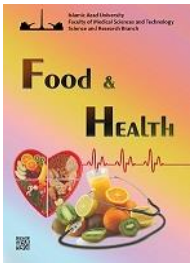

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Effects of synbiotic consumption on lipid profile in diabetic patients

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ABSTRACT

One of the most worldwide chronic diseases is diabetes which has affected a large population worldwide and it is predicted that 649 million adults will be diabetic by 2040. Many foods and ingredients were tested to combat diabetes. Both probiotics and prebiotics which are known as synbiotic have shown beneficial effects on many diseases including diabetes. Although several studies have evaluated the effect of synbiotic consumption on lipid profile in patients with diabetes, findings are inconsistent. The aim of this study was to evaluate the effects of synbiotics on lipid profile in diabetic patients. A systematic literature search of online databases including PubMed, Scopus, Google Scholar, Magiran, SID, and Cochrane's library was conducted up to January 2021. Randomized controlled trials (RCTs) investigating the effects of synbiotics on lipid profile in diabetic patients were included. A total of 11 RCTs with 662 participants were included. Synbiotic consumption resulted in a decrease in plasma concentrations of TC, TG, LDL, and an increase in plasma HDL levels compared to the control group (placebo supplements/control foods/conventional products). Synbiotic supplements may be profitable to ameliorate lipid profile in patients with diabetes and it should be suggested by both dietitians and healthcare clinics to diabetic patients.

1. Introduction

Diabetes is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The chronic hyperglycemia of diabetes is associated with long-time damage, dysfunction, and failure of various organs, particularly the eyes, kidneys, nerves, heart, and blood vessels (1). The prevalence of diabetes mellitus as one of the major endocrine diseases, has elevated worldwide (2); more than 415 million adults had diabetes all over the world in 2015 which will increase to 649 million by 2040, as stated in the International Diabetes Federation (IDF) (3). Several pathogenic processes are involved in the development of diabetes. These range from autoimmune destruction of the β-cells of the pancreas with consequent insulin deficiency to abnormalities that result in resistance to insulin action. The main cause of the abnormalities in macronutrients (carbohydrate, fat, and protein) metabolism in diabetes is impaired action of insulin on target tissues. Impaired insulin action is caused by insufficient secretion of insulin and/or reduced tissue responses to insulin at one or more points in the complicated pathways of hormone action. Insulin deficiency and defects in insulin action repeatedly occur in the same patients, and it is often obscure which abnormality, if either alone, is the primary reason for the hyperglycemia (1). Dyslipidemia is one of the important complications of diabetes mellitus with major abnormalities such as elevated triglycerides (TG) and lower levels of the high density of lipoprotein cholesterol (HDL-C), which reported to be particularly important for the development of CHD and neuropathy (4). Recent evidence mentions that there is an association between metabolic diseases and gut microbiota; it has been shown that types of bacteria in the gut of patients with diabetes were significantly associated with their glucose concentrations (5). Based on previous studies, altered gut microbiota interrelates with environmental and genetic factors resulting in increased intestinal permeability as well as changing the mucosal immune responses which all lead to the development of diabetes (6); that is to say, the administration of probiotics may ameliorate the prognosis and prevention of diabetes through modulation of intestinal microbiota (6-8). The word "probiotic" comes from Greek, and it means "for

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life". Based on FAO and WHO definition, probiotics are "live strains of strictly selected microorganisms which, when administered in adequate amounts, confer a health benefit on the host" (9,10). Results of RCT studies confirm the positive effects of probiotics on human health by increasing the body's immunity (immunomodulation) (11). Prebiotics which are non-digestible carbohydrates consumed by the microbiome for fermentation (12), are used to produce short-chain fatty acids (SCFAs) (13)such as inulin or fructooligosaccharides (FOS), which stimulate the growth and metabolism of probiotics in the intestine. Synbiotics are defined as a mixture of synergistically-acting probiotics and prebiotics (14). Several studies also show that the use of synbiotic foods may help control metabolic profiles, inflammatory factors, and oxidative stress biomarkers. Nevertheless, such effects have been mostly reported by animal models or nondiabetic patients (15). The hypoglycemic effects of Lactobacillus and Bifidobacterium have been investigated in several human studies. Several RCTs have suggested that probiotics and synbiotic compounds relieve or prevent increased blood glucose in diabetic and non-diabetic subjects (16). Previous studies have shown that the synergistic effects of synbiotic supplements on the intestine and immune system are significantly stronger than probiotics and prebiotics alone (17). Recently, few studies have also reported that synbiotic and probiotic intake can improve insulin sensitivity and reduce inflammatory factors (18). Therefore, many interventions have employed these dietary constituents to investigate their effects on lipid profile. However, the results of these studies are inconclusive. Therefore, the current study aims to investigate the effects of synbiotic consumption on lipid profile, including TC, TG, LDL-C, and HDL-C using randomized controlled trials (RCTs).

