [5]. Meanwhile, environmental factors that play a role include endocrine disruptor chemicals, viruses, excessive caloric intake, and the changes in gut microbiota patterns [6], [7].

Under physiological state, the gut microbiota plays an important role in maintaining homeostasis. The gut microbiota in healthy individuals is composed of more than 90% by only two phyla of bacteria which are *Bacteroidetes* phyla (73%) and *Firmicutes* phyla

(22%) [8], [9], [10]. Changes in both composition and function of the microbiota, known as dysbiosis, are a common feature of various metabolic disorders such as obesity and T2DM. Several studies have shown that increasing body weight is associated with changes in the *Firmicutes*/*Bacteroidetes* ratio (F/B ratio); meanwhile, obese subjects have the proportion of the *Firmicutes* population increases and *Bacteroidetes* decreases [11], [12]. Terminology of the F/B ratio (some researchers use the term B/F ratio) is widely investigated as a method for identifying the pattern or character of the gut microbiota.

The main concern in management of DM is the chronic complications that caused by poor glycemic control. Poor blood glucose control is closely related to the inability of insulin to work effectively on target organs (insulin resistance) or to a reduced amount of insulin secreted by pancreatic β-cells. Clinical parameters of these defects include an increase in fasting blood glucose (FBG) and post-prandial blood glucose (PPBG). Chronic increase in blood glucose levels will then lead to various kinds of complications, both macro- and microvascular.

Studies on the relationship between the F/B ratio and various clinical parameters in people with T2DM have not been done much. Larsen *et al*. [13] and Zhang *et al*. found a non-significant positive correlation between the decrease in the F/B ratio with both FBG and PPBG [14]. Wang *et al*. found a relationship between an increased F/B ratio and an increased risk of impaired insulin sensitivity [15].

Several studies on the relationship between the F/B ratio with several clinical parameters show varying results and have never been systematically studied. The present study summarized current findings on F/B ratio of gut microbiota in patients with T2DM in hope to provide useful new data to improve understanding of the role of the gut microbiota in the pathogenesis of T2DM.

Methods

The present study was a systematic review and was conducted in accordance with preferred reporting items for systematic review and meta-analysis (PRISMA) guideline. Clinical question was arranged with P: Patients with T2DM, I: Ratio of *Bacteroidetes*/*Firmicutes* of Gut Microbiota, C: -, O: Clinical Parameters of T2DM.

The literature search conducted on February 14–April 1, 2022. PubMed, ScienceDirect, and Google Scholar were searched systematically using the following keywords: "*Firmicutes* to *Bacteroidetes* Ratio" OR "Gut Microbiota" OR "Gut Microbiome" OR "B/F ratio" OR "F/B ratio" AND "T2DM." A bibliography search was also carried out from the studies obtained by hand searching and snowballing.

The studies included in this systematic review were studies involving people with T2DM according to the inclusion and exclusion criteria. There were no restrictions on the publication year of the included studies. The study inclusion criteria included: (1) cross-sectional, cohort, or case-control studies, (2) study subjects >18-years-old, and (3) including F/B ratio values. *In vitro* studies, *in vivo* studies on experimental animals, studies not published in English or Indonesian, and studies with interventions were excluded from the study selection.

To avoid the risk of assessment bias, the present study involved two reviewers who assessed the studies obtained separately. The first reviewer was YK and the second reviewer was IS. Differences in the results of the review between reviewer one and reviewer two were discussed together and if no agreement was reached, a third reviewer (ZA) is involved. The risk of bias was also minimized using the Newcastle–Ottawa scale (NOS) device which was adjusted for each research form, whether it was a cross-sectional, cohort, or case–control study.

All studies that have been collected were examined meticulously. The assessment of the suitability of the studies was ensured from the beginning through the title of the study; then, the characteristics of the study were presented in tabular form. Extraction was continued by examining the study abstracts and assessing the weight of the quality of the studies obtained. In dispute between two reviewers, a rating system would be implemented according to the agreement of the two reviewers.

