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RESEARCH ARTICLE

The Prospect for Type 2 Diabetes Mellitus Combined with Exercise and Synbiotics: A Perspective

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Abstract: Change in gut microbiome diversity (the so-called dysbiosis) is correlated with insulin resistance conditions. Exercise is typically the first management for people with type 2 diabetes mellitus (T2DM), which is generally well-known for improving glucose regulation. The new prebiotics and probiotics, like synbiotics, designed to target specific diseases, require additional studies. While the effectiveness of exercise combined with synbiotics seems promising, this review discusses these agents' possibility of increasing the gut microbiota's diversity. Therefore, they could enhance short-chain fatty acids (SCFA). In particular, the synbiotic interaction on gut microbiota, the exercise mechanism in improving gut microbiota, and the prospect of the synergistic effect of the combination of synbiotic and exercise to improve insulin sensitivity are 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 is identified based on the doctor's diagnosis of the population age ≥15 years, which has increased to 2% in 2018 [1]. Indonesia is also one of the top 10 countries with many diagnosed and undiagnosed patients with diabetes at present. It is estimated that as many as 16.6 million people will suffer from diabetes by 2045 [2]. Because of the prevalence of diabetes, some studies concerning diabetes management are being conducted, including lifestyle modification, medicinal plant identification, air pollution analysis, and their possible relations to biological changes in diabetes [3-5].

The gut microbiota and gut microbiome are interchangeable terms and refer to the same thing. The gut microbiota is defined as all organisms living in the gastrointestinal tract, primarily in the large intestine, and dominantly comprises *Bacteriodetes* and *Firmicutes* (90%) [6-8]. The gut microbiome is a collective genome of all microorganisms inhabiting the gut [9]. In contrast, human gut microbiota comprises 100 times more genes in the entire human body and acts to synthesize essential amino acids and essential fatty acids for the human body [10]. Human gut microbiota is flexible and can adapt to dietary changes by shifting its flora composition and gene content [11].

Healthier individuals are considered as having a more diverse gut microbiome because of fewer pathogenic bacterial species and their role in producing vitamins, essential nutrients by degrading complex polysaccharides and maintaining gut motility and immune function [12, 13]. Several gut microbiomes contribute to undigested food component fermentation, including fiber, which, in turn, change in the gut microbiome correlated with insulin resistance conditions [14]. Diabetic conditions in mice and humans have lipopolysaccharides (LPS), a bacterial endotoxin produced by gram-negative bacteria incrementally [15]. Toll-like receptors (TLRs), receptors for innate immunity, control gut microbiota composition, and correlate with T2DM.

Exercise is typically one of the first activities recommended for people with T2DM since it is generally well-known to improve glucose regulation. Exercise also has been proposed to have an immunomodulatory role in down-regulating TLR4 expression, thus eventually ameliorating gut microbiota diversity. Some exercise modalities are recommended for individuals with T2DM, such as aerobic, resistance, anaerobic-resistance training, and high-intensity interval training. All of them exert a beneficial effect on the diabetic condition, although the optimal amount of exercise needs further investigation [16]. During exercise, physiological changes occur. However, these changes are different in abrupt exercise and habitual exercise [17, 18]. Abrupt exercise exerts multiple effects on metabolite production and inflammatory mediators [17]. On the other hand, habitual exercise has the beneficial effect of inducing Peroxisome proliferator activated receptor gamma coactivator 1-alpha (PGC-1α) which is the most dominant regulator of mitochondrial function. PGC-1α induction leads to diverse gut microbiota through mitochondrial biogenesis [18]. Exercise has previously been described as a modulator for gut microbiota [19].

Prescriptions of prebiotics and probiotics do not seem to be effective for improving chronic inflammation-related dis-

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eases, including diabetes. Nevertheless, a recent study revealed that probiotic treatment diversifies the gut composition and improves the *Bacteriodetes/Firmicutes* ratio [20]. Furthermore, prebiotic intervention may alter the gut microbiota and intestinal permeability [21]. Thus, the new design of prebiotics and probiotics, like that of synbiotics, a form designed to target specific diseases, requires additional studies. The effectiveness of exercise and the combination of exercise and prescribed synbiotics seems promising. This review discusses the possibility of combining probiotics, prebiotics, and exercise to increase gut microbiota diversity. In particular, the interaction of synbiotics toward gut microbiota, the exercise mechanism in improving gut microbiota, and the prospect of the synergistic effect of the combination of synbiotics and exercise to improve insulin sensitivity are addressed.

