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Lactobacillus and Bifidobacterium Bacteria Profile in Healthy People and People with Type 2 Diabetes Mellitus

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Abstract

Lactobacillus and Bifidobacterium are two genera of gram-positive bacteria that are widely used as probiotic products. They improve the composition of the intestinal microbiota but until now the difference in the number of these bacteria in patients with type 2 diabetes mellitus and healthy people in Asia remains unclear. This study conducted a systematic review to analyze the differences in the number of Lactobacillus and Bifidobacterium bacteria in patients with type 2 diabetes and healthy people in Asia. The results showed that the number of Lactobacillus bacteria was higher in patients with type 2 diabetics than in healthy people. The number of Bifidobacterium bacteria in patients with type 2 diabetes tended to be lower than in healthy people, although there was some literature stating that there was no difference in the number of Bifidobacterium bacteria in patients with type 2 diabetes and in healthy people. Further research on the profile of Lactobacillus and Bifidobacterium bacteria per type (species) specifically in people with type 2 diabetes and healthy people of various ethnicities in Indonesia is needed to identify dysbiosis in people with type 2 diabetes and determine specific microbiota therapy for people with type 2 diabetes.

Introduction

Diabetes mellitus type 2 is one of the leading causes of death in Southeast Asia (1). The prevalence of people with type 2 diabetes mellitus in Indonesia based on Riskesdas Data also increases every year, wherein in 2013 it was 6.9% and increased to 10.9% in 2018 (2). Type 2 diabetes mellitus is a chronic disease with multifactorial causes, such as diet, lifestyle, and genetic. Several previous studies have also stated that the microbiota in the gastrointestinal tract is also a factor associated with type 2 diabetes mellitus (3). The composition of gut microbiota changes in people with type 2 diabetes mellitus. The number of gram-positive bacteria, such as Lactobacillus and Clostridium (phylum Firmicutes) and Bifidobacterium (phylum Actinobacteria) decrease. While, the number of gram-negative bacteria, such as phylum Bacteroidetes increase (3). A high number of gram-negative bacteria can increase the risk of macro and microvascular complications in people with type 2 diabetes.

Several previous studies have explained that increasing the number of gram-positive bacteria can be done by giving probiotic products, such as yoghurt so that they can improve the balance of the gut microbiota in people with type 2 diabetes mellitus. The results of research conducted by Ejtahed et al (2012) and Ruan et al (2015) stated that there was a decrease in the value of blood glucose and insulin resistance in people with type 2 diabetes mellitus who consumed yoghurt through a mechanism of reducing oxidative stress (4,5). Generally, yoghurt contains Lactobacillus and Bifidobacterium bacteria. Previous research stated that increasing Lactobacillus and Bifidobacterium through yoghurt consumption has benefits for people with type 2 diabetes mellitus. It can produce exopolysaccharides which function as inhibitors of oxidative stress (6,7). However, the effectiveness of using Lactobacillus and Bifidobacterium yoghurt is still questionable. A study conducted by Sato et al (2014) showed that Lactobacillus bacteria

tend to increase in people with type 2 diabetes mellitus in Japan, as well as what happened in the population of people with type 2 diabetes mellitus in Europe (8,9). This contradiction result raises a new question about the composition of the microbiota (especially *Lactobacillus* and *Bifidobacterium*) among people with type 2 diabetes mellitus.

Considering some of the above factors, we are interested in knowing the differences in the microbiota composition of *Lactobacillus* and *Bifidobacterium* in the gut between healthy individuals and people with type 2 diabetes mellitus in the Asian population in a systematic literature review. Consider the results of previous studies suggesting that the composition of *Lactobacillus* and *Bifidobacterium* in people with type 2 diabetes mellitus is still not known, especially among Asian include the Indonesian. Besides, the diet and genetics in Asian communities are different from other ethnicities so that they can affect the condition of the microbiota in the gut. The publication of systematic reviews on this topic among Asian populations is still limited. The results of this study are expecting to be one of the theories for the investigation of microbiota composition. Moreover, it becomes one of the bases for the development of alternative therapeutic products (probiotics, prebiotics, or synbiotics) that are compatible with the microbiota composition among people with type 2 diabetes mellitus in the Asia community, especially in Indonesia.

