

Relationship between Probiotics and Type 2 Diabetes Mellitus: A Review

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Abstract

Objective: Diabetes is a chronic medical condition that can be caused by either inherited or acquired insufficiency insulin secretion, or the body's inability to effectively utilize the insulin it produces. There are three primary classifications of diabetes: type 1, type 2, and gestational diabetes. Type 2 diabetes mellitus (T2DM) is characterized by elevated levels of fasting blood glucose (FBG) and glycosylated hemoglobin (HbA1c), indicating a disturbance in glucose metabolism. The term "probiotics" refers to living microorganisms that provide beneficial effects on the host's health. The effects of probiotics on T2DM in humans have shown conflicting results. Some studies have demonstrated that probiotic treatment substantially reduces HbA1c, FBG, or insulin resistance (IR) in patients with T2DM. However, other studies have found no significant difference between probiotic-treated patients and those receiving a placebo. The use of probiotics was found to enhance glucose metabolism and HbA1c levels in individuals with T2DM. These findings are in line with previous reviews conducted on this topic.


Keywords: Diabetes, Probiotics, Insulin

QR Code:



Citation: Kheirkhah A H, Forouzani-Moghaddam M J, Afkhami-Ardekani M. Relationship between Probiotics and Type 2 Diabetes Mellitus: A Review. IJDO 2023; 15 (2) :119-128

URL: <https://ijdo.ssu.ac.ir/article-1-795-en.html>

 10.18502/ijdo.v15i2.12971

Article info:

Received: 09 February 2023

Accepted: 08 May 2023

Published in June 2023



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Introduction

Diabetes is a chronic condition that can be either inherited or acquired. It occurs when the pancreas fails to produce enough insulin or when the body becomes resistant to the insulin it produces (1). Living with diabetes requires ongoing adjustments to one's lifestyle (2,3). Failure to control diabetes can lead to severe complications such as nephropathy, retinopathy and cardiovascular failure (4). Among all forms of diabetes, type 2 diabetes mellitus (T2DM) is the most prevalent and a significant public health concern (5). The global prevalence of diabetes has exceeded 420 million individuals, suggesting a potential upward trend (1). By 2045, it is anticipated that over 630 million individuals worldwide will be afflicted with T2DM (6). This highlights as a global issue that significantly impacts public healthcare spending. The estimated global cost of diabetes is projected to reach \$827 billion (7).

In Iran, diabetes affects approximately 4.5% to 6% of the population, with the province of Yazd reporting a frequency of 14.2% in individuals over 30 yearsold (8). Additionally, there are other types of diabetes, such as latent autoimmune diabetes in adults (LADA) (10). T1DM remains a mystery, and based on current understanding, it cannot be prevented (1).

Patients with T2DM may also experience various symptoms related to gastrointestinal dysfunction, such as delayed gastric emptying, diabetic gastroparesis, constipation, diarrhea, obesity, and other related conditions (12-14). As a result, the involvement of gastrointestinal dysfunction is considered a stage in the development of T2DM (15). T2DM is a prevalent and significant chronic disease. This mini-review demonstrates that the composition of the gastrointestinal microbiota is essential for comprehending the pathophysiology of T2DM. The ingestion of probiotics presents a potentially advantageous approach that yields favorable outcomes in the modulation of the gut microbiota compared to alternative

methods of managing T2DM. The investigation of probiotics for diabetes prevention, progression, and symptom amelioration is highlighted by the fact that multiple probiotic strains, especially those belonging to the *Lactobacillus* and *Bifidobacterium* spp., have shown the ability to enhance T2DM-related indicators. With advancements in molecular biology and the "omic" age, it is hoped that a better understanding of the mechanisms involving T2DM and gut microbiota will emerge, allowing for a more precise comprehension of the relationship between microbiota composition and diabetes. Lastly, the intestinal microbiota can play a crucial role in the management of this chronic disease (16).

The process by which T2DM develops is intricate but generally understood. T2DM is categorized as a chronic inflammatory illness (13). Insulin resistance (IR) resulting from inflammation is a particular trait of the majority of T2DM patients. A growing body of research suggests that variables associated with gut microbiota may also contribute to the development of T2DM (17). In addition to considering the gastrointestinal symptoms of T2DM, it is suspected that the gut microbiota plays a role in the pathogenesis of T2DM (18). The prevalence of T2DM increases with age; however, due to rising obesity, inactivity, and poor diet, this condition is also being observed in children, adolescents, and young adults (19). The significant risk factors for T2DM are hereditary factors, excessive calorie intake, and lack of exercise, which have been extensively discussed (20). Obesity is a significant risk factor for developing T2DM. The epidemic of obesity is influenced by multiple causal variables, including overall energy expenditure, level of exercise, food consumption, genetics, socioeconomic position, educational attainment, and intestinal microbiota, which have been associated with obesity (21). The recent literature review on obesity and microbiota suggests that the ratio