Results

Description and characteristics of studies

The initial search resulted 5388 studies obtained through database, 601 of them were excluded due to duplication in the database. After the title and abstract screening, 4764 studies were excluded for various reasons, including 1988 literature reviews, 79 books, 42 conference abstract, 22 editorials, 15 letters, 22 randomized controlled trials, 75 studies in non-T2DM patients (54 T1DM and 21 Gestational diabetes), and 2521 irrelevant original article (*in vivo* or *in vitro* studies). The number of studies after screening of titles and abstracts was 23 studies and was assessed for full-text eligibility. Furthermore, 14 studies were excluded, because they did not include the value of F/B ratio, so there were nine studies included in the qualitative synthesis. The study selection flow is shown in Figure 1.

Result of bias risk assessment

Nine studies included in qualitative synthesis were consisted of seven case–control studies and two

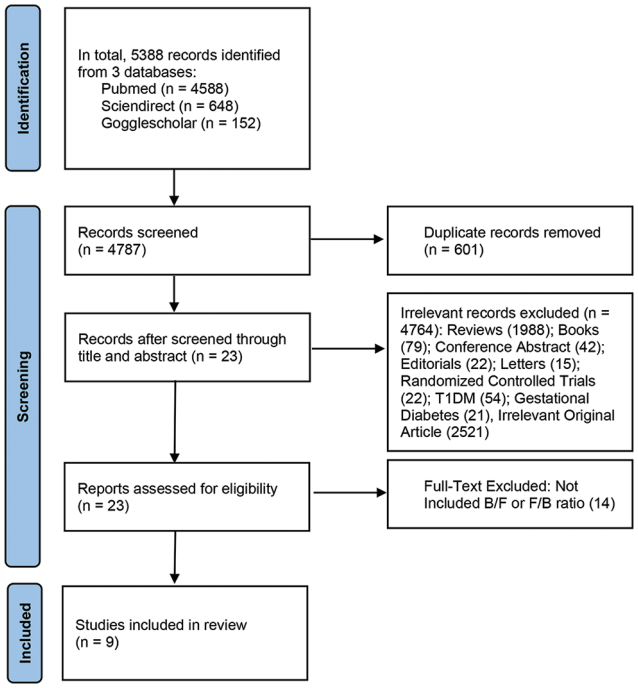

Figure 1: PRISMA flow diagram for the study selection known to have a case–control or cross-sectional study design. Seven studies were rated as good and two studies rated as medium based on the NOS assessment (Table 1)

cross-sectional studies. A bias risk assessment was carried out for the nine studies. In these nine studies, the risk of bias was assessed using the NOS which consists of three parts, namely, the selection, comparability, and outcome. The NOS used in this study was adapted to the type of research design in all studies.

Results of data extraction

Of the nine studies included in the systematic review, seven studies discussed the association between F/B ratio and glycemic control (HbA1C, FBG, and PPBG), one study identified an association between gut microbiota F/B ratio and anthropometric measurements, and one study discussed the association between gut microbiota F/B ratio and echocardiographic measurements for the identification of subclinical cardiovascular disease in T2DM patients. The results of data extraction are shown in Table 2.

The relationship between the F/B ratio of gut microbiota and the incidence of T2DM had been studied since the past two decades. The current review included seven studies that identified the F/B ratio of the gut microbiota and its relationship to the glycemic control index of patients with T2DM. Six studies identified F/B ratio using targeted approach of microbiota identification real time polymerase chain reaction or sequencing (RT-PCR) and found various results. Of six studies, two studies reported significant decreased F/B ratio, two studies reported significant increased F/B ratio, and two studies reported unsignificant change among patients with T2DM and control. A study by Salamon *et al*. found increased F/B ratio in patients with T2DM using next generation sequencing as untargeted approach. A study by Larsen *et al*. was the only study that identified the significant correlation between F/B ratio and FBG as clinical parameter of T2DM [13].

