Send Orders for Reprints to reprints@benthamscience.ae

Current Diabetes Reviews, **2019**, *15, Page Enation* **1**

PERSPECTIVE

Prospect for type 2 diabetes mellitus in the combination of exercise and synbiotic: a perspective

Luthfia Dewi[*a], Ali Rosidi[a], Etika Ratna Noer[b] and Annisa Ayuningtyas[a]

[a] *Nutrition Department, Faculty of Nursing and Health Science, Universitas Muhammadiyah 50273 Semarang, Indonesia;* [b] *Nutrition Department, Faculty of Medicine, Diponegoro University, Semarang, Indonesia*

ARTICLE HISTORY

Received:
Revised:
Accepted:

DOI:

Abstract: Change in gut microbiome diversity (the so-called dysbiosis) is correlated with insulin resistance conditions. Exercise is typically one of the first management for people with type 2 diabetes mellitus (T2DM), which is generally well-known for improved glucose regulation. The new design of prebiotic and probiotic, like synbiotic form, to target specific diseases is needed for additional studies. While the effectiveness of exercise and the combination of exercise and synbiotic prescription seems promising, this review discusses the possibility of these agents to increase the diversity of gut microbiota and therefore could enhance short-chain fatty acid (SCFA). In particular, the interaction of synbiotic towards gut microbiota, the mechanism of exercise in improving gut microbiota, and the prospect of the synergistic effect of the combination of synbiotic and exercise to improve insulin sensitivity is addressed.

Keywords: exercise, gut microbiota, insulin sensitivity, short-chain fatty acid, synbiotic, T2DM

1. INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a serious disease in Indonesia, as its prevalence based on doctor's diagnosis of the population age, ≥ 15 years has increased to 2% in 2018 [1]. Indonesia is also one of the top 10 countries with a high number of diagnosed and undiagnosed diabetes patients at present and is estimated as much as 16.6 million people will suffer diabetes in 2045 [2]. Since the prevalence of diabetes, some studies concerning diabetes management are carried out, including lifestyle modification, medicinal plant identification, and air pollution analysis, and their possible relations to biological changes in diabetes [3-5].

Gut microbiota and gut microbiome are two interchangeable things. Gut microbiota is defined as all organisms living in the gastrointestinal tract primarily in the large intestine which dominantly comprises *Bacteriodetes* and *Firmicutes* (90%) [6-8]. While gut microbiome is a collective genome of all microorganisms inhabiting the gut [9]. Human gut microbiota comprises 100 times more genes in the entire human body and it acts as essential amino acids and essential fatty acids for the human body [10]. Human gut microbiota has a flexible characteristic, which means that it can adapt to changing diet by shifting community membership and gene content [11].

A more diverse gut microbiome is considered as the healthier individuals because of the lowered the pathogenic bacterial species and its role to produce vitamin, essential nutrients with the degradation of complex polysaccharide, maintenance of gut motility and immune function [12, 13]. Several gut microbiomes contribute to the fermentation of undigested food components including fiber which, in turn, changes in gut microbiome diversity correlated with insulin resistance conditions [14]. Diabetic condition in mice and humans has been reported to have lipopolysaccharides (LPS), a bacterial endotoxin produced by gram-negative bacteria, increment [15]. It is suggested that Toll-like receptors (TLRs), as a receptor for innate immunity, govern gut microbiota composition which might correlate with T2DM.

Exercise is typically one of the first management for people with T2DM, which is generally well-known for improved glucose regulation. Exercise also has been proposed to have a role as immunomodulatory for downregulating TLR4 expression, thus eventually ameliorating gut microbiota diversity. Some modalities of exercise are recommended for individuals with T2DM such as aerobic, resistance, anaerobic-resistance training, and high-intensity interval training which all of them exert a beneficial effect for the diabetic condition even the dose of optimal exercise needs further investigation [16]. During exercise, some physiological changes occur, and

1573-3998 /19 $58.00+.00

it has differences in changes in abrupt exercise and habitual exercise [17,18]. Abrupt exercise exerts multiple metabolites production and inflammatory mediators [17]. On the other hand, habitual exercise gives a beneficial effect on inducing PGC-1α which has been reported as the most dominant regulator of mitochondrial function leading to diverse gut microbiota through biogenesis of mitochondria [18]. Exercise has previously been described as a modulator for gut-microbiota [19].

Prescription of prebiotic and probiotic do not seem effective to improve chronic inflammation-related diseases including diabetes. Nevertheless, a recent study reveals that probiotic treatment diversifies gut composition and improves the *Bacteriodetes/Firmicutes* ratio [20]. Furthermore, prebiotic intervention may alter gut microbiota and intestinal permeability [21]. Thus, the new design of prebiotic and probiotic, like synbiotic form, to target specific diseases is needed for additional studies. While the effectiveness of exercise and the combination of exercise and synbiotic prescription seems promising, this review discusses the possibility of the combination of probiotic, prebiotic, exercise to increase the diversity of gut microbiota. In particular, the interaction of synbiotic towards gut microbiota, the mechanism of exercise in improving gut microbiota, and the prospect of the synergistic effect of the combination of synbiotic and exercise to improve insulin sensitivity is addressed.

2. THE ROLE OF GUT MICROBIOTA AND TYPE 2 DIABETES MELLITUS

T2DM is associated with defective islet autophagy regulation and it can result from hepatic insulin resistance [22]. Autophagy is defined as a degradation of mitochondria and other cellular organelles to maintain homeostasis normal architecture and function of the islet [23, 24]. Autophagy takes the role to regulate LPS levels and to protect cells from lipopolysaccharides (LPS) exposure [22]. It has been reported that autophagy disruption occurred in hyperglycemia through inhibition of transcription factor EB (TFEB) nuclear translocation resulting in autophagy down-regulation [25]. T2DM which is featured by defective insulin to uptake glucose into the cell is a condition mediated by LPS leading to increase low-grade inflammation through toll-like receptor 4 signaling activation [9, 22]. Insulin resistance-associated gut microbiota diversity is might be influenced by the alteration of gut microbiota, thus the production of serum metabolome characterized by increasing of LPS and BCAA biosynthesis, and reduction of BCAA transport into bacterial cells, methanogenesis, and pyruvate oxidation [26, 27].