of Firmicutes to Bacteroidetes change with obesity. Therefore, a more comprehensive examination of the intestinal microbiome, encompassing bacterial families, genera, and species, is necessary to gain a deeper understanding of the connection between gut microbiota and obesity (22). The term "probiotics" is commonly defined as "beneficial microorganisms that are alive and can be given to a host to improve their health." It derives from the Greek words "Pro," meaning "promotion," and "Biotic," meaning "life" (23). In many various cultures and ethnicities, from the eastern to the western, fermented foods such as yogurt, kefir, kimchi, sauerkraut, tempeh, miso, and kombucha are a regular part of the meal (24-26). The term "probiotic" was coined by Ferdinand Vergin in a 1954 article titled "Anti-und Probiotika." The study investigated different types of microorganisms to compile a list of beneficial bacteria and to determine the negative impact of antibacterial agents and antibiotics on the gut microbiota (27). A few years later, Lilly and Stillwell defined probiotics as beneficial microbes that stimulate the growth of other microorganisms through the production of growth-promoting substances (28). Over time, with further research and clinical trials conducted in human and animal models, the definition of "probiotics" has evolved. According to the Food and Agriculture Organization (FAO) and the World Health Organization (WHO), probiotics are living microbe strains that enhance the host's health when administered in sufficient quantities (29). This definition is also endorsed by the International Scientific Association for Probiotics and Prebiotics (ISAPP) (30,31).

Probiotic benefits

The consumption of probiotics is an efficient and appealing method for modifying the microbial composition of the digestive tract, as well as for maintaining and improving human health (32). Probiotics work through key mechanisms such as enhancing the integrity of the epithelial barrier, enhanced adherence to

intestinal cells, and pathogen suppression through filling adhesion sites, generating antibacterial compounds, and influencing immune function (33). These processes contribute to the regulation of gut bacteria and inhibition of pathogen growth (34).

In recent years, the use of beneficial bacteria found in probiotics has shown effectiveness in the field of aquaculture (35). Lactic acid bacteria (LAB) and *Bacillus* spp. are among the most commonly used probiotic microorganisms in aquaculture (36-40). Probiotics have several beneficial impacts on health all over the limbs, including the suppression of the growth of pathogenic bacteria, production of short-chain fatty acids (SCFAs), modulation of gastrointestinal tract pH balance, and activation of the body's defense mechanisms. However, it is important to note that some of these effects may depend on the specific probiotic strain, underscoring the importance of strain identification in investigating their applicability in disease management (41). Studies on animals have indicated that probiotics may positively affect glucose metabolism and increase insulin sensitivity (42,43). However, there are conflicting reports about the impact of probiotics on T2DM. While some trials have shown significant reductions in HbA1c, fasting blood glucose (FBG), or insulin resistance (IR) in individuals with type 2 diabetes who received probiotic treatment (44,45), other research did not find a significant difference compared to those who received a placebo (46,47).

Researchers look at the impact of probiotics on three T2DM markers to fully assess the role of probiotics in T2DM patients and create the theoretical framework for probiotics to be widely used in clinical settings to treat T2DM-homeostasis model appraisal of IR (HOMA-IR), HbA1c, and FBG (48). Glycemic control comes with the genera *Lactobacillus*, *Bifidobacterium*, and *Streptococcus*. (46,49,50). Individuals with T2DM may experience dysbiosis (imbalance of microorganisms) in the gastrointestinal tract

and low-grade systemic inflammation. This dysbiosis and inflammation are associated with a higher ratio of Firmicutes to Bacteroidetes, the two main species in the GI tract, and a lower ratio of lactic acid-producing species such as *Lactobacillus*, *Bifidobacterium*, and *Streptococcus* (51). These organisms can produce SCFAs like acetate which can subsequently, via the use of cross-feeding mechanisms, be transformed into other SCFAs such as butyrate (50,52,53). SCFAs, such as butyrate and propionate, are able to increase glucagon-like peptide (GLP)-1, which is an incretin hormone that regulates postprandial insulin production by increasing the amount of insulin released in response to the consumption of glucose (54-56). Intestinal gluconeogenesis and glucose absorption through the portal vein are both controlled by SCFAs (55,57,58).

T2DM and Probiotics

T2DM is also defined by the possibility of an increased presence of pathogenic bacteria in the gastrointestinal tract, including Enterobacteriaceae. Inflammation and dysbiosis increase the risk of developing leaky gut syndrome, leading to impaired intestinal barrier function. Another concern is the elevated levels of lipopolysaccharide (LPS), which contribute to metabolic endotoxemia (51). The levels of LPS have a strong correlation with the integrity of the intestines. As a result, it is common knowledge that the intestinal barrier inhibits the circulation of LPS from the intestinal lumen into the rest of the body when the body is in a state of equilibrium (59). Tight junction proteins and adhesion of intestinal epithelial cells regulate intestinal permeability, forming a barrier that prevents the entry of pathogens, toxins, and products from the gut lumen into the circulation (60). It is possible that the release of LPS into the circulation as a result of a breakdown in the intestinal barrier would cause inflammation, leading to the development of a variety of disorders, including obesity (61), atherosclerosis (62),

and diabetes (63). Lowering LPS levels in the blood has been proposed as a potential treatment approach for T2DM (64).