The finding of current systematic review identified one study that reported the correlation between the F/B ratio of gut microbiota and the results of anthropometric measurements of patients with T2DM. Hung *et al*. reported that the correlation between lean tissue index (LTI) was significantly correlated ($r = 0.239$, $p = 0.001$) with the F/B ratio of gut microbiota [16]. They demonstrated in their study that patients with the highest LTI group had higher F/B ratios than those in the lower LTI group. In multivariate analysis, high bacterial counts in the phylum *Firmicutes* and high F/B ratio were associated with higher LTI. This study used the method of targeted rRNA RT-qPCR technique for gut microbiota identification and bioimpedance spectroscopy for anthropometric measurement.

There was one study evaluating the association between gut microbiota and cardiovascular disease as described by echocardiography in patients with T2DM. Tsai *et al*. evaluated the correlation of various measurements of echocardiographic examination results with gut microbiota identified by the targeted identification method using the 16S rRNA RT-qPCR technique. They reported that a high gut microbiota F/B ratio was associated with an increase in left atrial diameter [17].

Discussion

Studies about dysbiosis of gut microbiome have been done in the past decades, and the results discovered that dysbiosis has crucial roles in the

Table 1: Result of risk of bias in case-control studies

Process	Points evaluation	Larsen *et al*. [13]	Zhang *et al*. [14]	Salamon *et al*. [21]	Zhao *et al*. [20]	Fassa-toui *et al*. [19]	Wang *et al*. [15]	Hamasaki-Matos *et al*. [29]	Hung *et al*. [16]	Tsai *et al*. [17]
Selection	Case definition		*	*	*	*	*	*	*	*
	Case representation	*	*	*	*		*	*	*	*
	Election control	*	*	*	*	*	*	*	*	*
	Definition control	*	*	*	*	*	*	*	*	*
Comparability	Comparability of the outcome based on research design or analysis. Controlled confounding factors		**	*	*	*	*	**	**	*
Outcome	Evaluation outside	*	*	*	*	*	*	*	*	*
	Statistical test	*	*	*	*	*	*	*	*	*
Category quality		Moderate	High	High	High	Moderate	High	High	High	High

New Castle Ottawa Scale, Sums of Points indicating the quality of the studies: 7-10 High; 4-6 Moderate; 1-3 Low