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

T2DM is associated with defective islet autophagy regulation that potentially results from hepatic insulin resistance [22]. Autophagy is defined as the degradation of the mitochondria and other cellular organelles to maintain homeostasis and the islet's normal architecture and function [23, 24]. Autophagy plays a role in regulating LPS levels and protecting cells from LPS exposure [22]. Autophagy disruption occurs in hyperglycemia by inhibiting transcription factor EB (TFEB) nuclear translocation resulting in autophagy downregulation [25]. T2DM, which is characterized by having insufficient insulin to uptake glucose into the cell, is a condition mediated by LPS leading to increase low-grade inflammation through TLR4 signaling activation [9, 22]. Insulin resistance-associated gut microbiota diversity might be influenced by the alteration of gut microbiota, thus producing serum metabolome characterized by increasing LPS and BCAA biosynthesis and reducing BCAA transport into bacterial cells, methanogenesis, and pyruvate oxidation [26, 27].

3. EXERCISE-GUT MICROBIOTA INTERACTION

Exercise terminology is interchangeable with physical activity. It is defined as all structured movement that increases the energy used. Functionally speaking, exercise improves blood glucose control in T2DM [28, 29]. Exercise's effect on improving diabetes is linked to increased glucose transporter (GLUT)-4 content and amplification of insulin signaling in muscle. These effects enhance GLUT-4 expression in adipose tissue and skeletal muscle in the diabetic condition [16, 30]. It has been speculated that exercise can alleviate insulin resistance through gut microbiota composition diversity, such as enhancing *Firmicutes* phylum and short-chain fatty acids (SCFAs) [7]. SCFAs are a product of gut microbial fermentation of dietary fiber, which primarily comprises acetate, propionate, and butyrate [31-33]. According to a previous review of 10 human and animal laboratory studies, exercise *per se* modifies gut microbiota composition [8]. A previous study concluded that individuals who frequently exercise, showed gut microbiota diversity higher than control subjects with a low body mass index (BMI), followed by control subjects with a high BMI [19].

It seems that exercise and gut microbiota have a bidirectional interaction through mitochondrial genome regulation, including (i) reactive oxygen and nitrogen species (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 habitual exercise, suppressing basal pro-inflammatory cytokines [17]. This might be linked to the microbiota composition disruption product called LPS, which escalates β-cell apoptosis. It also causes the molecular onset of insulin resistance and hyperglycemia through nuclear factor kappa B (NFκB) [34]. Exercise has a role in suppressing LPS (a ligand for TLR4) levels. Hence, it inhibits TLRs signaling pathway in the liver, muscle, and adipose tissue [35, 36]. TLRs are a transmembrane receptor family that plays central roles in innate immunity. Their activation (particularly TLR4) has been postulated to influence insulin resistance and T2DM development [35, 37]. Exercise has been reported to enhance intestinal and plasma acetic acid promoting the autophagic mechanism in skeletal muscle *via* binding to the G-protein-coupled receptor 43 (GPR43), which eventually enhances insulin sensitivity [38].

Unfortunately, the effect of exercise on gut microbiota in T2DM needs additional studies. Relevant studies were conducted by Velikonja *et al.* and Denou *et al.* [13, 39]. A metabolic syndrome was defined as the existence of at least two inclusion criteria of metabolic syndrome (abdominal obesity, obesity, hyperglycemia, and hypertension) associated with a low concentration of gut microbiota composition and low SCFA composition [13]. Other studies revealed that exercise 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 shown in Table **1**. Some factors influencing gut microbiota composition include diet, stress, altitude, temperature, pollutants, noise, disease state, medications, host genetics, and exercise [12, 32]. The duration of exercise needs 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 in diversity or composition appears in such conditions as obesity and T2DM [48]. Since the previous study revealed that improving the gut microbiota depended on BMI status [49], the effect of exercise on the gut microbiota of individuals with T2DM still needs additional study. This is supported by Lambert *et al.*, who concluded that the interaction between exercise and gut microbiota composition in T2DM requires further investigation [50].

Table 1. Summary of the effects of exercise on gut microbiota.