Species of *Lactobacillus*, *Bifidobacterium*, and *Streptococcus* are responsible for regulating glycemic control through satiety signaling, maintaining gut integrity, and protecting pancreatic cells from free radical damage (41,55,57,65-67). It is known that the gut microbiota, in its eubiotic state, contributes to improved insulin sensitivity by inhibiting the expression of pro-inflammatory cytokines (e.g., tumor necrosis factor-alpha [TNF]-, interleukin [IL]-6, and IL1) that are linked to insulin resistance and the destruction of pancreatic beta cells via nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) (68-75). Therefore, dysbiosis observed in individuals with T2DM may negatively affect glycemic control, insulin production, and insulin activity (54-56).

Probiotic consumption has the potential to benefit various metabolic disorders associated with T2DM, including modifications to insulin exocytosis pathways, inflammation, and oxidative stress (51,76-78). Individuals with T2DM may benefit from probiotics, specifically the bacteria from the *Lactobacillus*, *Bifidobacterium*, and *Streptococcus* to restore a healthy microbial balance in the gut, thereby improving glucose metabolism and glycemic outcomes (51). In light of this, the primary purpose of this research is to assess the quality of randomized controlled trials (RCTs) that have investigated the effects of probiotic supplementation on glycemic outcomes in adults with T2DM, particularly fasting plasma glucose (FPG), fasting plasma insulin (FPI), A1c, and homeostatic model assessment of insulin resistance (HOMA-IR) (79).

Results of probiotics using for T2DM treatment

This review included a total of nine RCTs (44,46,76,80-85). Among these, four were placebo-controlled, double-blind experiments (80-83), and five were randomized, controlled,

parallel intervention trials with double blinding (44,46,76,84,85). The studies were conducted in various locations, including Iran, Brazil, Sweden, Malaysia, and Ukraine, with five of the investigations taking place in Iran (44,46,76,80-85). Four of the nine studies revealed that the average length of time between a patient's diagnosis of T2DM and subsequent treatment was roughly seven years (76,80,83,84). Five of the nine studies excluded patients who controlled their T2DM with insulin (44,76,80,81).

At the beginning of each of the nine trials, participants reported using oral hypoglycemic medicine and insulin, with no significant differences between the groups. The length of the intervention, probiotic dosage, the kind of medium used for probiotic administration, and the strain of bacterial probiotics varied across the studies (44,46,76,80-85). The intervention duration ranged from 6 to 12 weeks, and the colony-forming unit (CFU) dosages of the probiotics varied from seven million to over 100 billion per day (44,46,76,80-85). Products containing dairy were used as the vehicle for the administration of the probiotics (44,76,80,82,85) and capsules made from alternatives to dairy (81), powdered form (44,46,85), or supplements in liquid form (84). Bacterial species belonging to the genus *L* (*acidophilus*, *bulgaricus*, *casei*, and *rhamnosus*) were represented most frequently among the probiotic strains (44,46,76,80-85), *B* (*bifidum*, *breve*, *longum*, and *infantis*) (4,5,7-9,11,12,44,76, 80-82,85) and *S thermophiles* (76,80-82). Probiotics derived from dairy products were used in media for four different investigations, including goat's milk, kefir, and yogurt. In order to produce multi-strain probiotics, the dairy medium used by all four research teams was supplemented (76,80,82,83). Tonucci et al. utilized goat's milk with *S thermophilus* TA40, *L acidophilus* La5, and *B lactis* BB12 in it (76). Ostadrahimi et al. employed kefir with *S thermophilus*, *L casei*, *L acidophilus*, and *B lactis* (83). Yogurt that included *L bulgaricus*, *S thermophilus*, *B lactis* Bb12, and *L acidophilus* La5 was