3. EXERCISE-GUT MICROBIOTA INTERACTION

Exercise terminology is regularly interchangeable with physical activity. Defined as structured all movement that rise energy used, exercise has functionally speaking improved blood glucose control in T2DM [28, 29]. The impact of exercise on diabetic improvement links to increase of glucose transporter (GLUT)-4 content and amplification of insulin signaling in muscle and enhancing of GLUT-4 expression in adipose tissue and skeletal muscle in diabetic condition [16, 30]. It has been speculated that exercise can alleviate insulin resistance through gut microbiota composition diversity, *Firmicutes* phylum enhancement, and short-chain fatty acid (SCFA) enhancement [7]. SCFA is a product of gut microbial fermentation of the dietary fiber which primarily comprises acetate, propionate, and butyrate [31-33]. According to the previous review which accumulated 10 studies in human and animal laboratories, exercise *per se* modifies the composition of gut microbiota [8]. A previous study has concluded that individuals who frequently conduct exercise showing the diversity of gut microbiota higher than control subjects with low BMI followed by control subjects with high body mass index (BMI) [19].

It seems exercise and gut microbiota having a bidirectional interaction through mitochondrial genome regulation including (i) ROS and RONS production, (ii) immune and enterochromaffin secretory induction, (iii) functional gut modulation, and (iv) mitochondrial genetic variants and heteroplasmy [19]. Incidental exercise induces some metabolites and inflammatory mediators reversing to the habitual exercise which suppresses basal pro-inflammatory cytokines [17]. This might be linked to the product of disruption of microbiota composition named LPS which escalates the apoptosis of β-cell and cause the molecular onset of insulin resistance and hyperglycemia through nuclear factor kappa B (NFκB) [34]. Exercise has a role to suppress LPS (a ligand for TLR4) levels hence TLRs signaling pathway in the liver, muscle, and adipose tissue inhibited [35, 36] TLRs are transmembrane receptors family that roles as a central of innate immunity in which their activation (particularly TLR4) has been postulated influencing insulin resistance and T2DM development [35, 36]. Exercise has been reported to enhance intestinal and plasma acetic acid promoting autophagic mechanism in skeletal muscle via binding to the G-protein-coupled receptor 43 (GPR43) which eventually enhancing insulin sensitivity [38].

Unfortunately, the effect of exercise on gut microbiota in T2DM needs more studies. The studies which quite relevant are conducted by Velikonja *et al*., and Denou *et al.* (13, 39). A metabolic syndrome which defines as the existence of at least two inclusion criteria of metabolic syndrome (abdominal obesity, obesity, hyperglycemia, and hypertension) exerts low richness of gut microbiota composition and low of SCFA composition [13]. Other studies revealed that exercise was successfully increased the gut microbiota of the mouse distal gut [19, 39-46]. The studies examining the effect of exercise on microbiota abundance are quite extensive as can be seen in table 1. There are some factors influencing gut microbiota composition, including diet, stress, altitude, temperature, pollutants, noise, disease state, medications, host genetic, and exercise [12, 32]. The duration of exercise seems to need further study since a study by Taniguchi *et al*. concluded that a short-period endurance exercise had little effect on gut microbiota diversity and

composition in the elderly [47]. It is well-established that gut microbiota disruption either in the diversity or composition appears in such conditions as obesity and T2DM [48]. Since the previous study revealed that the improvement of gut microbiota depended on BMI status [49], exercise effect on the gut microbiota of individuals with T2DM still needs more study. This is supported by Lambert *et al*. concluded that the interaction between exercise and gut microbiota composition in T2DM required further investigation [50].

4. INTERACTION OF SYNBIOTIC TOWARDS GUT MICROBIOME

Synbiotics is known as the synergistic interaction between pro-and prebiotics which has been noticed since 1995 which was introduced by Gibson [51]. Probiotic *per se* has been well known to reserve the population of gut microbiota and the ingestion of specific fibers is successfully restored the homeostasis of the gut microbiome [27]. Synbiotic administration is aimed to activate the metabolism of microbiota thus can be positively beneficial for the host's health [51, 52]. Numerous studies have been conducted to reveal the beneficial effect of synbiotic in a diabetic condition which is summarized in Table 2. *Lactobacillus acidophilus* DSM20079 has 14.5 times higher of its existence when it was induced by inulin or pectin compared to glucose [53]. Therefore, either probiotics or prebiotics has the main role in maintaining gut microbiota survival.

As can be seen in table 2, synbiotic exerted the beneficial effect and lack of data showed synbiotic without any effect. The duration we found in the nine randomized clinical trials is at least 6 weeks, but the minimum doses still need further investigation. We found some meta-analysis that revealed synbiotic can modulate the immune system through SCFA production and therefore improves glucose homeostasis [54-59]. Nevertheless, a high dose of synbiotic consumption, due to SCFA production and greater fermentation may affect the discomfort feeling such as bloating and flatulence which varies individually [54, 60].

5. BRIGHT PROSPECT OF A COMBINATION OF SYNBIOTIC AND EXERCISE TO IMPROVE INSULIN SENSITIVITY

This is our speculation on the synergistic interaction between synbiotic consumption and exercise conduction since both of them induce SCFA production (shown in Figure 1.). SCFA correlates with glucagon-like peptide-1 (GLP-1) to alleviate pancreatic dysfunction in T2DM by activating G-protein coupled cell surface receptors [61]. GLP-1 is an incretin hormone produced by L-cells in the intestinal mucosa, a-cells in the pancreatic islet, and neurons in the nucleus of the solitary tract [61]. GLP-1 receptors such as FFAR2, FFAR3, and GPR120 are well explained for glucose homeostasis [62, 63]. Butyrate requires FFAR2 and FFAR3 to induce GLP-1 and subsequently stimulating insulin secretion through the downstream pathway leading to phospholipase C (PLC) mediated hydrolysis of phosphatidylinositol 4,5 bisphosphate (PIP2) to diacylglycerol (DAG) and inositol triphosphate (IP3) activating protein kinase C (PKC) leading to Caþ2 release from the endoplasmic reticulum. Furthermore, FFAR2 and FFAR3 are also can link to G/i/o subunits and inhibit adenylate cyclase, which decreases the concentration of cAMP, inhibiting protein kinase A (PKA) and exchange protein directly activated by cAMP (EPAC) mediated insulin release [62, 64]. Propionate, besides, stimulates glucose uptake via increasing GPR41 induction (SCFA receptor) [64]. It might become a great prescription but the side effect of discomfort GI need to be considered. Furthermore, the dose of synbiotic, the modalities of exercise, and the duration of the combination of synbiotic intake and exercise are the new topic and bright perspectives for future diabetic patients.