Table 2: Data extraction results

Author, year, design	Population	Sample, % male		Antihyperglycemia therapy	Genomics methods	B/F ratio and clinical indicator of T2DM
		Control	Case			
Larsen *et al*., 2010, Case-Control	Denmark	Normal, 10 (100%)	T2DM, 10 (100%)	Not reported	PyroSequencing 16S rRNA	F/B ratio decreased, B/F ratio correlated significantly with OGTT BG, but not with BMI
Zhang *et al*., 2013, Case-Control	China	Normal, 44 (27.3%)	Pre-DM, 64 (35.9%) T2DM, 13 (46.2%)	Not reported	16S rDNA sequencing	F/B ratio increased, B/F ratio was insignificantly correlated with FBG and PPBG
Salamon *et al*., 2018, Case Control	Poland	Normal, 23 (30.4%)	T2DM, 23 (65.2%)	Metformin 100%, Sulfonylurea 56.5%, DPP-4i 17.3%, GLP-1 8.7%, Acarbose 4.3%	Next genome sequencing	F/B ratio significantly increased compared to control, F/B ratio did not significantly correlate with any clinical parameters
Zhao *et al*., 2019, Case Control	China	Normal, 35 (51.4%)	T2DM, 65 (53.8%): T2DM+. 49 (57.1%), T2DM−7 (43.7%)	Without metformin	16S rRNA sequencing	F/B ratio significantly increased compared to control, and significantly increased in T2DM+compared to T2DM−
Fassatoui *et al*., 2019, Case Control	Tunis	Normal, 11 (27.0%)	T2DM, 10 (40.0%)	Not reported	RT-PCR	F/B ratio insignificantly decreased, there was no correlation between F/B and T2DM clinical parameters
Wang *et al*., 2020, Case Control	China	Normal, 37 (27.0%)	T2DM, 134 (51.2%)	No different mean between groups	Sequencing, HiSeq Amplicon	F/B ratio significantly increased. Two identified enterotype, Bacteroides Prevotella and Bacteroides related to increased risk to disturbance in insulin sensitivity
Hamasaki-Matos *et al*., 2021, Case Control	Peru	T2DM C 7 (57%)	T2DM UC, 12 (63%)	Not reported	RT-PCR	F/B ratio decreased among uncontrolled T2DM patient. There was no correlation between HbA1c and F/B ratio
Hung *et al*., 2021, Cross-Sectional	China (Taipei)		T2DM 179 (55.3%)	Metformin 81.6%, sulfonylurea 46.4%, DPP-4i 61.5%, insulin 15.1%, statin 49.1%	RTqPCR	F/B ratio significantly increased among T2DM patients with high LTI. F/B ratio was significantly correlated with LTI
Tsai *et al*., 2021, Cross-Sectional	China (Taipei)		T2DM 155 (57.4)	Metformin 84.6%, Sulfonylurea 52.3%, DPP-4i 65.2%, insulin 11.6%, statin 49.7%, thiazolidinedione 58.7%	qPCR	F/B ratio correlated negatively with left atrial diameter

DM: Diabetes mellitus, T2DM: Type-2 DM, T2DM C: T2DM Controlled, T2DM UC: T2DM Uncontrolled, T2DM+: T2DM with complication, T2DM−: T2DM without complication, FBG: Fasting blood glucose, PPBG: Postprandial blood glucose, BMI: Body mass index, LTI: Lean tissue index, HbA1c: Hemoglobin A1c, RT-PCR: Real time polymerase chain reaction, qPCR: Quantitative PCR, DPP: Dipeptidyl peptidase, GLP-1: Glucagon-like peptide-1, F/B: *Firmicutes* and Bacteroidetes phylum ratio, B/F: Bacteroidetes to Firmicutes phylum ratio.

egregious eleven of T2DM pathogenesis according to Schwartz *et al*. [18] A disequilibrium of the gut microbial community can make changes in the intestinal mucosal barrier and disrupt the metabolism pathways, which causes direct or indirect impact to insulin resistance in T2DM. The metabolites from microbiota will make interactions with epithelial cell receptors, liver, and heart. Changes in gut microbiota composition may shift the homeostasis and increase the energy utilization that leads to diabetes and obesity.

The ratio of F/B is one of the indicators of gut microbiota dysbiosis. The F/B ratio demonstrates the largest proportion of phylum in gut microbiota, which is *Bacteroidetes* and *Firmicutes*. The findings of the current systematic review identified seven studies evaluating the relationship of gut microbiota B/F ratio with glycemic control index of T2DM patients. Six studies were comparing the F/B ratio in a group of patients with T2DM and a group of patients with normal glycemic index. Three of them showed that the F/B ratio was increased in the T2DM group compared to the control group which had no disturbances of glucose metabolism. [13], [14], [16].

Other study failed to show any relationship between F/B ratio and T2DM. In addition, Larsen *et al*. reported a significant correlation between F/B ratio with FBG rate; however, five other studies did not report the same result [13], [14], [15], [19]. Meanwhile, Zhao *et al*. reported that F/B ratio was higher in T2DM patients with complication compared to patients without any complication [20].