utilized in the experiment that Ejtahed et al. conducted (80). Last but not least, Mohamadshahi et al. utilized a yogurt that contains *L bulgaricus*, *S thermophilus*, *B lactis* Bb12 (DSM 10140), and *L acidophilus* La5 (82). The remaining five studies all utilized non-dairy probiotic supplements that were capsuled, powdered, or delivered in liquid form (44,46,81,83,84). Asemi et al. gave the participants a capsule that included multiple strains of bacteria, including *L acidophilus*, *L casei*, *L rhamnosus*, *L bulgaricus*, *B breve*, *B longum*, and *S thermophiles* (81). A multi-strain sachet powder that contained *L acidophilus*, *L casei*, *L lactis*, *B bifidum*, *B longum*, and *B infantis* was given to the participants in the study by Firouzi et al. (44). Kobyliak et al. used a sachet powder that contained multiple strains of bacteria, including *Lactobacillus* strains, *Lactococcus* strains, *Bifidobacterium* strains, *Propionibacterium* strains, and *Acetobacter* strains (85). Mobini et al. inquired the effects of two distinct single-strain probiotic dosages of *L. reuteri* DSM 17938, both of which were delivered in the form of a stick-pack powder (46). Feizollahzadeh et al. offered *L Plantarum* A7 via soy milk (84). In eight of the nine investigations, the effects of FPG on blood sugar were assessed (44,76,80-85) and/or A1c (46,76,80-83). Five evaluated FPI (44,76,80,81,85), and four evaluated HOMA-IR (57,62,66,67). All four glycaemic outcomes were investigated in four of the nine trials (44,76,81,85). The probiotic interventions most frequently consisted of two or more of the bacterial strains *L acidophilus*, *S thermophilus*, *L bulgaricus*, and *B lactis* and were given for 6 to 12 weeks at doses ranging from seven million to over 100 billion CFU per day (44,46,76,80-85). Multi-strain, dairy-based probiotic interventions, particularly yogurt, and kefir, consistently led to statistically significant changes in glycemic parameters (76,79,85).

Conclusions

Based on this mini-review and quality assessment of nine RCTs, probiotic supplements show promise in improving glucose metabolism and have positive effects on glycaemic outcomes, in particular for the purpose of improving A1c in individuals with T2DM. This study seeks to do something new and exciting: emphasize the clinical relevance of a more targeted probiotic routine for the purpose of better glycemic results, including A1c, FPG, FPI, and HOMA-IR, among individuals with T2DM. Multi-strain probiotics containing *Lactobacillus acidophilus*, *Streptococcus thermophilus*, *Lactobacillus bulgaricus*, and *Bifidobacterium lactis* administered once daily for 6 to 12 weeks, at doses ranging from 7 million to 100 billion CFU, appear to have the most significant impact on these glycemic parameters. Minor gastrointestinal disturbances are the most commonly reported side effect, although each person is different and probiotic administration should be approached with caution in

immunocompromised patients. Based on the available evidence, it is suggested that individuals with T2DM, may benefit from incorporating probiotics as an adjunctive treatment option. However, this recommendation should be made on an individual basis, considering the specific needs and circumstances of each patient, and through collaborative discussion among all members of the healthcare team. Probiotic supplementation presents an appealing and emerging alternative for the management of T2DM, although further research is needed to fully understand its overall impact on glycemic control.

Acknowledgments

We especially thank Dr. Mohammad Afkhami-Ardekani (Diabetes Research Center, Shahid Sadougi University of Medical Sciences, Yazd, Iran) for providing technical support.

Conflict of Interest

No conflict of interest.

References

1. World Health Organization. World health statistics overview 2019: monitoring health for the SDGs, sustainable development goals. World Health Organization; 2019.
2. American Diabetes Association. Standards of medical care in diabetes—2009. *Diabetes care*. 2009;32(Suppl 1):S13.
3. Ahola AJ, Harjutsalo V, Forsblom C, Freese R, Mäkimmattila S, Groop PH. The self-reported use of probiotics is associated with better glycaemic control and lower odds of metabolic syndrome and its components in type 1 diabetes. *Journal of probiotics & health*. 2017.
4. Jalali-KhanAbadi B, Yaghmaei P, Salmani MH, Afkhami Ardakani M. The effect of zinc supplementation on glycosylated hemoglobin in type II diabetic patients. *Journal of Shahrekord University of Medical Sciences*. 2011;12(4):58-63.(in Persian)
5. Ezoddini Ardakani F, Afkhami Ardakani M, Mohammadi Z, Sheikhha MH. Evaluating calcified carotid artery atheromas in panoramic radiographs of patients with type 2 diabetes mellitus. *Oral Radiology*. 2007;23:6-9.
6. Bommer C, Heesemann E, Sagalova V, Manne-Goehler J, Atun R, Bärnighausen T, Vollmer S. The global economic burden of diabetes in adults aged 20–79 years: a cost-of-illness study. *The lancet Diabetes & endocrinology*. 2017 ;5(6):423-30.
7. Seuring T, Archangelidi O, Suhrcke M. The economic costs of type 2 diabetes: a global systematic review. *Pharmacoeconomics*. 2015;33:811-31.
8. Akha O, Makhloogh A, Khoddad T, Kharazm P. Evaluation of Microalbuminuria and its Related Risk Factors in Patients with Type II Diabetes Referred to Endocrinology Clinics in Sari, 2003-2009. *Journal of Mazandaran University of Medical Sciences*. 2013;23(107):12-8.
9. Xiang Y, Huang G, Shan Z, Pan L, Luo S, Yang L, et al. Glutamic acid decarboxylase autoantibodies are dominant but insufficient to identify most Chinese with adult-onset non-insulin requiring autoimmune diabetes: LADA China study 5. *Acta diabetologica*. 2015;52:1121-7.
10. Martinell M, Dorkhan M, Stålhammar J, Storm P, Groop L, Gustavsson C. Prevalence and risk factors for diabetic retinopathy at diagnosis (DRAD) in