In other aspects, the human microbiome is essential to our health and well-being, as they are the essential sources of metabolites for our body [10, 11]. Yet, the overgrown of any strain of the microbiota (dysbiosis) as a source of overnutrition, is one of the contributing factors of morbid obesity and metabolic syndromes like T2DM [27]. So restrictive eating should be performed when there is a diverse spectrum of the microbiome to revert T2DM [65-67]. This is because, serum fasting is a strong inducer for autophagy, which plays a pivotal role in cellular homeostasis, cell repairing, and cytotoxic proteins and damaged organelles removal [22-25, 68].

*Address correspondence to this author at the Department of Nutrition, Faculty of Nursing and Health Science, Universitas Muhammadiyah Semarang, Semarang, Indonesia, Tel/Fax: +62823-2535-8329 E-mails: luthfia@unimus.ac.id

CONCLUSION

Available data present the beneficial effect of exercise and synbiotic consumption *per se* for diabetic patients. The combination of exercise and synbiotic consumption might have a greater positive effect compared to a single treatment. Furthermore, the side effects of the combination treatment need further effort.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declared no potential conflicts of interest concerning the research, authorship, and/or publication of this article.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] (Indonesia) MoH. Main Outcome of Basic Health Research 2018. 2018. Available from: **https://www.kemkes.go.id/resources/download/info-terkini/hasil-riskesdas-2018.pdf** [cited: 25th August 2020]
[2] International Diabetes F. IDF Diabetes Atlas Ninth edition 2019. 2019.
[3] Dewi L, Sulchan M, Kisdjamiatun. Potency of Cape Gooseberry (Physalis Peruviana) Juice in Improving Antioxidant and Adiponectin Level of High Fat Diet Streptozotocin Rat Model. Romanian Journal of Diabetes, Nutrition and Metabolic Diseases 2018;25(3):253-60.
[4] Mendes R, Sousa N, Almeida A, Subtil P, Guedes-Marques F, Reis VM, et al. Exercise prescription for patients with type 2 diabetes - A synthesis of international recommendations: Narrative review. British Journal of Sports Medicine 2016;50(22):1379-81.
[5] Thiering E, Heinrich J. Epidemiology of air pollution and diabetes. Trends in Endocrinology and Metabolism 2015;26(7):384-94.
[6] Santos-Marcos JA, Perez-Jimenez F, Camargo A. The role of diet and intestinal microbiota in the development of metabolic syndrome. Journal of Nutritional Biochemistry 2019;70:1-27.
[7] Dalton A, Mermier C, Zuhl M. Exercise influence on the microbiome–gut–brain axis. Gut Microbes 2019;10(5):555-68.
[8] Mach N, Fuster-Botella D. Endurance exercise and gut microbiota: A review. Journal of Sport and Health Science 2017;6(2):179-97.
[9] Hills RD, Pontefract BA, Mishcon HR, Black CA, Sutton SC, Theberge CR. Gut microbiome: Profound implications for diet and disease. Nutrients 2019;11(7):1-40.
[10] Yu B, Yu B, Yu L. Commentary: Reconciling Hygiene and Cleanliness: A New Perspective from Human Microbiome. Indian J Microbiol 2020;60(2):259-61.
[11] McFall-Ngai M, Hadfield MG, Bosch TC, Carey HV, Domazet-Loso T, Douglas AE, et al. Animals in a bacterial world, a new imperative for the life sciences. Proc Natl Acad Sci U S A 2013;110(9):3229-36.
[12] Gubert C, Kong G, Renoir T, Hannan AJ. Exercise, diet and stress as modulators of gut microbiota: Implications for neurodegenerative diseases. Neurobiology of Disease 2020;134:104621-.
[13] Velikonja A, Lipoglavšek L, Zorec M, Orel R, Avguštin G. Alterations in gut microbiota composition and metabolic parameters after dietary intervention with barley beta glucans in patients with high risk for metabolic syndrome development. Anaerobe 2019;55:67-77.
[14] Conlon MA, Bird AR. The impact of diet and lifestyle on gut microbiota and human health. Nutrients 2015;7(1):17-44.
[15] Aydin Ö, Nieuwdorp M, Gerdes V. The Gut Microbiome as a Target for the Treatment of Type 2 Diabetes. Current Diabetes Reports. 2018;18(8).
[16] Dewi L. Modalities of Exercise Intervention for Type 2 Diabetes Mellitus: Narrative Review 2019.
[17] O'Sullivan O, Cronin O, Clarke SF, Murphy EF, Molloy MG, Shanahan F, et al. Exercise and the microbiota. Gut Microbes 2015;6(2):131-6.
[18] Clark A, Mach N. The crosstalk between the gut microbiota and mitochondria during exercise. Frontiers in Physiology 2017;8.
[19] Clarke SF, Murphy EF, O'Sullivan O, Lucey AJ, Humphreys M, Hogan A, et al. Exercise and associated dietary extremes impact on gut microbial diversity. Gut 2014;63(12):1913-20.
[20] Qu L, Ren J, Huang L, Pang B, Liu X, Liu X, et al. Antidiabetic Effects of Lactobacillus casei Fermented Yogurt through Reshaping Gut Microbiota Structure in Type 2 Diabetic Rats. Journal of Agricultural and Food Chemistry 2018;66(48):12696-705.
[21] Ho J, Reimer RA, Doulla M, Huang C. Effect of prebiotic intake on gut microbiota, intestinal permeability and glycemic control in children with type 1 diabetes: Study protocol for a randomized controlled trial. Trials 2016;17(1):1-8.
[22] van Niekerk G, du Toit A, Loos B, Engelbrecht AM. Nutrient excess and autophagic deficiency: explaining metabolic diseases in obesity. Metabolism 2018;82:14-21.
[23] Ebato C, Uchida T, Arakawa M, Komatsu M, Ueno T, Komiya K, et al. Autophagy is important in islet homeostasis and compensatory increase of beta cell mass in response to high-fat diet. Cell Metab 2008;8(4):325-32.
[24] Glick D, Barth S, Macleod KF. Autophagy: cellular and molecular mechanisms. J Pathol 2010;221(1):3-12.
[25] Ji J, Petropavlovskaia M, Khatchadourian A, Patapas J, Makhlin J, Rosenberg L, et al. Type 2 diabetes is associated with suppression of autophagy and lipid accumulation in beta-cells. J Cell Mol Med 2019;23(4):2890-900.
[26] Pedersen HK, Gudmundsdottir V, Nielsen HB, Hyotylainen T, Nielsen T, Jensen BA, et al. Human gut microbes impact host serum metabolome and insulin sensitivity. Nature 2016;535(7612):376-81.