Methods

This research conducted using a systematic literature review design or method. The search for the data carried out using search engines or databases such as Scopus, PubMed, Science Direct, Springer Link and Google Scholar. The keywords relevant that used in this research following the Boolean rule: "diabetes mellitus type 2 AND probiotic OR *Lactobacillus* OR *Bifidobacterium*".

The eligibility criteria for the journals were: 1) examine the composition of the microbiota in the gut, both in healthy individuals and people with type 2 diabetes mellitus; 2) the research respondents are the Asian community or population; 3) *Lactobacillus* and or *Bifidobacterium* quantified from stool samples; 4) published during the last 10 years (2011-2020); 5) articles in English or Indonesian, and 6) available in full text. The review method of the scientific research done with the help of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) checklist. After the search and selection process of literature meets the criteria, the research is continued by synthesizing and analyzing data. The summary made using a table containing information on the name of the researcher, research title, population, methods, results, and conclusions of compatible articles. The contents of the table then are discussed for the conclusion of the systematic review.

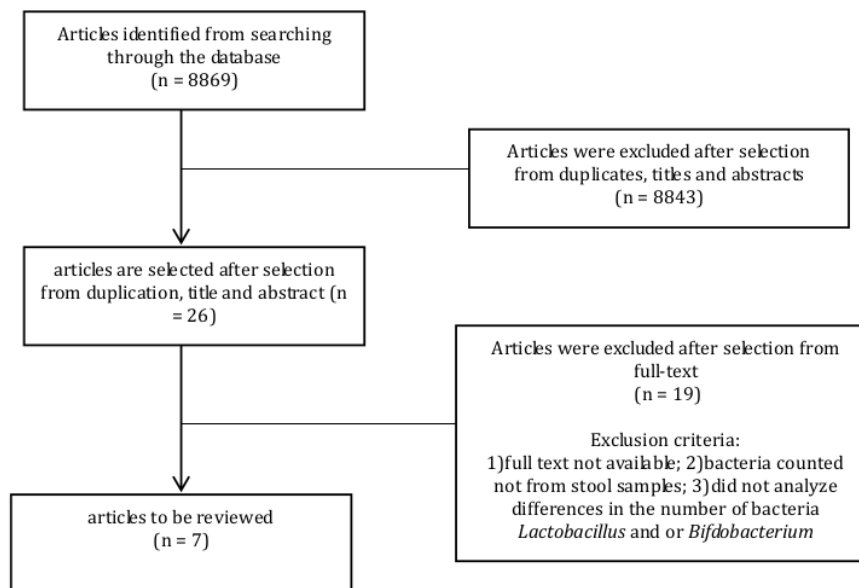


Figure 1. Flowchart of Systematic Literature Search

Results

Based on the literature search and selection guidelines, the researcher summarizes the literature search and selection process in Figure 1. A total of 7 articles were eligible for this review. The review listed in Table 1.