The different results got from the studies mentioned above show the inconsistency of the F/B ratio in T2DM patients. The contentious result could be due to different method, diet and drug consumption, including diabetic medication. Five studies identified F/B ratio using targeted bacteria group or species identification of RT-PCR or sequencing, while study by Salamon *et al*. reported identification method using untargeted *Next Genome Sequencing*, a novel technique to map the gut microbiota [21]. All studies had not mentioned any description of the subject's dietary pattern due to the recall bias. Description of the history of taking medication was also important, because number of medications may lead to dysbiosis of gut microbiota. Anti-diabetic medication including biguanides, alpha-glucosidase inhibitors, incretin agents, glucagon-like peptide-1 receptor agonists, dipeptidyl peptidase-4 inhibitors, and thiazolidinediones could influence the gut microbiota [22].

Hamasaki-Matos *et al*. compared the F/B ratio between the group of T2DM patients with adequate glycemic control and the group of T2DM patients with inadequate glycemic control. The group of T2DM patients with adequate glycemic control had no significant differences in F/B ratio with the poor glycemic control group.

Obesity, central adiposity, and body mass index play significant roles in the pathophysiology of T2DM. The present studies showed the role of gut microbiota in obesity. Changes in the gut microbiota composition, especially the dominant phylum *Firmicutes* and *Bacteroidetes,* were first described in obese animals that show high F/B ratio [23].

Ley *et al*. [24] reported that obese patients who were on calorie restrictions for 1 year showed the enhancement of total *Bacteroidetes,* normal F/B ratio, and loss of significant weight [22]. In addition, a study was conducted in animals with high fat or high fiber intake revealed the increase of total *Firmicutes*

and *Bacteroidetes* community [25]. The community of *Firmicutes* was known more effective in extracting energy from food than the *Bacteroidetes*. Therefore, *Firmicutes* promote more efficient absorption of calories and consequences in gaining weight. More of that, the changes of the F/B ratio are considered to be the marker of dysbiosis gut microbiota in obesity [11].

The association of the F/B ratio with anthropometry measurement in the population with T2DM showed different results. Hung *et al.* reported a higher F/B ratio in the T2DM group with a high LTI [16]. This could happen, because *Firmicutes* uses energy more effectively than *Bacteroidete*s. Thus, the utilization of nutrition could be more effective in patients with high F/B ratio.

The relationship between gut microbiota and clinical parameters of cardiovascular disease in T2DM was demonstrated by Tsai *et al*., where an increased gut microbiota F/B ratio was correlated with a decrease in the left atrial diameter [19]. Other studies reported association between gut microbiota and various cardiovascular disease variables. Mamic *et al*. reported an association between changes in gut microbiota composition and heart failure [26]. Yuzefpolskaya *et al*. reported that the quantity of phylum Bacteroidetes decreased in patients with heart failure [27]. Kamo *et al*. also reported that the portion of the phylum Bacteroidetes was smaller in elderly patients with heart failure than in younger people, although the difference between the two groups was not statistically significant [28].

The relationship between the gut microbiota with T2DM and cardiovascular disease was intricate. Insulin resistance and hyperglycemia induced endothelial dysfunction and promoted a pro-inflammatory state, both of which were significant contributors to cardiovascular dysfunction. The interaction effect between gut microbiota and T2DM might predispose to the development of subclinical cardiovascular disease into more progressive clinical entities. Therefore, further studies were needed to retest the finding.

The contentious finding among studies about gut microbiota's dysbiosis in T2DM could be resulted from different methods of genomics. The targeted studies using sequencing or RT-PCR included only a sorted predefined group of bacteria and might cause lost-identification of other bacteria, resulting in bias. The used of untargeted methods, that is, next genome sequencing might be the solution for this issue.

Conclusion

The current systematic review demonstrated that gut microbiota dysbiosis played a role in the pathogenesis of T2DM. The gut microbiota's F/B ratio varied in various conditions of T2DM and was associated with various clinical parameters. The F/B ratio increased in T2DM and was significantly positively correlated with OGTT blood glucose but not significantly correlated with FBG, PPBG and HbA1C. The F/B ratio might increase in T2DM and was negatively correlated with LTI and left atrial size.

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