[27] Wang B, Yao M, Lv L, Ling Z, Li L. The Human Microbiota in Health and Disease. Engineering 2017;3(1):71-82.

[28] Colberg SR, Sigal RJ, Yardley JE, Riddell MC, Dunstan DW, Dempsey PC, et al. Physical activity/exercise and diabetes: A position statement of the American Diabetes Association. Diabetes Care 2016;39(11):2065-79.

[29] Colberg SR, Sigal RJ, Fernhall B, Regensteiner JG, Blissmer BJ, Rubin RR, et al. Exercise and type 2 diabetes: The American College of Sports Medicine and the American Diabetes Association: Joint position statement. Diabetes Care 2010;33(12).

[30] Schwingshackl L, Missbach B, Dias S, König J, Hoffmann G. Impact of different training modalities on glycaemic control and blood lipids in patients with type 2 diabetes: A systematic review and network meta-analysis. Diabetologia 2014;57(9):1789-97.

[31] Zadeh-Tahmasebi M, Duca FA, Rasmussen BA, Bauer PV, Côté CD, Filippi BM, et al. Activation of short and long chain fatty acid sensing machinery in the ileum lowers glucose production in vivo. Journal of Biological Chemistry 2016;291(16):8816-24.

[32] Baothman OA, Zamzami MA, Taher I, Abubaker J, Abu-Farha M. The role of Gut Microbiota in the development of obesity and Diabetes. Lipids in Health and Disease 2016;15(1):1548-62.

[33] Mailing LJ, Allen JM, Buford TW, Fields CJ, Woods JA. Exercise and the Gut Microbiome: A Review of the Evidence, Potential Mechanisms, and Implications for Human Health. American College of Sports Medicine 2019;47.

[34] Li C, Li X, Han H, Cui H, Peng M, Wang G, et al. Effect of probiotics on metabolic profiles in type 2 diabetes mellitus. Medicine (United States) 2016;95(26).

[35] Codella R, Luzi L, Terruzzi I. Exercise has the guts: How physical activity may positively modulate gut microbiota in chronic and immune-based diseases. Digestive and Liver Disease 2018;50(4):331-41.

[36] Lancaster GI, Febbraio MA. The immunomodulating role of exercise in metabolic disease. Trends in Immunology 2014;35(6):262-9.

[37] DeFronzo RA. Insulin resistance, lipotoxicity, type 2 diabetes and atherosclerosis: the missing links. The Claude Bernard Lecture 2009. Diabetologia 2010;53(7):1270-87.

[38] Yang L, Lin H, Lin W, Xu X. Exercise Ameliorates Insulin Resistance of Type 2 Diabetes through Motivating Short-Chain Fatty Acid-Mediated Skeletal Muscle Cell Autophagy. Biology (Basel) 2020;9(8).

[39] Denou E, Marcinko K, Surette MG, Steinberg GR, Schertzer JD. High-intensity exercise training increases the diversity and metabolic capacity of the mouse distal gut microbiota during diet-induced obesity. American Journal of Physiology - Endocrinology and Metabolism 2016;310(11):E982-E93.

[40] Carbajo-Pescador S, Porras D, Garcia-Mediavilla MV, Martinez-Florez S, Juarez-Fernandez M, Cuevas MJ, et al. Beneficial effects of exercise on gut microbiota functionality and barrier integrity, and gut-liver crosstalk in an in vivo model of early obesity and non-alcoholic fatty liver disease. DMM Disease Models and Mechanisms 2019;12(5).

[41] Allen JM, Mailing LJ, Cohrs J, Salmonson C, Fryer JD, Nehra V, et al. Exercise training-induced modification of the gut microbiota persists after microbiota colonization and attenuates the response to chemically-induced colitis in gnotobiotic mice. Gut Microbes 2018;9(2):115-30.

[42] Allen JM, Berg Miller ME, Pence BD, Whitlock K, Nehra V, Gaskins HR, et al. Voluntary and forced exercise differentially alters the gut microbiome in C57BL/6J mice. J Appl Physiol (1985) 2015;118(8):1059-66.

[43] Brandt N, Kotowska D, Kristensen CM, Olesen J, Lützhøft DO, Halling JF, et al. The impact of exercise training and resveratrol supplementation on gut microbiota composition in high-fat diet fed mice. Physiological Reports 2018;6(20):1-11.

[44] Campbell SC, Wisniewski PJ, Noji M, McGuinness LR, Häggblom MM, Lightfoot SA, et al. The effect of diet and exercise on intestinal integrity and microbial diversity in mice. PLoS ONE 2016;11(3):1-17.

[45] Nagano T, Yano H. Effect of dietary cellulose nanofiber and exercise on obesity and gut microbiota in mice fed a high-fat-diet. Bioscience, Biotechnology and Biochemistry 2020;84(3):613-20.

[46] Zhao X, Zhang Z, Hu B, Huang W, Yuan C, Zou L. Response of gut microbiota to metabolite changes induced by endurance exercise. Frontiers in Microbiology 2018;9(APR):1-11.

[47] Taniguchi H, Tanisawa K, Sun X, Kubo T, Hoshino Y, Hosokawa M, et al. Effects of short-term endurance exercise on gut microbiota in elderly men. Physiological Reports 2018;6(23):1-16.

[48] Rinninella E, Raoul P, Cintoni M, Franceschi F, Miggiano GAD, Gasbarrini A, et al. What is the healthy gut microbiota composition? A changing ecosystem across age, environment, diet, and diseases. Microorganisms 2019;7(1).

[49] Allen JM, Mailing LJ, Niemiro GM, Moore R, Cook MD, White BA, et al. Exercise Alters Gut Microbiota Composition and Function in Lean and Obese Humans 2018. 747-57 p.

[50] Lambert JE, Myslicki JP, Bomhof MR, Belke DD, Shearer J, Reimer RA. Exercise training modifies gut microbiota in normal and diabetic mice. Applied Physiology, Nutrition and Metabolism 2014:1-15.

[51] Markowiak P, Ślizewska K. Effects of probiotics, prebiotics, and synbiotics on human health. Nutrients 2017;9(9).

[52] Vallianou N, Stratigou T, Christodoulatos GS, Dalamaga M. Understanding the Role of the Gut Microbiome and Microbial Metabolites in Obesity and Obesity-Associated Metabolic Disorders: Current Evidence and Perspectives. Current Obesity Reports 2019;8(3):317-32.