Table 1. Journal Reviews

Study	Populations	Research method		Results		Conclusion
		Study Design	Bacterial Count Method	Type of Bacteria	The number of bacteria	
Hanieh Sadat Ejtahed et al. (2020)	49 people with type 2 diabetes mellitus (T2DM), 21 people with type 1 diabetes mellitus (T1DM), and 40 healthy people (control) in Iran	Case control	Quantitative polymerase chain reaction (qPCR) 16S rRNA	<i>Lactobacillus</i>	people with T2DM : $6,8 \pm 0,4 \log^{10}$ CFU/g people with T1DM : $6,8 \pm 0,4 \log^{10}$ CFU/g Control : $4,4 \pm 0,9 \log^{10}$ CFU/g <i>p-value</i> : $<0,001^*$	There was a significant difference between the number of <i>Lactobacillus</i> in people with T2DM, T1DM, and healthy people
				<i>Bifidobacterium</i>	people with T2DM : $5,7 \pm 0,9 \log^{10}$ CFU/g people with T1DM : $5,5 \pm 0,8 \log^{10}$ CFU/g Control : $6,0 \pm 1,0 \log^{10}$ CFU/g <i>p-value</i> : $0,04^*$	
Chen et al. (2019)	50 people with T2DM and 50 healthy people (control) in Taiwan	Case control	Quantitative polymerase chain reaction (qPCR) 16S rRNA	<i>Lactobacillus</i>	people with T2DM : $4,9 \pm 1,1 \log^{10}/g$ Control : $4,2 \pm 1,2 \log^{10}/g$ <i>p-value</i> : $0,0005^*$	There was a significant difference between the number of <i>Lactobacillus</i> in people with T2DM and healthy people
				<i>Bifidobacterium</i>	people with T2DM : $6,8 \pm 1,5 \log^{10}/g$ Control : $7,0 \pm 1,1 \log^{10}/g$ <i>p-value</i> : $0,482$	
Adachi et al. (2019)	59 people with T2DM and 59 healthy people (controls) in Japan	Case control	polymerase chain reaction (PCR) 16S rDNA	<i>Bifidobacterium</i>	people with T2DM : $25,7 (12,4-38,5)$ (Population, % total sequences) Control: $5,5 (1,5-12,0)$ (Population, % total sequences) <i>p-value</i> : $<0,01^*$	There was a significant difference between the number of <i>Bifidobacterium</i> in people with T2DM and healthy people
Sedighi et al. (2017)	18 people with T2DM and 18 healthy people (controls) in Iran	Case control	Quantitative polymerase chain reaction (qPCR) 16S rRNA	<i>Lactobacillus</i>	people with T2DM : $6,65E6 \pm 2,02E6/g$ Control : $1,22E6 \pm 6,51E5/g$ <i>p-value</i> : $0,00^*$	There was a significant difference between the number of <i>Lactobacillus</i> in people with T2DM and healthy people
				<i>Bifidobacterium</i>	people with T2DM : $1,82E7 \pm 1,88E7/g$ Control : $5,24E8 \pm 1,36E7/g$ <i>p-value</i> : $0,00^*$	

Table 1. Journal Reviews (Cont.)

Study	Populations	Research method		Results		Conclusions
		Study Design	Bacterial Count Method	Type of Bacteria	The number of bacteria	
Navab-Moghadam et al. (2017)	18 people with T2DM and 18 healthy people (controls) in Iran	Case control	Quantitative polymerase chain reaction (qPCR) 16S rDNA	<i>B. fragilis</i>	people with T2DM : 1,08±1,12 (After data transformation) Control: 1,59±1,63 (After data transformation) <i>p-value</i> : 0,38	There was no significant difference between the number of <i>B. fragilis</i> in people with T2DM and healthy people
				<i>B. Longum</i>	people with T2DM : 1,08±0,74 (After data transformation) Control: 1,08±0,76 (After data transformation) <i>p-value</i> : 0,93	There was no significant difference between the number of <i>B. Longum</i> in people with T2DM and healthy people
Sato et al. (2014b)	50 people with type 2 diabetes mellitus and 50 healthy people (control) in Japan	Case control	16S rRNA-targeted RT-quantitative PCR (qPCR)	<i>Lactobacillus</i>	people with T2DM: 7,0±1,5 log ¹⁰ sel/g Control: 6,4±1,2 log ¹⁰ sel/g <i>p-value</i> : <0,05*	There was a significant difference between the number of <i>Lactobacillus</i> in people with T2DM and healthy people
				<i>Bifidobacterium</i>	people with T2DM: 9,2±0,8 log ¹⁰ sel/g Control: 9,2±0,8 log ¹⁰ sel/g <i>p-value</i> : >0,05	There was no significant difference between the number of <i>Bifidobacterium</i> in people with T2DM and healthy people
Lê et al. (2013)	50 people with type 2 diabetes mellitus and 30 healthy people in South China	Case control	Quantitative polymerase chain reaction (qPCR)	<i>Lactobacillus</i>	people with T2DM: 7,8±0,9 (Data after logarithm transformation) Healthy people (control) : 6,6±0,5 (Data after logarithm transformation) <i>p-value</i> : <0,0001*	There was a significant difference between the number of <i>Lactobacillus</i> in people with T2DM and healthy people
				<i>Bifidobacterium</i>	people with T2DM: 10,7±0,7 (Data after logarithm transformation) Control : 11,6±0,9 (Data after logarithm transformation) <i>p-value</i> : <0,0001*	There was a significant difference between the number of <i>Bifidobacterium</i> in people with T2DM and healthy people

