



Probiotics Usage as Therapy on Diabetes Mellitus Type II: A Literature Review

*Lendy Nugroho Wisnu Murti**, *Nur Palestin Ayumuyas*, *Suharjono*

Master of Clinical Pharmacy Programme, Faculty of Pharmacy, Airlangga University, Surabaya, Indonesia

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ABSTRAK

Background: Type 2 diabetes has turned into a worldwide medical issue. Probiotics as the microorganisms in the intestinal tract has the potential impact to anticipate the improvement of insulin opposition and glycemic control in patients with type 2 diabetes. This literature review focused on the effects, mechanism of action and potential utilization of probiotics in type 2 diabetes. We use the journal article related to probiotics in type II diabetes that published on 2002 until 2016 for critical appraisal. **Results:** As therapy in type 2 diabetes, probiotics ready to bring down fasting glucose, HbA1C and HOMA-IR percentage or increment insulin levels. **Discussion:** The impact of the probiotics agent acquired on type 2 diabetes through the decrease of lipopolisaccharide (LPS), increased short chain fatty acids (SCFA), inhibition of immune response and oxidative stress, increased glucagon like peptide-1 (GLP-1), secretion of insulinotropic polypeptides, or increased activity of glucose transporter-4 (GLUT 4). **Conclusion:** From the review we concluded that probiotics can be a choice to keep up insulin sensitivity and anticipate the beginning of hyperglycemia in type 2 diabetes.

1. Introduction

Epidemiology transition from communicable to non-communicable diseases and lifestyle modifications that have an impact in disease patterns changes has placed diabetes as one of the health problems of people around the world. About 439 million people are expected to have diabetes by 2030¹. In Indonesia, the proportion of people with diabetes reached 6.9%, with people with impaired glucose tolerance (IGT) reached 29.9% and people with impaired fasting glucose (IFG) reached 36.6%². Types of diabetes included diabetes mellitus due to absolute insulin deficiency (type 1 DM), diabetes mellitus due to relative insulin deficiency or insulin resistance (type 2 DM), gestational diabetes mellitus (GDM) and other types of diabetes mellitus³.

Type 2 diabetes is the most prevalent diabetes type in the world³. Two primary pathophysiological processes play a role in the development of type 2 DM, reduced (sensitivity) response of body tissues to insulin and a gradual decline in pancreatic beta cell function due to the chronic imbalance of insulin and glucagon secretion patterns⁴. Diabetes mellitus (DM) can be characterized as chronic hyperglycemia that can cause destruction and dysfunction of many organs such as blood vessels (micro and macrovascular), eyes, kidneys, nerves, and heart⁵.

In addition to the given (curative) therapy, type 2 DM is a disease that is often underdiagnosed. About 30% of people with type 2 diabetes are not aware of the disease and when the diagnosis is made, about 25% of patients with type 2 diabetes have already suffered from microvascular complications⁶. The average delay from onset to diagnosis is established at about seven years^{7,8}. Therefore, preventive interventions must be given to keep blood glucose levels within the average threshold, i.e., before the onset of type 2 DM occurs.

Alternative management in the form of prevention can lead to a increase in insulin sensitivity and glycemic control, without causing a decline in the long-term treatment efficacy, is an advantage offered by probiotics as a therapy for type 2 DM⁵. Probiotics are normal microorganisms in the gastrointestinal tract, which will provide beneficial effects for the host's body if given in adequate amounts⁹. Bacteria from the genus *Bifidobacterium* and *Lactobacillus* are most often used as probiotics¹⁰.

Results from previous studies show that periodic probiotics consumption can reduce blood glucose levels and decrease glucose tolerance in patients with type 2 diabetes^{5,11,12}. Probiotics may also able to delay the onset of insulin resistance, delay the onset of diabetes by reducing oxidative stress, reduce inflammatory response and improve peripheral glucose uptake^{5,10}.

Although previous evidence shows the possibility of probiotics influences on blood glucose level and prevents type 2 DM, it is unfortunate that recent studies have limitations, namely the efficacy of probiotics there are not

many people with type 2 DM examined and the actual effects that may occur on the host's body cannot be clearly described¹³. This literature review tried to explore the impact of and the mechanism of probiotics which has the potential to maintain blood glucose level while preventing the onset of type 2 DM in high risk population, as well as the future potential application of probiotics in patients with type 2 DM.