[53] Kim YA, Keogh JB, Clifton PM. Probiotics, prebiotics, synbiotics and insulin sensitivity. Nutrition Research Reviews 2017:1-17.

[54] Mahboobi S, Rahimi F, Jafarnejad S. Effects of prebiotic and synbiotic supplementation on glycaemia and lipid profile in type 2 diabetes: A meta-analysis of randomized controlled trials. Advanced Pharmaceutical Bulletin 2018;8(4):565-74.

[55] Zheng HJ, Guo J, Jia Q, Huang YS, Huang WJ, Zhang W, et al. The effect of probiotic and synbiotic supplementation on biomarkers of inflammation and oxidative stress in diabetic patients: A systematic review and meta-analysis of randomized controlled trials. Pharmacological Research 2019;142(February):303-13.

[56] Sáez-Lara MJ, Robles-Sanchez C, Ruiz-Ojeda FJ, Plaza-Diaz J, Gil A. Effects of probiotics and synbiotics on obesity, insulin resistance syndrome, type 2 diabetes and non-alcoholic fatty liver disease: A review of human clinical trials. International Journal of Molecular Sciences 2016;17(6):1-15.

[57] Tabrizi R, Moosazadeh M, Lankarani KB, Akbari M, Heydari ST, Kolahdooz F, et al. The Effects of Synbiotic Supplementation on Glucose Metabolism and Lipid Profiles in Patients with Diabetes: a Systematic Review and Meta-Analysis of Randomized Controlled Trials. Probiotics and Antimicrobial Proteins 2018;10(2):329-42.

[58] Tabrizi R, Ostadmohammadi V, Lankarani KB, Akbari M, Akbari H, Vakili S, et al. The effects of probiotic and synbiotic supplementation on inflammatory markers among patients with diabetes: A systematic review and meta-analysis of randomized controlled trials. European Journal of Pharmacology 2019;852(April):254-64.

[59] Roshan H, Ghaedi E, Rahmani J, Barati M, Najafi M, Karimzedeh M, et al. Effects of probiotics and synbiotic supplementation on antioxidant status: A meta-analysis of randomized clinical trials. Clinical Nutrition ESPEN 2019;30:81-8.

[60] Barengolts E. Gut microbiota, prebiotics, probiotics, and synbiotics in management of obesity and prediabetes: Review of randomized controlled trials. Endocrine Practice 2016;22(10):1224-34.

[61] Canfora EE, Jocken JW, Blaak EE. Short-chain fatty acids in control of body weight and insulin sensitivity. Nature Reviews Endocrinology 2015;11(10):577-91.

[62] Mandaliya DK, Seshadri S. Erratum: Short Chain Fatty Acids, pancreatic dysfunction and type 2 diabetes (Pancreatology (2019) 19(4) (616), (S1424390319301000), (10.1016/j.pan.2019.04.012)). Pancreatology 2019;19(4):617-22.

[63] Im DS. FFA4 (GPR120) as a fatty acid sensor involved in appetite control, insulin sensitivity and inflammation regulation. Molecular Aspects of Medicine 2018;64:92-108.

[64] Müller M, Hernández MAG, Goossens GH, Reijnders D, Holst JJ, Jocken JWE, et al. Circulating but not faecal short-chain fatty acids are related to insulin sensitivity, lipolysis and GLP-1 concentrations in humans. Scientific Reports 2019;9(1):1-9.

[65] Hutchison AT, Regmi P, Manoogian ENC, Fleischer JG, Wittert GA, Panda S, et al. Time-Restricted Feeding Improves Glucose Tolerance in Men at Risk for Type 2 Diabetes: A Randomized Crossover Trial. Obesity (Silver Spring) 2019;27(5):724-32.

[66] Chaix A, Manoogian ENC, Melkani GC, Panda S. Time-Restricted Eating to Prevent and Manage Chronic Metabolic Diseases. Annu Rev Nutr 2019;39:291-315.

[67] Sutton EF, Beyl R, Early KS, Cefalu WT, Ravussin E, Peterson CM. Early Time-Restricted Feeding Improves Insulin Sensitivity, Blood Pressure, and Oxidative Stress Even without Weight Loss in Men with Prediabetes. Cell Metab 2018;27(6):1212-21 e3.

[68] Liu H, Javaheri A, Godar RJ, Murphy J, Ma X, Rohatgi N, et al. Intermittent fasting preserves beta-cell mass in obesity-induced diabetes via the autophagy-lysosome pathway. Autophagy 2017;13(11):1952-68.

[69] Lambert JE, Myslicki JP, Bomhof MR, Belke DD, Shearer J, Reimer RA. Exercise training modifies gut microbiota in normal and diabetic mice. Applied Physiology, Nutrition, and Metabolism 2015.

[70] Palareti G, Legnani C, Cosmi B, Antonucci E, Erba N, Poli D, et al. Comparison between different D-Dimer cutoff values to assess the individual risk of recurrent venous thromboembolism: Analysis of results obtained in the DULCIS study. International Journal of Laboratory Hematology 2016;38(1):42-9.

[71] Lai ZL, Tseng CH, Ho HJ, Cheung CKY, Lin JY, Chen YJ, et al. Fecal microbiota transplantation confers beneficial metabolic effects of diet and exercise on diet-induced obese mice. Scientific Reports 2018;8(1):1-11.

[72] Ribeiro FM, Ribeiro CFA, Cláudia M. G A, Castro AP, Almeida JA, Franco OL, et al. Limited effects of low-to-moderate aerobic exercise on the gut microbiota of mice subjected to a high-fat diet. Nutrients 2019;11(1).

[73] Asemi Z, Khorrami-Rad A, Alizadeh SA, Shakeri H, Esmaillzadeh A. Effects of synbiotic food consumption on metabolic status of diabetic patients: A double-blind randomized cross-over controlled clinical trial. Clinical Nutrition 2014;33(2):198-203.

[74] Akram Kooshki A, Tofighiyan T, Rakhshani MHa. Effects of Synbiotics on Inflammatory Markers in Patients With Type 2 Diabetes Mellitus. Global journal of health science 2015;7(7):1-5.

[75] Kooshki A, Tofighian T, Akbarzadeh R. Effect of synbiotic supplementation on weight , body mass index and blood sugar in type II diabetic patients. Journal of Reserach & Health 2017;7(2):771-6.