- patients recently diagnosed with type 2 diabetes (T2D) or latent autoimmune diabetes in the adult (LADA). *Journal of diabetes and its complications*. 2016;30(8):1456-61.
11. DeFronzo RA. Pathogenesis of type 2 diabetes mellitus. *Medical clinics*. 2004;88(4):787-835.
 12. Horowitz M, Harding PE, Maddox AF, Wishart JM, Akkermans LM, Chatterton BE, et al. Gastric and oesophageal emptying in patients with type 2 (non-insulin-dependent) diabetes mellitus. *Diabetologia*. 1989;32:151-9.
 13. Chang J, Rayner CK, Jones KL, Horowitz M. Diabetic gastroparesis—backwards and forwards. *Journal of gastroenterology and hepatology*. 2011;26:46-57.
 14. Azpiroz F, Malagelada C. Diabetic neuropathy in the gut: pathogenesis and diagnosis. *Diabetologia*. 2016;59(3):404-8.
 15. Wu SL. Staging of type 2 diabetes mellitus. *Genetics and Molecular Research*. 2015 Mar 20;14(1):2118-21.
 16. Salgado MK, Oliveira LG, Costa GN, Bianchi F, Sivieri K. Relationship between gut microbiota, probiotics, and type 2 diabetes mellitus. *Applied microbiology and biotechnology*. 2019;103:9229-38.
 17. Qin J, Li Y, Cai Z, Li S, Zhu J, Zhang F, Liang S, Zhang W, Guan Y, Shen D, Peng Y. A metagenome-wide association study of gut microbiota in type 2 diabetes. *Nature*. 2012;490(7418):55-60.
 18. Kobyliak N, Virchenko O, Falalyeyeva T. Pathophysiological role of host microbiota in the development of obesity. *Nutrition journal*. 2015;15:1-2.
 19. Cho NH, Shaw JE, Karuranga S, Huang Y, da Rocha Fernandes JD, Ohlrogge AW, et al. IDF Diabetes Atlas: Global estimates of diabetes prevalence for 2017 and projections for 2045. *Diabetes research and clinical practice*. 2018;138:271-81.
 20. Lyssenko V, Jonsson A, Almgren P, Pulizzi N, Isomaa B, Tuomi T, et al. Clinical risk factors, DNA variants, and the development of type 2 diabetes. *New England Journal of Medicine*. 2008;359(21):2220-32.
 21. Dugas LR, Lie L, Plange-Rhule J, Bedu-Addo K, Bovet P, Lambert EV, et al. Gut microbiota, short chain fatty acids, and obesity across the epidemiologic transition: the METS-Microbiome study protocol. *BMC public health*. 2018 Dec;18:1-0.
 22. Bianchi F, Duque AL, Saad SM, Sivieri K. Gut microbiome approaches to treat obesity in humans. *Applied microbiology and biotechnology*. 2019;103:1081-94.
 23. Gerritsen J, Smidt H, Rijkers GT, de Vos WM. Intestinal microbiota in human health and disease: the impact of probiotics. *Genes & nutrition*. 2011;6:209-40.
 24. Swain MR, Anandharaj M, Ray RC, Rani RP. Fermented fruits and vegetables of Asia: a potential source of probiotics. *Biotechnology research international*. 2014;2014:250424.
 25. Chilton SN, Burton JP, Reid G. Inclusion of fermented foods in food guides around the world. *Nutrients*. 2015;7(1):390-404.
 26. Kothari D, Patel S, Kim SK. Probiotic supplements might not be universally-effective and safe: A review. *Biomedicine & Pharmacotherapy*. 2019;111:537-47.
 27. Vergin F. Antibiotics and probiotics. *Hippokrat*. 1954;25(4):116-9.
 28. Lilly DM, Stillwell RH. Probiotics: growth-promoting factors produced by microorganisms. *Science*. 1965;147(3659):747-8.
 29. Tsuda H, Miyamoto T. Production of exopolysaccharide by *Lactobacillus plantarum* and the prebiotic activity of the exopolysaccharide. *Food Science and Technology Research*. 2010;16(1):87-92.
 30. Hill C, Guarner F, Reid G, Gibson GR, Merenstein DJ, Pot B, et al. Expert consensus document: The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. *Nature reviews Gastroenterology & hepatology*. 2014;11(8):506-14.
 31. Markowiak P, Śliżewska K. Effects of probiotics, prebiotics, and synbiotics on human health. *Nutrients*. 2017;9(9):1021.
 32. Hotel AC, Cordoba A. Health and nutritional properties of probiotics in food including powder milk with live lactic acid bacteria. *Prevention*. 2001;5(1):1-0.
 33. Rijkers GT, Bengmark S, Enck P, Haller D, Herz U, Kalliomaki M, Kudo S, Lenoir-Wijnkoop I, Mercenier A, Myllyluoma E, Rabot S. Guidance for substantiating the evidence for beneficial effects of probiotics: current status and recommendations for future research. *The Journal of nutrition*. 2010;140(3):671S-6S.
 34. de Almada CN, Nunes de Almada C, Martinez RC, Sant'Ana AD. Characterization of the intestinal microbiota and its interaction with probiotics and health impacts. *Applied Microbiology and Biotechnology*. 2015;99:4175-99.
 35. Pérez-Sánchez T, Ruiz-Zarzuela I, de Blas I, Balcázar JL. Probiotics in aquaculture: a current assessment. *Reviews in Aquaculture*. 2014;6(3):133-46.
 36. Beck BR, Kim D, Jeon J, Lee SM, Kim HK, Kim OJ, et al. The effects of combined dietary probiotics *Lactococcus lactis* BFE920 and *Lactobacillus plantarum* FGL0001 on innate immunity and disease resistance in olive flounder (*Paralichthys*

