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ROLE OF PROBIOTICS IN TYPE 2 DIABETES MELLITUS PATIENTS WITH HYPERTENSION: A REVIEW

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ABSTRACT

Background: Type 2 Diabetes Mellitus (DM) is one of a global health problem. One of the comorbidities that often occurs in patients with type 2 DM is hypertension. Hypertension can increase the risk of cardiovascular complications. One of the causes of type 2 DM and hypertension is gut dysbiosis. An imbalance of gastrointestinal microbiota contributes to chronic inflammation and effects on the insulin action, increases insulin resistance, and leads to endothelial dysfunction. The role of this inflammatory mediator is a new therapeutic target in type 2 DM patients with hypertension. **Objective:** to describe how probiotic effect in type 2 diabetic patients with hypertension. **Methods:** All articles were obtained by conducting an electronic search through Pubmed and Google Scholar. **Results:** Probiotics help to restore the balance of the gastrointestinal microbiota, produce anti-inflammatory mediators, and suppress the pro-inflammatory mediators to control the glycemic profile and blood pressure of patients with type 2 DM with hypertension. All the clinical trial showed that probiotic help to maintaining clinical outcome in diabetic patients with hypertension. **Conclusion:** Probiotic effective for glycemic control and blood pressure in type 2 DM with hypertension.

Keywords: Diabetes; Hypertension; Gut dysbiosis; Probiotics; Inflammation mediators

INTRODUCTION

Type 2 Diabetes Mellitus (DM) is a condition in which chronic hyperglycemia occurs due to insulin resistance or decreased insulin secretion by the pancreas. This condition is caused by several factors, such as excessive caloric intake, genetics, obesity, lack of physical activity, and dysbiosis of the normal flora in the gastrointestinal tract. [1]

The number of people suffering from type 2 DM continues to increase year by year worldwide. According to 2021 International Diabetes Federation, there are 537 million people who have type 2 DM and it's estimated to continue to increase by 46% in 2046. It has become one of the global health problems, where type 2 DM requires more attention to be able to control their diabetic control and to prevent complications. [2]

Patients with type 2 DM usually have several comorbidities including, hypertension. The incidence of hypertension in type 2 DM patients reach more than 75%. Hypertensive conditions in type 2 DM patients will increase the risk of cardiovascular complications 4 times greater than in type 2 DM patients without hypertension. [3]

Type 2 diabetes mellitus with hypertension requires special attention, including comprehensive therapy that involves health care workers to plan and achieve treatment goals, such as control of glycemic profiles, blood pressure, and prevent the complications. [2,4]

In addition to the main therapy of type 2 diabetes mellitus with hypertension, it is very important to fulfill the nutritional needs of type 2 DM patients with

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hypertension. One of the concerns those patients is the status of commensal gastrointestinal bacteria. Several studies have shown that the composition of the commensal gastrointestinal bacteria was altered in patients with type 2 DM with hypertension compared to patients without type 2 DM with hypertension. Patients with type 2 DM and hypertension were known to have dysbiosis of the commensal gastrointestinal bacteria, or it is commonly referred to as gut dysbiosis. The arised commensal abnormalities lead to more gram-negative bacteria, thus causing systemic a inflammation, reducing the insulin action, increasing insulin resistance, and also causing the endothelial dysfunction that increasing blood pressure in patients. [1,5]

Administration of probiotics to type 2 diabetic patients with hypertension aimed to correct imbalances of the normal flora in the gastrointestinal tract and reduce inflammatory mediators. In addition, probiotics can improved nutritional status in hypertensive type 2 diabetic patients. The bacteria in the probiotics produced *short-chain fatty acids* (SCFAs), which also helped reducing inflammatory mediators, such us interleukin-6 (IL-6), tumor necrosis factor α (TNF-α) and tumor growth factor β (TGF- β), and the gram-positive bacteria like lactobacillus spp. metabolized nutrients from the food that consumed by patients into substances, which was easier to be absorbed through the patient`s gastrointestinal tract, thus improve the nutritional status in type 2 diabetic patients with hypertension. [5,6,7]

This review aims to describe how type 2 diabetic patients with hypertension exposed to gut dysbiosis, the impact of inflammatory mediators on, and the effect of probiotics for type 2 diabetic patients with hypertension.

METHODS

All articles were obtained by conducting an electronic search through Pubmed on October 25, 2022 and Google Scholar on October 26, 2022. The search used the following keywords: 'Diabetes mellitus type 2' 'hypertension' 'dysbiosis' 'probiotic'. All articles in the form of reviews, randomized control trials, and meta-analyses were selected and reviewed by the authors and then compiled for writing this review.