[76] Tajabadi-Ebrahimi M, Sharifi N, Farrokhian A, Raygan F, Karamali F, Razzaghi R, et al. A randomized controlled clinical trial investigating the effect of synbiotic administration on markers of insulin metabolism and lipid profiles in overweight type 2 diabetic patients with coronary heart disease. Experimental and Clinical Endocrinology and Diabetes 2017;125(1):21-7.

[77] Tunapong W, Apaijai N, Yasom S, Tanajak P, Wanchai K, Chunchai T, et al. Chronic treatment with prebiotics, probiotics and synbiotics attenuated cardiac dysfunction by improving cardiac mitochondrial dysfunction in male obese insulin-resistant rats. European Journal of Nutrition 2018;57(6):2091-104.

[78] Horvath A, Leber B, Feldbacher N, Tripolt N, Rainer F, Blesl A, et al. Effects of a multispecies synbiotic on glucose metabolism, lipid marker, gut microbiome composition, gut permeability, and quality of life in diabesity: a randomized, double-blind, placebo-controlled pilot study. European Journal of Nutrition 2019(0123456789).

[79] Kassaian N, Feizi A, Aminorroaya A, Amini M. Probiotic and synbiotic supplementation could improve metabolic syndrome in prediabetic adults: A randomized controlled trial. Diabetes and Metabolic Syndrome: Clinical Research and Reviews 2019;13(5):2991-6.

[80] Soleimani A, Motamedzadeh A, Zarrati Mojarrad M, Bahmani F, Amirani E, Ostadmohammadi V, et al. The Effects of Synbiotic Supplementation on Metabolic Status in Diabetic Patients Undergoing Hemodialysis: a Randomized, Double-Blinded, Placebo-Controlled Trial. Probiotics and Antimicrobial Proteins 2019;11(4):1248-56.

[81] Ban Q, Cheng J, Sun X, Jiang Y, Zhao S, Song X, et al. Effects of a synbiotic yogurt using monk fruit extract as sweetener on glucose regulation and gut microbiota in rats with type 2 diabetes mellitus. Journal of Dairy Science 2020;103(4):2956-68.

[82] Morshedi M, Saghafi-Asl M, Hosseinifard ES. The potential therapeutic effects of the gut microbiome manipulation by synbiotic containing-Lactobacillus plantarum on neuropsychological performance of diabetic rats. Journal of Translational Medicine 2020;18(1):1-14.

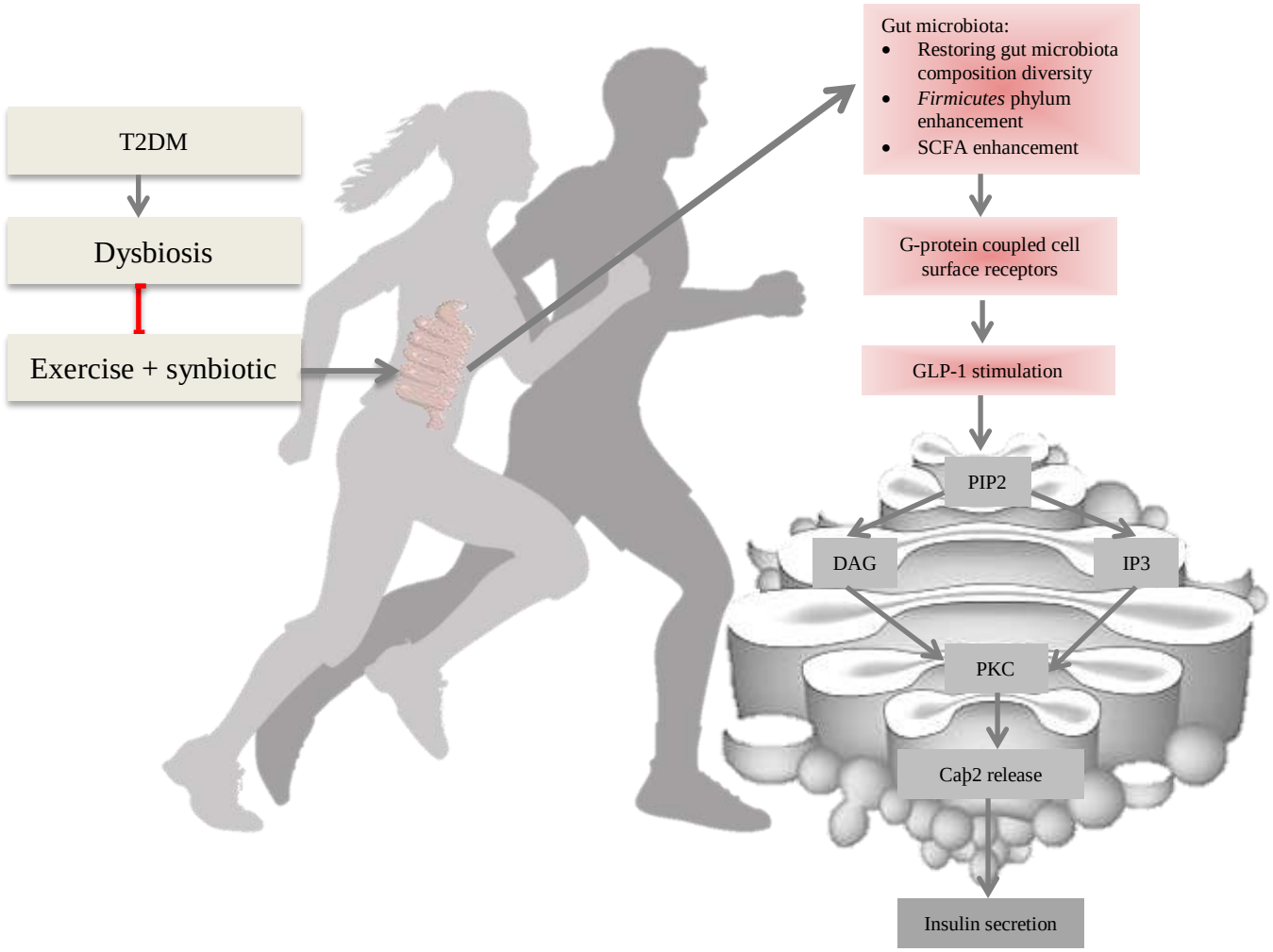

Figure 1 Exercise and synbiotic consumption intercorrelation. Dysbiosis occurred in T2DM and it might be improved by the combination of exercise and synbiotic treatment. Exercise and synbiotic consumption exert a richness for gut microbiota, increasing Firmicutes phylum, and therefore inducing SCFA (acetate, propionate, butyrate) production. SCFA subsequently stimulates GLP-1 in L-cells by activating G-protein coupled cell surface receptors and hydrolyzes PIP2 afterwards to DAG and IP3 in endiplasmic reticulum of β-cell. This activates PKC which induces Caþ2 release and finally insulin is secreted by β-cell.