2. Discussion

Insulin Resistance and Beta Cell Dysfunction in Type 2 DM

Type 2 diabetes is a metabolic disorder characterized by conditions such as chronic hyperglycemia due to defects in insulin function. In type 2 diabetes, an increase in glucose levels begins with the occurrence of an insulin resistance (function)¹⁴. Reduced of insulin function in body tissues can trigger a decrease glucose level response. This mechanism begins with an increase in post-prandial glucose levels that remains high post-phase 1 insulin secretion or acute insulin secretion response (AIR). Phase 1 secretion is insulin secretion, which occurs as soon as there is any stimulation of beta cells, marked by insulin production that appears and ends quickly¹⁵.

Increased glucose level does not only triggers compensation in the form of increasing phase 1 secretions above normal. Additional (extra) synthesis and insulin secretion are still needed in above normal phase 2 (sustained phase, latent phase). In phase 2 secretion, insulin increases slowly and lasts for a relatively long time. Therefore, in the early stages of type 2 DM hyperinsulinemia can be found during beta cells compensation. Clinically, only in decompensation stage, IGT and IFG can be detected and referred as prediabetic state¹⁵.

Insulin resistance can be caused by several factors such as high calories consumption, lack of physical activity, aging, obesity, or frequent consumption of alcohol¹⁶. The role of genetics can also influence the risk of insulin resistance, especially in individuals who have a family history of type 2 diabetes mellitus. According to familial history, an identified mutation in *KCNQ1* gene may also plays a role in abnormal insulin secretion in people with type 2 DM who live in Asia region¹⁷.

Insulin resistance does not only occur due to lack of insulin receptors in cell membranes but can also be caused by disorders of post receptors¹⁸. Disorders can occur in insulin receptor substrates (IRS) such as IRS-1 as an effector for insulin receptors and various processes of intracellular receptor phosphorylation¹⁹. Disorders can also occur in the synthesis and translocation of glucose transporters (GLUT) which play a role in the transfer of glucose from the blood into cells which are then metabolized¹⁸. GLUT is divided into five subtypes according to the specificity of the substrate, kinetic profile,

and distribution in body tissues. The deficiency of GLUT 4 which facilitates the entry of glucose into muscle cells and adipose is a disorder that is often found in type 2 DM²⁰.

Insulin resistance has only just begun to play a role since conversion from IGT to type 2 DM or when decompensation occurred. Several mechanisms underlie the progression of beta cell dysfunction which cause changes in the dynamics of insulin secretion during type 2 DM¹⁵. For example, systemic inflammatory response and oxidative stress due to lipopolysaccharide (LPS) which not only play a role in decreasing insulin sensitivity but also the destruction of pancreatic beta cells that causes hypoinsulinemia in type 2 DM^{21,22}. Furthermore, inflammatory responses and oxidative stress play a role in glucotoxicity and lipotoxicity that underlies chronic complications in type 2 DM.

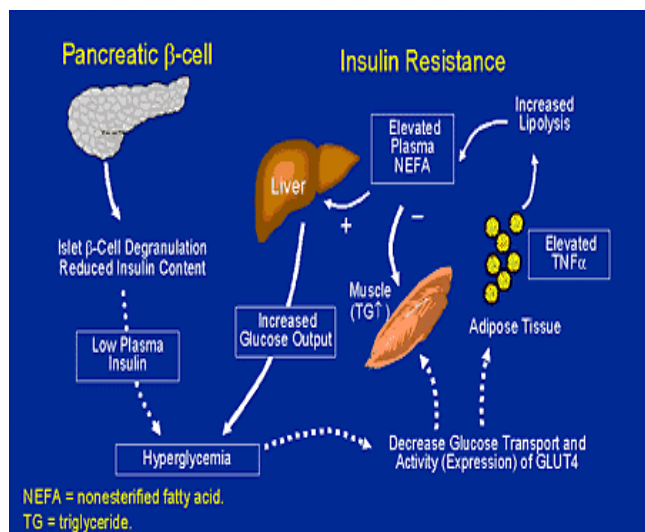


Figure 1. Insulin Resistance and β -Cell Dysfunction Produce Hyperglycemia in Type 2 DM³³.

Working Mechanism of Probiotics Agents in Type 2 DM

There are more than 100 trillion microorganisms, including bacteria, yeasts, and parasites in the human intestinal tract. The population will be renewed automatically every three days and actively produces metabolites for the host's needs. Compositional microorganisms' imbalance in the intestinal tract will underlie the pathogenesis of various diseases. Therefore it is crucial to maintain the composition of useful microorganisms to maintain health²³.

Probiotics ferment LPS and oligosaccharides to short-chain fatty acids (SCFA) such as acetate and lactate, which are converted back as butyrate for intestinal mucosa energy sources. Probiotics can also reduce the permeability of the intestinal mucosa to LPS directly. Decreasing LPS in the body can reduce the systemic inflammatory response and oxidative stress associated with insulin resistance in the pathogenesis of type 2 DM²².