THE ROLE OF COMMENSAL GASTROINTESTINAL BACTERIA IN NORMAL CONDITIONS

The normal flora of the gastrointestinal tract acts as an immunomodulator, protects the gastrointestinal tract, and influences the structure and function of the gastrointestinal tract. The mechanism and role of normal flora bacteria varies depending on the species. There are bacteria be able to regulate dendritic cells, increase IgA secretion, or maintain the barrier of the gastrointestinal tract. [7]

a. Maturation and Development of the Mucosal and Systemic Immunity.
   Certain of commensal bacterias have specific structures that can stimulate the host's immune system. When pathogens enter the body, the bacteria stimulate the immune system. *Lactobacillus species* (*Lactobacillus spp*.) has a regulating effect on dendritic cells, leading to T cells differentiation and release of inflammatory mediators against these pathogens, *Lactobacillus spp.* also modulates the T cells to produce anti-inflammatory mediators for body homeostasis. The cell walls gram-negative bacteria were made of lipopolysaccharide (LPS). This LPS stimulates the formation of solitary lymphoid follicles (ILFs) through signaling from nucleotide-binding oligomerization domain-containing protein 1 (NOD1). LPS also binds to tool-like receptors (TLRs) and releases inflammatory mediators. *Phylum bacterioides* has the ability to stimulate Th17 cells, and *E. coli* can upregulate dendritic cells to activate the host's immune system. [7]

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b. Gastrointestinal Mucosal Tolerance
Commensal bacteria such as *Lactobacillus spp.* maintain the gastrointestinal barrier by inducing TLSP in the gastrointestinal epithelial cells. *Thetaiomicron* bacteria inhibit NF-kB activation, preventing the formation of pro-inflammatory mediators and also improving the function of gastrointestinal mucosal barrier function. [7]

c. Regulates Proliferation of Commensal Gastrointestinal Bacteria
The commensal bacteria of the digestive tract may become overgrowth. When this situation occurs, gram negative bacteria such as *Bacterioides* stimulate the gastrointestinal mucosa to produce IgA and control bacterial growth in the gastrointestinal tract. [7]

d. Protective Agent by Reducing Inflammatory Mediators
Bacteria in the digestive tract have enzymes that can ferment and metabolize carbohydrates. Carbohydrates are broken down into monosaccharides and oligosaccharides and fermented into SFCA. The resulting SCFA is composed of propionic acid, butyric acid, and acetic acid with a composition ratio of 1:1:3. These formed SCFAs can induce the expression of LL-37 *cathelicidin*. Furthermore, SCFAs are taken up by gastrointestinal epithelial cells. Another function of SCFAs is to reduce the production of pro-inflammatory mediators such as *butyrate*, which has anti-inflammatory and anti-cancer properties. [5,8]

THE ASSOCIATION OF GUT DYSBIOSIS AND TYPE 2 DM WITH HYPERTENSION

1. Conditions Predisposing Gut Dysbiosis

The main conditions that alter the commensal gastrointestinal bacteria are the presence of an unbalanced diet and obesity. An imbalanced diet with high in carbohydrates and sugars reduces pH changes in the gastrointestinal tract, leading to an imbalance in the bacterial composition. A fatty diet also influences this state of gut dysbiosis. Individuals who consume high-fat foods have increased numbers of the gram negative bacterial such as *Bacteroides, Clostridium,* and *Enterobacteriaceae*. These reduce the number of SCFA- and butyrate-producing bacteria in patients with type 2 DM and hypertension. [6,8]

2. Pathophysiology Of Gut Dysbiosis In Type 2 Diabetes Mellitus With Hypertension

Hight diets in carbohydrates, sugars, and fats cause changes in the composition of the commensal bacteria in the gastrointestinal tract. In diabetic patients with hypertension, *Bacteroides* which are gram negative bacteria are more numerous than *Firmicutes* which are gram positive. [5,7]

As the number of gram-negative bacteria increase, the production of endotoxins derived from lipopolysaccharide (LPS), a component of the cell wall of gram-negative bacteria, increases. The endotoxin produced increases the permeability of the gastrointestinal cell wall and causes impaired cross-linking of the gastrointestinal membrane, which allows endotoxin to enter the systemic circulation. Endotoxin then binds to TLR-4 in adipose tissue, triggering the release of proinflammatory cytokines. Furthermore, endotoxin also upregulates nuclear factor kappa B (NF-kB), causing the release of proinflammatory mediators, such as tumor necrosis factor α (TNF-α) and interleukin-6 (IL-6), which can increase insulin resistance and will cause hyperglycemia. [5]

These proinflammatory mediators will lead to oxidative stress and free radicals. These free radicals oxidize LDL and then oxidized LDL inhibit the

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production of nitric oxide from endothelial cells. It increases the production of endothelin-1 which acts as a vasoconstrictor and leading to an increase in blood pressure. [5,9,10]