Study	Design	Subject	Intervention	Duration of Intervention	Impact On Gut Microbiota/Results
Clarke *et al.* (2014) [19]	Cross-sectional study	Male rugby players with a mean BMI 29.1 (n = 40); healthy male controls with BMI ≤25 (n = 23), and healthy male controls with BMI >28 (n = 23).	-	-	The gut microbiota diversity of the athletes was significantly higher compared with both control groups and taxa identified in the gut microbiota of athletes; low BMI control and high BMI control were 22, 11, and nine phyla, respectively.
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 influenced the richness and evenness of bacterial flora, except for *Bacteroidetes* and *Firmicutes* (as the major bacterial phyla 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 histology, whereas the obese sedentary had villi twice as wide as 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 Each group was fed a standard and high-fat diet.	Low- and high-intensity training	12 weeks	Both low- and high-intensity-induced a significant difference in intestinal microbiota with standard chow, but there was no significant difference in intestinal 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 had a higher abundance of genera: *Anaerostipes spp, Akkermansia spp,* Family *Lachnospiraceae,* and a lower prevalence of *Prevotella spp.* than the control group.
Allen *et al.* (2018) [49]	Longitudinal study	Lean females (n = 18) and obese females (n = 14).	Endurance exercise	6 weeks	SCFAs increased in lean but not in obese subjects.
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 at an average of 50 km/week	16 weeks	Exercise successfully increased the alpha diversity of gut microbiota and had a higher abundance of Bacteroidetes than *Firmicutes*.
Zhao *et al.* (2018) [46]	Randomized controlled trial	Healthy amateur runners males (n = 16) and females (n = 4).	Endurance running	Before and after the marathon.	Special taxa from phylum to genus were detected after running than before running.

(Table 1) contd....

Study	Design	Subject	Intervention	Duration of Intervention	Impact On Gut Microbiota/Results
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) 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)	Treadmill (18 m/min, 30 min/day, 5 days/week)	16 weeks	Diet was more influential than exercise in shaping the gut microbiota.
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	Low-to-moderate exercise was less effective in modulating the composition of gut microbiota in mice fed 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 decreased *Erysipelotrichaceae* and *Rikenellaceae* and increased *Ruminococcaceae* and *Eubacteriaceae,* which increased with the amount of acetate.

*BMI: Body Mass Index.

4. INTERACTION OF SYNBIOTICS TOWARDS THE GUT MICROBIOME

Synbiotics are the synergistic interactions between pro and prebiotics, which have been known since 1995 when they were introduced by Gibson [51]. Probiotics *per se* have been well-known to supply a gut microbiota population that enables the ingestion of specific fibers and successfully restore gut microbiome homeostasis [27]. Synbiotic administration aims to activate the metabolism of the microbiota. Thus, it can be positively beneficial for the host's health [51, 52]. Numerous studies have been conducted demonstrating the beneficial effects of synbiotics in the diabetic condition and are summarized in Table **2**. The effect of *Lactobacillus acidophilus* DSM20079 was 14.5 times higher when it was induced by inulin or pectin compared with that of glucose [53]. Therefore, either probiotics or prebiotics have main roles in maintaining gut microbiota survival.

As shown in Table **2**, synbiotics exerted beneficial effects, but the lack of data showed that synbiotics had no effect. The nine randomized clinical trials' duration was at least six weeks, but the minimum doses require further investigation. Other meta-analyses revealed that synbiotics could modulate the immune system through SCFA production and, therefore, improve glucose homeostasis [54-59]. Nevertheless, a high dose of synbiotic consumption, due to SCFA production and greater fermentation, might cause feelings of discomfort, such as bloating and flatulence, which vary individually [54, 60].

5. THE BRIGHT PROSPECT OF THE COMBINATION OF SYNBIOTICS AND EXERCISE TO IMPROVE INSULIN SENSITIVITY

We propose a synergistic interaction between synbiotic consumption and exercise conduction since both induce SCFA production (Fig. **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 (FFAR) 2, FFAR3, and (GPR) 120, are well described for glucose homeostasis [62, 63]. Butyrate requires FFAR2 and FFAR3 to induce GLP-1 and subsequently stimulates insulin secretion through a downstream pathway. This leads to phospholipase C (PLC)-mediated hydrolysis of phosphatidylinositol 4,5 bisphosphate (PIP2) to diacylglycerol (DAG) and inositol triphosphate (IP3) activated protein kinase C (PKC), land then to Caþ2 release from the endoplasmic reticulum. Furthermore, FFAR2 and FFAR3 can also link to G/i/o subunits and inhibit adenylate cyclase. This decreases the concentration of cAMP, inhibiting protein kinase A (PKA) and exchanging protein directly activated by cAMP (EPAC) mediated insulin release [62, 64]. Also, propionate stimulates glucose uptake by increasing GPR41 induction (SCFA receptor) [64]. A synbiotic supplement might become a great prescription, but the GI side effects need to be considered. Furthermore, the dose of synbiotics, the modalities of exercise, and the duration of the combination of synbiotic intake and exercise are the new topics that hold future promise for diabetic individuals.