The effect of LPS in insulin resistance starts with the inflammatory response by Toll-like receptor-4 (TLR-4). TLR-4 is a group of glycoproteins that function as trans-membrane receptors in the intestine and is involved in innate immune responses to exogenous pathogens (LPS) and endogenous pathogens (free fatty acid)^{24,25}. A decrease in LPS resulting from probiotics fermentation will reduce the signal to activate cytokines, chemokines and various pro-inflammatory mediators that can interfere with the IRS-1 phosphorylation process for glucose entry into cells²⁶. Thus, a decrease in LPS, TLR-4 signal, and inflammatory response to the consumption of probiotics may prevent the occurrence of insulin resistance¹³.

SCFA products (butyrate, propionate, and acetate) formed by probiotics in the small intestine and colon not only act as an energy source but also as a signal modulator to various body systems²³.

The absorbed SCFA can modulate the levels of some intestinal hormones involved in glucose and energy homeostasis. One of them is glucagon-like peptide-1 (GLP-1), produced by L-cells in the ileum and colon to reduce blood glucose levels during conditions of hyperglycemia by stimulating insulin secretion and reducing glucose dependence^{23,27}. GLP-1 can also stimulates feeling of fullness and delay emptying in the stomach through a mechanism in the central nervous system by reducing post prandial glucose levels²⁸. Activation of G-protein coupled receptor (Gpr43) due to SCFA in adipose can also improve insulin sensitivity by increasing GLP-1 secretion in the intestine²¹.

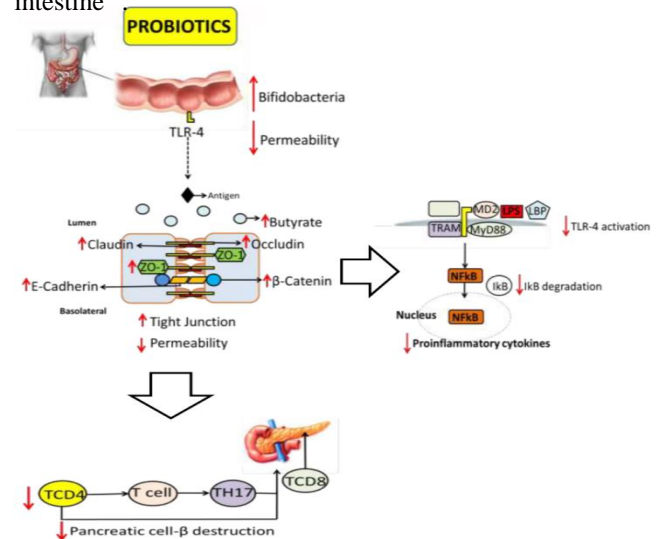


Figure 2. Schematic representation of probiotics actions in type 1 and type 2 diabetes¹³.

In addition to preventing oxidative stress that can cause pancreatic beta cell destruction and insulin resistance through decreased levels of LPS, probiotics are also able to influence the level and activity of antioxidant enzymes through the cross-kingdom cell to cell signaling process²⁹. Probiotics work to inhibit lipid peroxidation and increase endogenous antioxidants such as catalase, glutathione

peroxidase, glutathione, and superoxide dismutase (SOD) which prevent the onset of type 2 DM¹². Directly, probiotics are also able to secrete insulinotropic polypeptides metabolites in their hosts which may induce an increase in glucose uptake in tissues and glycogen accumulation in the liver⁵.

Probiotics consumption, such as *Lactobacillus* and *Bifidobacterium* may also increases GLUT 4 mRNA expression as a glucose transporter molecule²³. Through Grp41 and Grp43 activation, an increase in GLUT 4 will be followed by an increase in glucose uptake in the tissue so that it can prevent hyperglycemia and insulin resistance³⁰.

Potential of Probiotics in Type 2 DM

The administration of probiotics in patients with type 2 diabetes mellitus is able to give a significant reduction in GDP and HbA1C¹⁰. This decrease is very significant in preventing the occurrence of hyperglycemia and its complications. 1% reduction in HbA1C alone is associated with a reduced risk of developing type 2 DM by 21% and the emergence of microvascular complications by 37%²².

Probiotics in type 2 DM work by increasing insulin level and its function. Probiotics can also influence insulin sensitivity by reducing the value of homeostasis model assessment of insulin resistance (HOMA-IR). The HOMA-IR value is obtained from fasting plasma insulin × fasting plasma glucose / 22,5 which indicates the level of a person's insulin resistance³¹. The results of meta-analysis showed a significant increase in fasting insulin concentration (mIU / L), a significant reduction in HOMA-IR, HbA1c, and fasting plasma glucose (FPG) levels after probiotics administration¹².