THE ROLE OF INFLAMMATION MEDIATORS IN TYPE 2 DM WITH HYPERTENSION

Inflammatory mediators that play a critical role in the process of type 2 DM and hypertension are interleukin-6 (IL-6), tumor necrosis factor α (TNF-α), and tumor growth factor β (TGF-β). The pro-inflammatory mediator IL-6 will result in activation of the suppressor of cytokine signaling (SOCS) protein which results in signal disturbances in signal transducer and activator of transcription 5B (STAT5B). This is one of the transducers on insulin binding to insulin receptor. The disruption of STAT5B signaling impairs insulin signaling and ultimately leads to insulin resistance.[11]

The TNF-α causes insulin resistance by activating Jun NH2-terminal kinase (JNK) causes disruption of serine 307 phosphorylase in IRS-1. It results in impaired insulin signaling at insulin receptors and contribute to insulin resistance. [11]

A pro-inflammatory mediators TGF-β, play an important role in the pathogenesis of hypertension. Increased reactive oxygen species (ROS) and the activation of nuclear factor kappa B (NF-kB) increase TGF-β. TGF-β plays a role in the repair process of injured cells, but persistent activation of TGF-β leads to collagen accumulation, excessive vascular proliferation, decreased elasticity of the vessel wall, end up in a state of endothelial dysfunction and furthermore an inflammation cause an increase in blood pressure. [11]

THE ROLE OF PROBIOTICS IN TYPE 2 DIABETES MELLITUS AND HYPERTENSION CONDITIONS

Lactobacillus spp. is one of the most studied probiotic strains recently. *Lactobacillus spp*. belongs to the phylum *Firmicutes* which is a gram-positive bacterium. It has the effect of reducing pro-inflammatory mediators and may prevent the development of pathogenic bacteria in certain conditions such as diabetes mellitus and infections. [12]

Lactobacillus has the effect of increasing the barrier function and permeability of the gastrointestinal mucosa by increasing the cross-linking between the epithelial cells of the gastrointestinal mucosa. It can also decreases circulating lipopolysaccharides from gram-negative bacteria in the systemic circulation and enhance the release of glucagon-like peptide 1, leading to insulin release from the pancreas. [12]

Modulatory effects of dendritic cells on *Lactobacillus spp.* cause alterations in the regulation of regulatory T cells (Treg) that affect the homeostatic regulation of immune processes in the body. Through dendritic cell regulation, these cells are recognized by T cells, which differentiate into helper T-1 (Th-1) cells, then subsequently produce IL-10 as anti-inflammatory mediator and produces interferon gamma (IFNγ) that protects other cells. *Lactobacillus* species such as *L. acidophilus* and *L. plantarum* have inhibitory effects on pro-inflammatory mediators such as Il-6 and TNF-α. [12,13]

Probiotics also cause an increase in the barrier function of the epithelial cells of the gastrointestinal tract. Administration of probiotics increase protein adhesions, namely *β-catenin* and *E-cadherin*, which can stabilize cross-linking of epithelial cells of the gastrointestinal tract. [6]

CLINICAL EVIDENCE OF THE PROBIOTICS IN TYPE 2 DM PATIENTS

1. Pre-Clinical Trials

The benefits of *Lactobacillus plantarum* for patients with type 2 DM have also been tested preclinically with a randomized control trial using 25 male Wistar rats aged 12-16 weeks that have

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been induced to DM. The rats were then divided into 2 groups, where the probiotic group would be given 1.0 ml of *Lactobacillus plantarum* suspension every 24 hours and the placebo group for 7 days. The study found that there was a significant difference between the probiotic group and the placebo group in terms of reducing fasting blood glucose levels in probiotic group with $p = 0.009$. [14]

2. Clinical Trials

In a randomized controlled trial administration of probiotics containing *Lactobacillus casei* 10^8 CFU in 40 patients with type 2 DM, Results showed probiotics significantly reduced fasting blood glucose levels by 28.32% compared to the placebo group (mean difference (MD -28.32; 95% CI -50.23 to -6.41), $p = 0.013$. Insulin levels were also reduced in the probiotic group, with administration of the probiotic *Lactobacillus casei* significantly lowering insulin levels by 3.12% compared to the placebo group (MD: -3.12; 95% CI -5.90 to -0.35) $p = 0.028$. SIRT1 score was also significantly increased in the probiotics group, with a 0.52% increase in SIRT1 compared to the placebo group (MD: ± 0.52; 95% CI 0.026 to 1.02), $p = 0.040$. Probiotic also significantly reduced fetuin A levels, with a 17.56 decreased in fetuin A in the probiotic group compared to the placebo group (MD: - 17.56; 95% CI -32.54 to -2.58, $p = 0.023$). Result in HbA1C values, administration of probiotics to DM patients did not show a significant difference between the two groups at $p = 0.077$. [15]