Table **1**. Summary of the effect of exercise on gut microbiota.

Study	Design	Subject	Intervention	Long of Intervention	Impact on gut microbiota/ Result
Clarke et al. (2014) (19)	Cross-sectional	Male rugby players with a mean BMI 29.1 (n=40); healthy men controls with BMI ≤ 25 (n=23), and healthy men control with BMI >28 (n=23).	-	-	The gut microbiota diversity of the athlete was significantly higher compared to both control groups and taxa identified in the gut microbiota of athlete, low BMI control, and high BMI control were respectively 22, 11, and 9 phyla.
Lambert et al. (2014) (69)	Experimental study	Male db/$^{+}$ mice comprised: exercised control (n=10) and sedentary control (n=10); type 2 diabetic db/db (C57BL/KsJ-lepr*db*/lepr*db*) comprised exercised group (n=10) and sedentary group (n=9).	Low-intensity treadmill running	6 weeks	Exercise influenced the increase in *Bifidobacterium* spp. In exercised normal but not in exercised diabetic mice/
Allen et al. (2015) [31]	Experimental study	Male C57BL/6J mice comprised forced treadmill running group (n=10); voluntary wheel running (n=10); and sedentary controls (n=9).	Forced moderate treadmill running and free access to telemetered running wheels.	30 days	Exercise training influences the richness and the evenness of bacterial community except for Bacteroidetes and Firmicutes (as the major phyla of bacteria in the gut).
Denou et al. (2016) (39)	Experimental study	Male C57BL/6 mice comprised: 1) high-fat diet-induced obesity group (n=9); 2) High-fat diet-induced obesity with exercise training (n=7).	High-intensity interval training (HIIT)	6 weeks	HIIT increased alpha diversity and Bacteroidetes/Firmicutes ratio of the distal gut and fecal microbiota.
Campbell et al. (2016) (44)	Experimental study	Male C57BL/6NTac mice were divided: 1) lean sedentary; 2) diet-induced obesity sedentary; 3) lean exercise; and diet-induced obesity exercise.	Free running wheel	12 weeks	Both lean and obese exercise showed normal histologic whereas the obese sedentary presented the villi wide twice compared normal villi.
Palareti *et al*. (2016) (70)	Experimental study	Rats (n=57) were assigned to: 1) Control 2) Sedentary 3) Light intensity trained 4) High intensity trained	Light and high-intensity training	12 weeks	Both light and high intensity induced a significant difference in intestinal microbiota in standard chow, but there was no significant difference in intestinal

		Each group was given by standard and high fed diet.			microbiota in the groups fed a high-fat diet.
Taniguchi et al. (2018) (47)	Randomized crossover trial	Healthy elderly (n=33)	Endurance exercise	5 weeks	There was no change in α-diversity indices between the control period and the exercise program.
Allen et al. (2018) (41)	Experimental study	C57B1/6N mice comprised the control group (n=10) and the exercise group (n=10).	n/a	42 days	The exercise group appeared a higher abundance of genera: *Anaerostipes spp*, *Akkermansia spp*, Family *Lachnospiraceae*, and lower prevalence of *Prevotella spp.* Compared to the control group.
Allen et al. (2018) (49)	Longitudinal	Lean female (n=18) and obese female (n=14)	Endurance exercise	6 weeks	Short-chain fatty acids (SCFAs) increased in lean but not in the obese subject.
Brandt et al. (2018) (43)	Experimental study	Male C57BL/6N mice comprised: 1) untrained control group receiving standard rodent chow; 2) Untrained group receiving high-fat diet; 3) untrained group receiving high-fat diet supplemented with resveratrol; 4) exercise-trained group and receiving high-fat diet.	Running wheel in an average 50 km/week	16 weeks	Exercise successfully increased the alpha diversity of gut microbiota and has Bacteroidetes abundance higher compared to Firmicutes.
Zhao *et al.* (2018) (46)	Randomized trial control	Health amateur runner male (n=16) and female (n=4).	Endurance running	Before and after the marathon.	Special taxa from phylum to genus were detected after running than before.
Lai *et al.* (2018) (71)	Experimental study	Male mice C57BL/6JNarl (n=49) were divided by: 1) High-fat diet group/H (n=6) 2) High fat diet-exercise group/HE (n=7) 3) Normal fat diet/N (n=7) 4) Normal fat diet-exercise group/NE (n=6) 5) High-fat diet group receiving Fecal Microbiota Transplantation from HE (n=7)	Treadmill (18 m/min, 30 min/day, 5 days/week)	16 weeks	Diet was more influential than an exercise in shaping the gut microbiota.

		6) High-fat diet group receiving Fecal Microbiota Transplantation from NE (n=7) 7) Normal fat diet receiving Fecal Microbiota Transplantation from NE (n=7)			
Ribeiro *et al*. (2019) (72)	Experimental study	Male C57BI/6 mice (n=40) were divided into: 1) The standard diet control group 2) The high-fat diet control group 3) Standard diet trained group 4) High-fat diet trained group	Low-to-moderate training (30 min/day, 5 days/week)	8 weeks	A low-to-moderate exercise was less effective to modulate the composition of gut microbiota in mice fed by a high-fat diet.
Nagano and Hiromi (2020) (45)	Experimental study	Male C57BL/6N mice designed as: 1) Cellulose nanofiber-untreated sedentary groups (n=8); 2) exercise group (n=8); 3) Cellulose nanofiber sedentary groups (n=8); 4) Cellulose nanofiber-exercise group (n=8)	Free running wheel	7 weeks	Exercise had an impact on decreasing of *Erysipelotrichaceae* and *Rikenellaceae* and had an effect on increasing *Ruminococaceae* and *Eubacteriaceae* which concomitantly increased with the amount of acetate.

*BMI : Body Mass Index

Table **2**. Summary of the effect of synbiotic on the diabetic condition.