Note: * there is a significant difference (p <0.05)

Discussion

Following the objectives of the study, the researchers reviewed the differences in the number of *Lactobacillus* and *Bifidobacterium* bacteria in healthy people and people with type 2 diabetes in Asia. *Lactobacillus* and *Bifidobacterium* are two genera of gram-positive bacteria that commonly exist in the human digestive tract (10). Four articles analyzed the difference in the number of *Lactobacillus* bacteria between people with type 2 diabetes mellitus (type 2 diabetes) and healthy people in Asia. An article analyzed the difference in the number of *Lactobacillus* bacteria between people with type 2 diabetes, type 1 diabetes mellitus and healthy people in Asia. All articles conclude that there are differences in the number of *Lactobacillus* bacteria between people with type 2 diabetes and healthy people and there are differences in the number of *Lactobacillus* bacteria between people with type 2 diabetes, people with type 1 diabetes, and healthy people. In general, all articles show that the number of *Lactobacillus* bacteria is higher in people with type 2 diabetes than in healthy people.

According to previous research, not all bacteria from the genus *Lactobacillus* have a positive effect on people with type 2 diabetes. *Lactobacillus* is a genus that has a positive response on modulating blood

glucose, while for another genus has different effects (11, 12). Based on these reasons, the researchers suggest further research to identify differences in the number of bacteria from the *Lactobacillus* genus per type so that the research results are detailed.

Other possibilities could be the cause of the higher number of genus *Lactobacillus* bacteria in people with type 2 diabetes mellitus compared to healthy people. The intestinal microbiota influenced by the type of drug consumed in people with type 2 diabetes mellitus (13). Several previous studies or reviews stated that there is a tendency to decrease the number of *Lactobacillus* bacteria in the gastrointestinal tract of people with type 2 diabetes. But, this may change if the patient starts to conduct new habits such as eating high-probiotic foods, high-fibre foods and or taking anti-hyperglycemic drugs. High-probiotic foods such as yoghurt, kefir, cheese, or milk and foods high in insoluble fibre have shown to increase the number of *Lactobacillus* bacteria in the digestive tract (14).

When viewed from the population characteristics of the articles reviewed, there is a tendency for the habit of eating foods high in probiotics among Iranian, Japanese, and parts of Chinese. All three populations of these countries have long had a culture of consuming a high probiotic diet, which probiotic products accessed easily from pharmacies and health facilities (22). Japan is known as the global market leader in the field of probiotics. Japanese usually consume products high in probiotics for health (22). The results of a review of research in Iran also show that Iranians have begun to realize the importance of consuming foods or products high in probiotics so that the need for food or probiotic products increases (23). The tradition of changing milk into fermented products has also long been applied in China so that Chinese people are most likely already accustomed to consuming fermented milk that contains probiotics, one of which is the genus *Lactobacillus* (24). These reasons can be the cause of the higher number of *Lactobacillus* bacteria in people with type 2 diabetes than in healthy people.