A meta-analysis of 13 RCTs involving 818 people with type 2 DM confirmed the effects of 6-12 weeks of probiotic on blood glucose, lipid and blood pressure profiles. The results showed that there was a significant difference in fasting blood glucose levels (SMD = -0.91; 95% CI: -1.48 to -0.33) and no significant difference in HbA1c levels (SMD = -0.16; 95% CI: -0.68 to 0.36), and there was a significant difference in the incidence of insulin resistance as measured by HOMA IR (SMD = -0.48; 95% CI: -0.65 to 0.32). There was no significant difference in LDL scores when probiotics were administered compared to placebo (SMD = -0.04; 95% CI: -0.21 to 0.14). Regarding blood pressure results, probiotics were found to significantly reduce systolic blood pressure (SMD = -3.26; 95% CI; -6.44 to -0.08) and diastolic blood pressure (SMD = -2.66; 95%). CI: -4.53 to -0.80) compared to placebo. [16]

Another study, which was an RCT involving 53 patients with type 2 DM who were given multi-strain probiotics for 8 weeks, showed that there was a decrease in HOMA IR from 6.85 ± 0.76 to 5.13 ± 0.49 ($p = 0.047$). The outcome of HbA1c was also a significant decrease of 0.25% ($p = 0.068$) compared to placebo. While the outcome of inflammatory mediators was a significant decrease in TNF-α mediators 7.95 ± 1.27 pg/mL ($p = 0.001$) and IL-6 3.45 ± 1.48 pg/mL ($p = 0.027$) compared to placebo. [17]

CLINICAL EVIDENCE THE ROLE OF PROBIOTICS IN HYPERTENSIVE PATIENTS

1. Pre-Clinical Trial

In a preclinical study, 30 Wistar rats that had been induced to hypertension were given *Lactobacillus fermentum* and *Lactobacillus gasseri* at a dose of $3.3x10^{10}$ cfu per day for 5 weeks and the control group was given a placebo. The results showed that the probiotics *Lactobacillus fermentum* and *Lactobacillus gasseri* significantly reduced systolic blood pressure (13.4±1.9% vs 14.7±1.9%) in the intervention group and control group with $p < 0.01$, while there was no

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difference in heart rate outcomes in both groups.[18]

2. Clinical Trial

The administration of *Lactobacillus casei* for hypertensive patients has been investigated by Sperry et. al. in 2018. The study was conducted using a randomized double-blind pilot study with 30 hypertensive patients who were given probiotics containing *Lactobacillus casei* $5x10^9$ cfu compared to placebo for 4 weeks. The outcomes are systolic blood pressure and diastolic blood pressure. The results showed that there was a significant decrease in systolic and diastolic blood pressure in the probiotic group. The systolic blood pressure after being given intervention in the placebo group was 136±1.31 mmHg compared to the probiotic group, which was 120.1±1.83 mmHg with p = 0.0001. The diastolic blood pressure after the intervention in the placebo group was 92.4 ± 1.76 mmHg compared to the probiotic group of 86.3 ± 1.56 mmHg with p = 0.0001.[19]

A randomized double-blind clinical trial involving 40 patients with type 2 DM was given a soy milk containing *Lactobacillus plantarum* as much as 200 ml/day for 8 weeks. The outcome was a decrease in systolic and diastolic blood pressure after had been given a soy milk containing *Lactobacillus plantarum*. There was a significant difference between the probiotic group and the placebo group in reducing the participants' systolic and diastolic blood pressure. The decreased in systolic blood pressure was 14.7±0.48 in the intervention group, meanwhile the control group showed 13.05±0.16; p = 0.001 The reduction in diastolic blood pressure was 10 ± 0.7 in the intervention group compared to the control group and the placebo group 9.1 ± 1; p = 0.031. [20]

CONCLUSION

Abnormalities in normal gastrointestinal microbiota lead to chronic inflammation, which results in increased production of pro-inflammatory mediators. These inflammatory mediators cause increased insulin resistance and endothelial dysfunction leading to type 2 DM and hypertension or exacerbating both diseases. Probiotics are used as additional therapy to the main treatment of type 2 diabetes with hypertension, including to control blood sugar profile and blood pressure and to prevent the complications of both diseases. Probiotics have been found to be effective in lowering fasting blood glucose levels, 2-hour postprandial blood glucose levels, lowering blood pressure, reducing pro-inflammatory mediators and increasing anti-inflammatory mediators. Further studies with a larger number of patients are recommended to determine the greater effect of the probiotic administration and possible side effect monitoring, in type 2 diabetic patient with hypertension.

CONFLICT OF INTEREST

There is no conflict of interest in this article.

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