Study	Design	Subject	Intervention	Long of Intervention	Impact on gut microbiota/ Result
Asemi *et al.* (2014) (73)	Randomized controlled trial	Diabetic patients were divided into: 1) Synbiotic group (n=62) 2) Control group (n=62)	The synbiotic contained *Lactobacillus sporogenes* (1×10^7 CFU) and 0.04 g inulin (HPX).	6 weeks	Synbiotic treatment significantly improved serum insulin levels, fasting plasma glucose, serum triglycerides, serum hs-CRP, and plasma total GSH compared to the control group.
Kooshki *et al.*(2015) (74)	Randomized controlled trial	Diabetic patients (n=44) were divided into: 1) Synbiotic (n=22) 2) Placebo (n=22)	The synbiotic was on the tablet.	8 weeks	Synbiotic successfully decreased hs-CRP, IL-6, and TNF-α
Kooshki *et al.* (2017) (75)	Clinical double-blind trial	Diabetic subjects (n=43) were	The synbiotic tablet-form and placebo tablet were provided to the subjects.	8 weeks	Synbiotic supplementation was successfully reduced the blood glucose level of the diabetic subjects.
Tajabadi-Ebrahimi *et al.* (2017) (76)	Randomized controlled clinical trial	Overweight diabetic patients with coronary heart disease (n-60) were divided into: 1) Group A (n=30) received the synbiotic supplement 2) Group B (n=30) received placebo	Synbiotic supplement contained 3 probiotic bacteria *Lactobacillus acidophilus* 2×10^9, *Lactobacillus casei* 2×10^9, *Bifidobacterium bifidum* 2×10^9 CFU/g plus 800 mg inulin.	12 weeks	Synbiotic treatment significantly reduced fasting plasma glucose, serum insulin concentration, the homeostasis model of assessment-estimated β-cell function, and significantly increased quantitative insulin sensitivity check index compared with the placebo.
Tunapong *et al.* (2018) (77)	Experimental study	Male obese-insulin resistant rats (48) were divided into: 1) Normal diet rats treated by vehicle 2) High fat diet-fed rats treated by vehicle 3) Normal diet rats treated by prebiotics 4) High-fat diet rats treated by prebiotics 5) Normal diet rats treated by	Prebiotics: xylooligosaccharides (XOS) Probiotics: *Lactobacillus paracasei* STII01 HP4 Synbiotic: the combination both of XOS and *Lactobacillus paracasei* STII01 HP4	12 weeks	Prebiotics, probiotics, and synbiotic had similar efficacy for attenuating insulin resistance by improving plasma glucose, plasma insulin, and HOMA index.

		probiotics 6) High-fat diet rats treated by probiotics 7) Normal diet rats treated by synbiotic 8) High-fat diet rats treated by synbiotic			
Horvath *et al.* (2019) (78)	Randomized clinical trial	Diabetic patients (n=26) which divided into 2 groups: 1) Allocated to synbiotic group (n=12) 2) Allocated to the placebo group (n=14)	Synbiotic, in the powder-form, contained Ecologic Barrier brand (6 g) as probiotic and Omnilogic Plus brand (10 g) as prebiotic.	6 months	There were no significant changes in HbA1c, fasting plasma glucose, fasting plasma insulin, C-peptide, $AUC_{glucose}$ in minutes during *mixed meal tolerance test* (MTT), $AUC_{insulin}$ in minutes during MTT, $AUC_{c\text{-}peptide}$ in minutes during MTT detected in the synbiotics group compared to the placebo group.
Kassaian *et al.* (2019) (79)	Randomized controlled trial	Diabetic participants either male or female (n=120) were assigned into 3 groups: 1) Probiotic group (n=40) 2) Synbiotic group (n=40) 3) Placebo group (n=40)	Probiotics contained freeze-dried *Lactobacillus acidophilus*, Bifidobacterium bifidum, *Bifidobacterium lactis*, and *Bifidobacter longum* (1.5×10^9 for each). Synbiotics contained the aforementioned probiotics plus inulin. The probiotics and synbiotics were supplemented as much as 6 g/d.	24 weeks	Either probiotics or synbiotic successfully improved hyperglycemia in the 24-weeks.
Soleimani *et al.* (2019) (80)	Randomized, Double-Blinded, Placebo-Controlled Trial	Diabetic patients with hemodialysis (n=60) were divided into: 1) Synbiotic capsule (n=30) 2) Placebo capsule (n=30)	The synbiotic capsule contained *Lactobacillus acidophilus*, *Lactobacillus casei*, and *Bifidobacterium bifidum* (2×10^9 CFU/g each), plus 0.8 g/day of inulin	12 weeks	Synbiotic treatment reduced fasting plasma glucose, insulin levels, and insulin resistance significantly. In contrast, synbiotic increased the quantitative insulin sensitivity check index compared with the placebo. The synbiotic provision also

					successfully reduced high-sensitivity C-reactive protein and malondialdehyde levels. Moreover, total antioxidant capacity enhanced significantly.
Ban *et al.* (2020) (81)	Experimental study	Type 2 diabetic rats (n=70) were divided into 7 groups: 1) Non-diabetic control group 2) The diabetes control group (SIDR) 3) Control yogurt group (CY) 4) Low-dose yogurt group (MY-L) 5) Medium-dose yogurt group (MY-M) 6) High-dose yogurt group (MY-H) 7) Metformin group (Dix)	Synbiotic was the freeze-dried direct-to-vat inoculation stater culture containing *Streptococcus thermophiles* and *Lactobacillus delbrueckii* ssp. *Bulgaricus*, with *Bifidobacterium* BB-12 and Lactobacillus acidophilus *LA-5* as a starter and inulin as a prebiotic.	6 weeks	Synbiotic successfully improved insulin resistance and glycosylated hemoglobin compared with yogurt sweetened with sucrose and they showed a remarkable improvement in short-chain fatty acid levels and gut microbiota status. Synbiotic treatment was also restored the islets of Langerhans.
Morshedi *et al.* (2020) (82)	Experimental study	Diabetic rats (n=48) were divided into 6 groups: 1) Healthy control 2) Diabetic control 3) Diabetic + probiotic 4) Diabetic + prebiotic 5) Diabetic + synbiotic 6) Diabetic sham group	Treatments in supplement the form were ascribed as follows: *L. Plantarum* was used as a probiotic. Inulin was used as prebiotic. Combination of *L. Plantarum* and inulin was used as synbiotic.	8 weeks	Synbiotic resulted in the best effect on the improvement of serum SOD, serum GPx, serum MDA, serum TAC, hippocampal SOD, hippocampal GPx, hippocampal MDA, hippocampal TAC, the pre-frontal cortex (PFC) SOD, PFC GPx, PFC TAC

CFU, colony forming units, XOS, xylooligosaccharides,