- olivaceus). *Fish & shellfish immunology*. 2015;42(1):177-83.
37. Xia Y, Wang M, Gao F, Lu M, Chen G. Effects of dietary probiotic supplementation on the growth, gut health and disease resistance of juvenile Nile tilapia (*Oreochromis niloticus*). *Animal Nutrition*. 2020;6(1):69-79.
 38. Liu W, Wang W, Ran C, He S, Yang Y, Zhou Z. Effects of dietary scFOS and lactobacilli on survival, growth, and disease resistance of hybrid tilapia. *Aquaculture*. 2017;470:50-5.
 39. Chai PC, Song XL, Chen GF, Xu H, Huang J. Dietary supplementation of probiotic *Bacillus* PC465 isolated from the gut of *Fenneropenaeus chinensis* improves the health status and resistance of *Litopenaeus vannamei* against white spot syndrome virus. *Fish & shellfish immunology*. 2016;54:602-11.
 40. Sun YZ, Yang HL, Ma RL, Song K, Lin WY. Molecular analysis of autochthonous microbiota along the digestive tract of juvenile grouper *Epinephelus coioides* following probiotic *Bacillus pumilus* administration. *Journal of applied microbiology*. 2011;110(4):1093-103.
 41. Kechagia M, Basoulis D, Konstantopoulou S, Dimitriadi D, Gyftopoulou K, Skarmoutsou N, et al. Health benefits of probiotics: a review. *International Scholarly Research Notices*. 2013;2013.
 42. Kobylak N, Conte C, Cammarota G, Haley AP, Styriak I, Gaspar L, et al. Probiotics in prevention and treatment of obesity: a critical view. *Nutrition & metabolism*. 2016;13(1):1-3.
 43. Toupin April K, Moher D, Stinson J, Byrne A, White M, Boon H, et al. Measurement properties of questionnaires assessing complementary and alternative medicine use in pediatrics: a systematic review. *PLoS One*. 2012;7(6):e39611.
 44. Firouzi S, Majid HA, Ismail A, Kamaruddin NA, Barakatun-Nisak MY. Effect of multi-strain probiotics (multi-strain microbial cell preparation) on glycemic control and other diabetes-related outcomes in people with type 2 diabetes: a randomized controlled trial. *European journal of nutrition*. 2017;56:1535-50.
 45. Khalili L, Alipour B, Jafar-Abadi MA, Faraji I, Hassanalilou T, Abbasi MM, et al. The effects of lactobacillus casei on glycemic response, serum sirtuin1 and fetuin-a levels in patients with type 2 diabetes mellitus: a randomized controlled trial. *Iranian biomedical journal*. 2019;23(1):68-77.
 46. Mobini R, Tremaroli V, Ståhlman M, Karlsson F, Levin M, Ljungberg M, et al. Metabolic effects of *Lactobacillus reuteri* DSM 17938 in people with type 2 diabetes: A randomized controlled trial. *Diabetes, Obesity and Metabolism*. 2017;19(4):579-89.
 47. Razmpoosh E, Javadi A, Ejtahed HS, Mirmiran P, Javadi M, Yousefinejad A. The effect of probiotic supplementation on glycemic control and lipid profile in patients with type 2 diabetes: A randomized placebo controlled trial. *Diabetes & Metabolic Syndrome: Clinical Research & Reviews*. 2019;13(1):175-82.
 48. Tao YW, Gu YL, Mao XQ, Zhang L, Pei YF. Effects of probiotics on type II diabetes mellitus: a meta-analysis. *Journal of translational medicine*. 2020;18(1):1-1.
 49. Hoerr RA, Bostwick EF. Bioactive proteins and probiotic bacteria: modulators of nutritional health. *Nutrition (Burbank, Los Angeles County, Calif.)*. 2000;16(7-8):711-3.
 50. Karlsson FH, Tremaroli V, Nookaew I, Bergström G, Behre CJ, Fagerberg B, et al. Gut metagenome in European women with normal, impaired and diabetic glucose control. *Nature*. 2013;498(7452):99-103.
 51. Brown K, DeCoffe D, Molcan E, Gibson DL. Diet-induced dysbiosis of the intestinal microbiota and the effects on immunity and disease. *Nutrients*. 2012;4(8):1095-119.
 52. Kasińska MA, Drzewoski J. Effectiveness of probiotics in type 2 diabetes: a meta-analysis. *Pol Arch Med Wewn*. 2015;125(11):803-13.
 53. Rios-Covian D, Gueimonde M, Duncan SH, Flint HJ, de Los Reyes-Gavilan CG. Enhanced butyrate formation by cross-feeding between *Faecalibacterium prausnitzii* and *Bifidobacterium adolescentis*. *FEMS microbiology letters*. 2015;362(21):fnv176.
 54. Reichardt N, Duncan SH, Young P, Belenguer A, McWilliam Leitch C, et al. Phylogenetic distribution of three pathways for propionate production within the human gut microbiota. *The ISME journal*. 2014;8(6):1323-35.
 55. Tremaroli V, Bäckhed F. Functional interactions between the gut microbiota and host metabolism. *Nature*. 2012;489(7415):242-9.
 56. Tolhurst G, Heffron H, Lam YS, Parker HE, Habib AM, Diakogiannaki E, et al. Short-chain fatty acids stimulate glucagon-like peptide-1 secretion via the G-protein-coupled receptor FFAR2. *Diabetes*. 2012;61(2):364-71.
 57. Wellen KE, Hotamisligil GS. Inflammation, stress, and diabetes. *The Journal of clinical investigation*. 2005;115(5):1111-9.
 58. De Vadder F, Kovatcheva-Datchary P, Goncalves D, Vinera J, Zitoun C, Duchamp A, et al. Microbiota-generated metabolites promote metabolic benefits via gut-brain neural circuits. *Cell*. 2014;156(1-2):84-96.
 59. Medina-Vera I, Sanchez-Tapia M, Noriega-López L, Granados-Portillo O, Guevara-Cruz M, Flores-López A, Avila-Nava A, Fernández ML, Tovar AR, Torres N. A dietary intervention with functional