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 probiotics 6) High-fat diet rats treated by probiotics 7) Normal diet rats treated by synbiotic 8) High-fat diet rats treated by synbiotic	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.
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.

(Table 2) contd....

Study	Design	Subject	Intervention	Long of Intervention	Impact on gut microbiota/ Result
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 (SI-DR) 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.

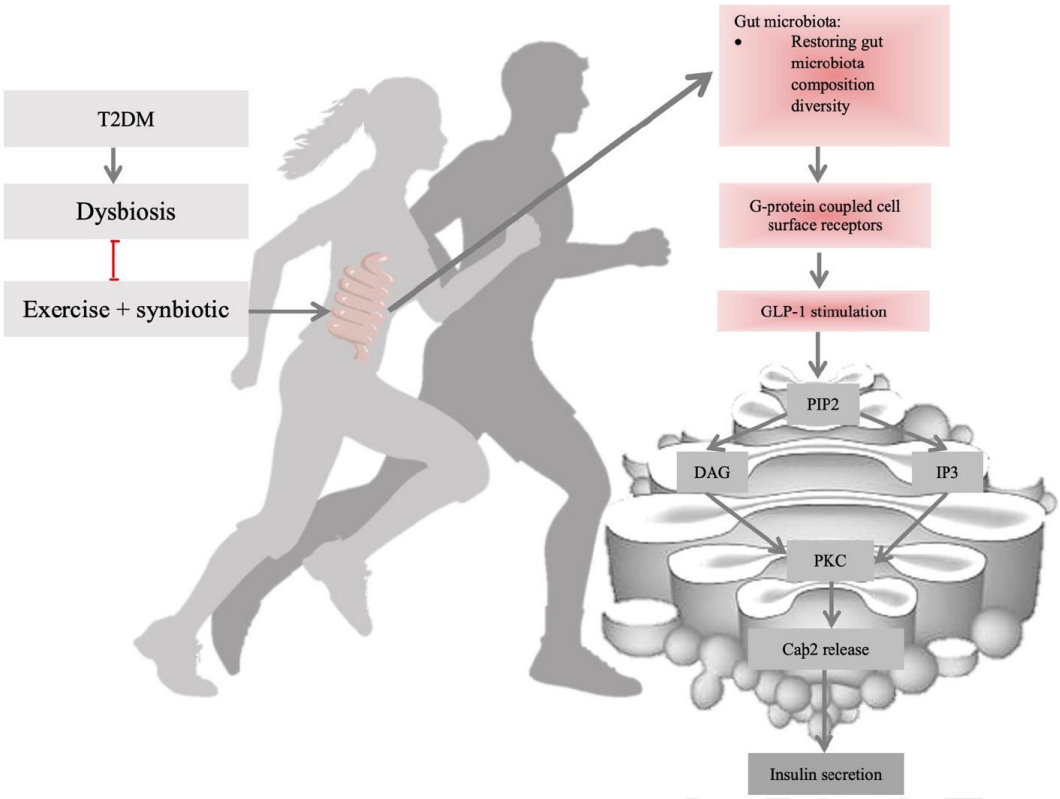

Fig. (1). Exercise and synbiotic consumption intercorrelation. Dysbiosis occurred in T2DM and it might be improved by the combination of exercise and synbiotic treatment. Exercise and synbiotic consumption exert a richness for gut microbiota, increasing Firmicutes phylum, and therefore inducing SCFA (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. SCFA: Short Chain Fatty Acid; GLP-1: glucagon-like peptide-1; PIP2: phosphatidylinositol 4,5 bisphosphate; IP3: inositol triphosphate; PKC: protein kinase C. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

In other aspects, the human microbiome is essential to our health and well-being, as they are the essential sources of our body's metabolites [10, 11]. However, the overgrowth 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 a diverse spectrum of the microbiome is used to reverse T2DM [65-67]. This is because serum fasting is a strong inducer of autophagy, which plays a pivotal role in cellular homeostasis, cell repair, cytotoxic protein elimination, and damaged organelle removal [22-25, 68].

CONCLUSION

The available data present the beneficial effects of exercise and synbiotic consumption *per se* for people with T2DM. The combination of exercise and synbiotic consumption might have greater positive effects compared with a single treatment. Furthermore, the side effects of the combination treatment need further investigation.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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