The review of the number of *Bifidobacterium* bacteria among people with type 2 diabetes and healthy people in Asia obtained from 5 journals. One journal analyzed the differences in the number of *Bifidobacterium* bacteria in people with type 2 diabetes, people with type 1 diabetes, and healthy people showed the results that the number of *Bifidobacterium* was higher in healthy people than in people with type 2 and type 1 diabetes. Three journals concluded that there was a significant difference in the number of *Bifidobacterium* bacteria in people with type 2 diabetes and healthy people. Moreover, two journals showed that the number of *Bifidobacterium* bacteria was higher in the control group (healthy people) compared to the group of people with type 2 diabetes mellitus. Otherwise, a journal shows the opposite result. Two journals that analyzed the difference in the number of *Bifidobacterium* bacteria between the two groups showed insignificant differences. In general, it concluded that there is still debate about the number of *Bifidobacterium* bacteria in people with type 2 diabetes and healthy people. However, when compared with previous studies, it can be concluded that there is a tendency for the number of *Bifidobacterium* bacteria to be higher in the digestive tract of healthy people compared to people with type 2 diabetes. This evidence was not remarkable because the bacteria of the genus *Bifidobacterium* have anti-inflammatory effects which people with dietary habits are high in fat and people with metabolic disorders such as diabetes mellitus will experience a decrease in the composition of the bacterial genus *Bifidobacterium* (25,26).

The decrease in the number or composition of *Bifidobacterium* bacteria in people with type 2 diabetes may not always occur because generally, the number of each type of the genus *Bifidobacterium* is also different. Based on another article that reviewed, it showed that the number of bacteria with the species *Bifidobacterium fragilis* and *Bifidobacterium longum* did not differ significantly in the digestive tract of people with type 2 diabetes mellitus and healthy people. The results of these studies differ from the study of Le et al (2013), which showed that there was a significant difference in the number of *Bifidobacterium adolescentis* bacteria in the digestive tract of people with type 2 diabetes and healthy people. There is a tendency for the higher number of *Bifidobacterium adolescentis* in the digestive tract of healthy people (21). The results of the study which state that there is a significant difference between the number of *Bifidobacterium* bacteria with type 2 diabetes mellitus and healthy people are generally consistent with the result of the number of bacteria from the genus *Bifidobacterium* is higher in healthy people than people with type 2 diabetes (15,18). This study is indeed limited in reviewing the differences between *Lactobacillus* and *Bifidobacterium* bacteria because it only analyzes genus, even though the effects of probiotics are broad and vary depending on the probiotic type. Therefore, researchers suggest further research on the number of type of bacteria from the genus *Bifidobacterium* and *Lactobacillus* in people with type 2 diabetes mellitus and healthy people. We also recommend that microbiota-based therapy for people with type 2 diabetes be developed, especially from the genus *Bifidobacterium* and several types of *Lactobacillus*, which do have a positive effect on reducing blood glucose. Because there has been no research on a topic like this in Indonesia, we also suggest that a specific study be conducted to observe the number of *Bifidobacterium* and *Lactobacillus* bacteria in people with type 2 diabetes mellitus and healthy people in Indonesia.

Conclusion

This Systematic Literature Review study concludes that there is a difference in the number of Lactobacillus bacteria in the digestive tract of people with type 2 diabetes and healthy people in Asia populations. There is also a tendency for the number of Lactobacillus bacteria in the digestive tract of people with type 2 diabetes to be greater than in healthy people. Based on an article that reviewed, there is still debate about the difference in the number of Bifidobacterium bacteria in the digestive tract of people with type 2 diabetes and healthy people. But the results of studies show that there are differences in the number of Bifidobacterium bacteria in the digestive tract of people with type 2 diabetes and healthy people in Asian populations. It consistently shows a decrease in the number of Bifidobacterium bacteria in the digestive tract of people with type 2 diabetes. Further research on the profile of Lactobacillus and Bifidobacterium bacteria per type (species) specifically in people with type 2 diabetes and healthy people of various ethnicities in Indonesia is needed to identify dysbiosis in people with type 2 diabetes. Further study also be required to determine specific microbiota therapy for people with type 2 diabetes.

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