2. Materials and methods

2.1. Search strategy

To identify studies with information on the effects of synbiotic consumption on lipid profile in diabetic patients, we conducted a comprehensive search of literatures published before January 2021 in PubMed, Scopus, Google Scholar, Magiran, SID, and Cochrane library. Two reviewers searched the aforementioned databases to identify RCTs on the effects of synbiotic consumption on lipid profile, using the following MeSH and text keywords: ("synbiotic" or "symbiotics") and ("lipid" or "cholesterol" or "hypercholesterolemia" or "triglyceride" or "hypertriglyceridemia" or "TG" or "TAG" or "lipoprotein" or "LDL" or "LDL-C" or "HDL" or "HDL-C").

2.2. Study selection

Before the screening process, all publications identified through the literature search were exported to the Endnote X8 software (Clarivate Analytics, Philadelphia, PA) and checked for duplicated publications. Next, the title, abstract, and full text of potential studies were reviewed for eligible studies. Studies were considered eligible only if they: (1) were human clinical randomized controlled trials; (2) only included diabetic patients; (3) the intervention was synbiotic, and placebo/control foods/conventional products were applied as a comparison to the intervention; (4) reported change from baseline to endpoint for at least one of the following outcomes: TC, TG, LDL-C, and HDL-C. Trials were excluded if: (1) subjects had recently used the probiotics or antibiotics; (2) They administrated synbiotic in combination with any other drugs, minerals, or botanicals (unless a separate arm controlled the effect of the mixed substance); (3) Crucial data are incomplete; (4) studies that probably used relevant samples; (5) reported duplicate data (in this case, the one with complete follow-up and outcome measures was included).

2.3. Data extraction

The following information was extracted from each study: first author's name, publication year, location of studies, participant characteristics (including mean age, baseline body mass index (BMI), gender, and health status), the design of the study, duration of intervention, dose and type of intervention in experimental and comparison groups, probiotics strains, and mean and standard deviation (SD) of outcome measures at baseline, post-intervention and if possible their change from the baseline.

3. Results

3.1. Studies characteristics

Fig. 1 presents the flow chart of study selection. Overall, 11 studies (12, 15, 19–27) with a total of 662 participants were included in this analysis. Table 1 outlines the main characteristics of included studies. Included trials were conducted between 2012 and 2020. All studies followed a parallel design except two15, 20 that used a cross-over design. Of the 11 trials, 10 were conducted in Iran (15, 19–27) and 1 in Brazil (12). Men and women were included in all trials, except three studies (12, 21, 25) that included only women. Participants were in the age range of 4 and > 60 years. The total daily dose of probiotic consumption varied between 10^7-10^{10} colony-forming units (CFU), and the duration of administration varied between 4 to 12 weeks. Seven studies (12, 21–26) used a combination of more than one strain, and four studies (15, 19, 20, 27) used a single species of probiotics. Synbiotics were delivered via capsules in 6 trials (21–26), and in 5 studies (12, 15, 19, 20, 27) food was used as a vehicle for delivering synbiotics. The Control group consumed placebo capsules or control food. In 5 studies (15, 19–21, 27) participants adhered to a special diet or dietary/physical activity advice, but no specific recommendation or requirement was reported in other trials.

3.2. The effects of synbiotic consumption on TC

The effect of synbiotics consumption on TC was examined

in 11 trials (12, 15, 19–27). Overall, just one study showed that synbiotics significantly decrease TC (15).

3.3. The effects of synbiotic consumption on TG

Eleven trials reported on the effect of the synbiotics consumption on TG (12, 15, 19–27). Synbiotics significantly reduced TG compared to placebo in three studies (19–21).

3.4. The effects of synbiotic consumption on LDL

The effect of synbiotics consumption on TC was examined in 10 trials (15, 19–27). Overall, one study showed that synbiotics significantly decrease LDL-C15.

3.5. The effects of synbiotic consumption on HDL

The effect of synbiotics consumption on HDL-C was reported in 11 clinical trials (12, 15, 19–27). Synbiotic consumption significantly increased HDL-C level in 5 studies compared to control (12, 19, 22, 24, 25).