- foods reduces metabolic endotoxaemia and attenuates biochemical abnormalities by modifying faecal microbiota in people with type 2 diabetes. *Diabetes & metabolism*. 2019;45(2):122-31.
60. Vancamelbeke M, Vermeire S. The intestinal barrier: a fundamental role in health and disease. *Expert review of gastroenterology & hepatology*. 2017;11(9):821-34.
 61. von Scholten BJ, Andresen EN, Sørensen TI, Jess T. Aetiological factors behind adipose tissue inflammation: an unexplored research area. *Public health nutrition*. 2013;16(1):27-35.
 62. Wiesner P, Choi SH, Almazan F, Benner C, Huang W, Diehl CJ, et al. Low doses of LPS and minimally oxidized LDL cooperatively activate macrophages via NF-kappaB and AP-1: Possible mechanism for acceleration of atherosclerosis by subclinical endotoxemia. *Circulation research*. 2010;107(1):56.
 63. Creely SJ, McTernan PG, Kusminski CM, Fisher FM, Da Silva NF, Khanolkar M, et al. Lipopolysaccharide activates an innate immune system response in human adipose tissue in obesity and type 2 diabetes. *American Journal of Physiology-Endocrinology and Metabolism*. 2007;292(3):E740-7.
 64. Trøseid M, Nestvold TK, Rudi K, Thoresen H, Nielsen EW, Lappégard KT. Plasma lipopolysaccharide is closely associated with glycemic control and abdominal obesity: evidence from bariatric surgery. *Diabetes care*. 2013;36(11):3627-32.
 65. Kim YA, Keogh JB, Clifton PM. Probiotics, prebiotics, synbiotics and insulin sensitivity. *Nutrition research reviews*. 2018;31(1):35-51.
 66. Yadav H, Jain S, Sinha PR. Oral administration of dahi containing probiotic *Lactobacillus acidophilus* and *Lactobacillus casei* delayed the progression of streptozotocin-induced diabetes in rats. *Journal of Dairy Research*. 2008;75(2):189-95.
 67. Yadav H, Jain S, Sinha PR. Antidiabetic effect of probiotic dahi containing *Lactobacillus acidophilus* and *Lactobacillus casei* in high fructose fed rats. *Nutrition*. 2007;23(1):62-8.
 68. Ruan Y, Sun J, He J, Chen F, Chen R, Chen H. Effect of probiotics on glycemic control: a systematic review and meta-analysis of randomized, controlled trials. *PLoS one*. 2015;10(7):e0132121.
 69. Prawitt J, Caron S, Staels B. Bile acid metabolism and the pathogenesis of type 2 diabetes. *Current diabetes reports*. 2011;11:160-6.
 70. Thomas C, Gioiello A, Noriega L, Strehle A, Oury J, Rizzo G, et al. TGR5-mediated bile acid sensing controls glucose homeostasis. *Cell metabolism*. 2009;10(3):167-77.
 71. Shyangdan DS, Royle P, Clar C, Sharma P, Waugh N, Snaith A. Glucagon-like peptide analogues for type 2 diabetes mellitus. *Cochrane Database of Systematic Reviews*. 2011(10).
 72. Bastard JP, Maachi M, Lagathu C, Kim MJ, Caron M, Vidal H, et al. Recent advances in the relationship between obesity, inflammation, and insulin resistance. *European cytokine network*. 2006;17(1):4-12.