Table 1.The Effect of Probiotics¹².

Study	Intervention/ control (sample size)	Duration (weeks)	Dose (CFU)	Probiotics	Placebo
Asemi, Z. et al, 2014	Synbiotic food/placebo food (62/62)	8	0,2-20x10 ⁹	FPG: 143,8±55,60 HbA1c: 7,71±1,92 Insulin: 5,7±4,16 HOMA-IR: 1,98±1,7 1	FPG: 134,5±49,88 HbA1c: 6,35±1,56 Insulin: 5,82±5,2 HOMA-IR: 2,03±2,29
Ejtahed. et al, 2012	Probiotic yoghurt/ conventional yoghurt (30/30)	6	6,04-7,23 x10 ⁶	FPG: 145,89±45,07 HbA1c: 7,29±1,21 Insulin: 747±4,89	FPG: 133,04±23,17 HbA1c: 6,87±0,81 Insulin: 6,31±3,72
Mazloom, Z. et al, 2013	Probiotic capsules/ placebo capsules (16/18)	6	-	FPG: 158,56±54,80 Insulin: 10,14±15,82 HOMA-IR: 2,92±5,08	FPG: 149,83±59,65 Insulin: 6,18±2,10 HOMA-IR: 1,75±1,29

Evidences from Clinical Studies

A summarized list of studies evaluating the effects of probiotic administration in clinical investigations in

diabetes mellitus is presented in Tables 2.

Table 2.Effect of Probiotics Administration on DM – Clinical Studies¹³

Probiotics	Study Design/ subjects	Quantity	Study Period	Results
<i>Lactobacillus acidophilus</i> and <i>Bifidobacterium bifidum</i>	Double-blinded, placebo-controlled, randomized study, T2D females aged 50–65 years	2 daily doses of 100 mL symbiotic shake containing 4 × 10 ⁸ CFU/100 mL <i>L.acidophilus</i> , 4 × 10 ⁸ CFU/100 mL <i>B. bifidum</i>	45 days	↓ Glycemia
<i>Lactobacillus acidophilus</i> La5 and <i>Bifidobacterium lactis</i> Bb12	Double-blinded, randomized controlled clinical trial, T2D patients aged 30–60 years	300 g/day of probiotic and conventional yogurt day 1: 7,23 × 10 ⁶ of <i>L. acidophilus</i> La5 and 6,04 × 10 ⁶ cfu/g of <i>B. lactis</i> Bb12	6 weeks	↓ Fasting blood glucose and HbA1c ↑ Erythrocyte SOD and GPx ↑ Total antioxidant capacity
<i>Lactobacillus rhamnosus</i> GG, ATCC 53 103 and <i>Bifidobacterium lactis</i> Bb12	Randomized, prospective, parallelgroup, combined dietary counselling, pregnant women	<i>Lactobacillus rhamnosus</i> : 10 ¹⁰ CFU/day; <i>Bifidobacterium lactis</i> Bb12: 10 ¹⁰ CFU/day	18 months	↓ Blood glucose ↓ Insulin ↓ Insulin sensitivity

Future Challenges and Opportunities for the Application of Probiotics Agents in Type 2 DM

The usage of more than one bacteria strain in probiotics is a promising step in preventing the development of type 2 DM. This will have a superadditive effect on the effectiveness of the therapy given¹⁰. These probiotics can also be used in various practical and interesting preparations. Not limited to capsules, powders, or oral tablets, but can also be used as processed food²⁹.

Compared to existing oral anti-diabetes drugs (OAD), probiotics have several advantages. First, the production process can be easily bred and manufactured without the availability of state of the art technology. Also, probiotics are parts of good microbes that generally exist in the intestinal tract so that they are safe for consumption. The human body can well tolerate probiotics with minimal side effects. Probiotics also do not go through pharmacokinetic process unlike OAD; therefore, it can provide maximum impact according to its composition in the intestinal tract²⁹.

Nevertheless, there are various considerations and challenges in the application of probiotics agents. There is still no appropriate therapeutic dose, which required further research related to its dosage. In addition to that, it should be noted that the application in patients with immune system deficiency or who are on immunosuppression therapy might need to be contraindicated since it may

cause bacteremia in the patient²⁹.

3. Conclusion

Probiotics have the potential effects to prevent insulin resistance and increase blood glucose. The effects of probiotics are obtained through decreased LPS, increased SCFA, increased GLP-1, increased GLUT 4, secretion of insulinotropic polypeptides, and suppression of immune reactions and oxidative stress. As a therapy for type 2 DM, probiotics can decrease GDP, HbA1C, HOMAIR values, and increase insulin levels, but the dosage and the clinical condition of the recipient should be monitored.

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