 73. Borst SE. The role of TNF- α in insulin resistance. *Endocrine*. 2004;23:177-82.
 74. Lin X, Zhang Z, Chen JM, Xu YY, Ye HR, Cui J, et al. Role of APN and TNF- α in type 2 diabetes mellitus complicated by nonalcoholic fatty liver disease. *Genet. Mol. Res*. 2015;14:2940-6.
 75. Muoio DM, Newgard CB. Molecular and metabolic mechanisms of insulin resistance and β -cell failure in type 2 diabetes. *Nature reviews Molecular cell biology*. 2008;9(3):193-205.
 76. Tonucci LB, Dos Santos KM, de Oliveira LL, Ribeiro SM, Martino HS. Clinical application of probiotics in type 2 diabetes mellitus: A randomized, double-blind, placebo-controlled study. *Clinical nutrition*. 2017;36(1):85-92.
 77. Wang S, Zhu H, Lu C, Kang Z, Luo Y, Feng L, et al. Fermented milk supplemented with probiotics and prebiotics can effectively alter the intestinal microbiota and immunity of host animals. *Journal of Dairy Science*. 2012;95(9):4813-22.
 78. Hsieh FC, Lee CL, Chai CY, Chen WT, Lu YC, Wu CS. Oral administration of *Lactobacillus reuteri* GMNL-263 improves insulin resistance and ameliorates hepatic steatosis in high fructose-fed rats. *Nutrition & metabolism*. 2013;10:1-4.
 79. Tiderencel KA, Hutcheon DA, Ziegler J. Probiotics for the treatment of type 2 diabetes: A review of randomized controlled trials. *Diabetes/metabolism research and reviews*. 2020;36(1):e3213.
 80. Ejtahed HS, Mohtadi-Nia J, Homayouni-Rad A, Niafar M, Asghari-Jafarabadi M, Mofid V. Probiotic yogurt improves antioxidant status in type 2 diabetic patients. *Nutrition*. 2012;28(5):539-43.
 81. Asemi Z, Zare Z, Shakeri H, Sabihi SS, Esmailzadeh A. Effect of multispecies probiotic supplements on metabolic profiles, hs-CRP, and oxidative stress in patients with type 2 diabetes. *Annals of nutrition and metabolism*. 2013;63(1-2):1-9.
 82. Mohamadshahi M, Veissi M, Haidari F, Shahbazian H, Kaydani GA, Mohammadi F. Effects of probiotic yogurt consumption on inflammatory biomarkers in patients with type 2 diabetes. *BioImpacts: BI*. 2014;4(2):83.
 83. Ostadrahimi A, Taghizadeh A, Mobasseri M, Farrin N, Payahoo L, Gheshlaghi ZB, et al. Effect of probiotic fermented milk (kefir) on glycemic control and lipid profile in type 2 diabetic patients: a randomized double-blind placebo-controlled clinical trial. *Iranian journal of public health*. 2015;44(2):228.

84. Feizollahzadeh S, Ghiasvand R, Rezaei A, Khanahmad H, Sadeghi A, Hariri M. Effect of probiotic soy milk on serum levels of adiponectin, inflammatory mediators, lipid profile, and fasting blood glucose among patients with type II diabetes mellitus. *Probiotics and antimicrobial proteins*. 2017;9:41-7.
85. Kobyliak N, Falalyeyeva T, Mykhalchyshyn G, Kyriienko D, Komissarenko I. Effect of alive probiotic on insulin resistance in type 2 diabetes patients: randomized clinical trial. *Diabetes & Metabolic Syndrome: Clinical Research & Reviews*. 2018;12(5):617-24.