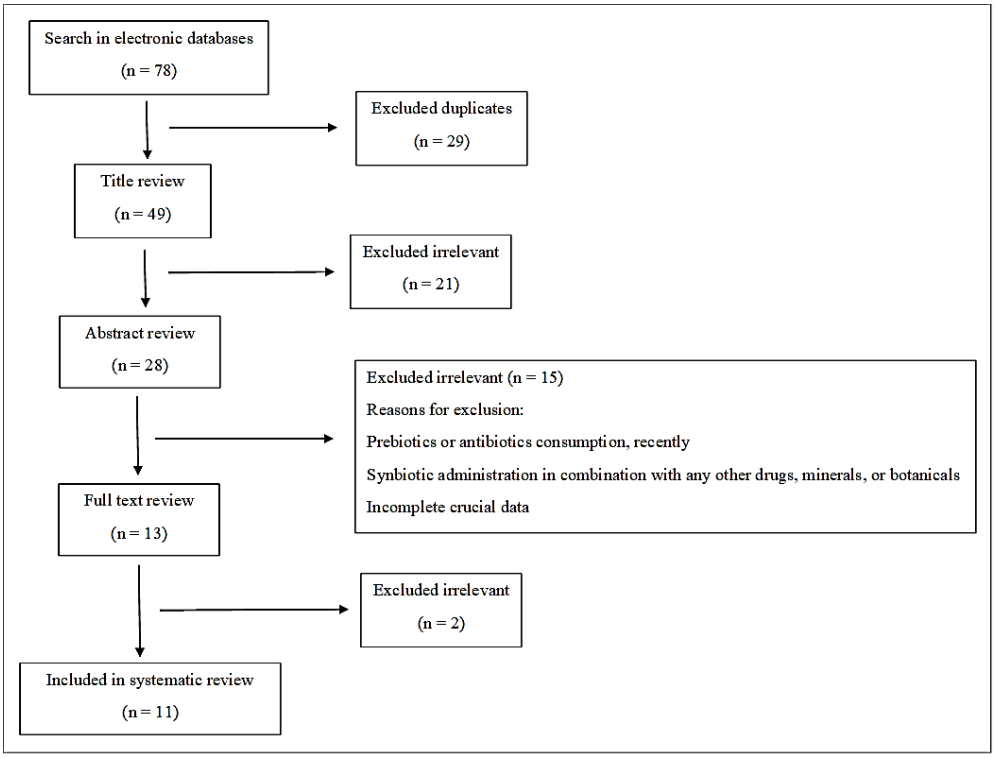

Fig. 1 Flow chart of study selection for inclusion in the systematic review

Table 1. Characteristics of included trials.

First author (publication year)	Country	Total sample size (M/F)	Target population	Mean age (year)	Mean BMI (Kg/m^2)	RCT design (blinding)	Duration (weeks)	Intervention of experimental group (Dose)	Number of bacteria	Intervention of control group	Outcomes
Moroti (2012) [12]	Brazil	20 F	T2DM	55	28	Parallel (Yes)	4	Synbiotic shake (1×10^8 CFU of *Lactobacillus acidophilus*, *Bifidobacterium bifidum* + 2 g fructooligosaccharide)	2	Placebo shake	TC, TG, HDL-C
Asemi (2014) [15]	Iran	19 M/43 F	T2DM	53	29	Cross-over (Yes)	6	Synbiotic food (1×10^7 CFU of *Lactobacillus sporogenes* + 0.04 g inulin)	1	Control food	TC, TG, LDL-C, HDL-C
Shakeri (2014) [19]	Iran	15 M/63 F	T2DM	53	30	Parallel (Yes)	8	Synbiotic bread (1×10^8 CFU of *Lactobacillus sporogenes* + 0.07 g inulin)	1	Control bread	TC, TG, LDL-C, HDL-C

Table 1. Characteristics of included trials.

First author (publication year)	Country	Total sample size (M/F)	Target population	Mean age (year)	Mean BMI (Kg/m^2)	RCT design (blinding)	Duration (weeks)	Intervention of experimental group (Dose)	Number of bacteria	Intervention of control group	Outcomes
Asemi (2015) [20]	Iran	16 M/32 F	T2DM	53	30	Cross-over (Yes)	6	Synbiotic fortified food (1×10^7 CFU of *Lactobacillus sporogenes* + 0.1 g + 0.05 g beta-carotene)	1	Control food	TC, TG, LDL-C, HDL-C
Ahmadi (2016) [21]	Iran	70 F	GDM	28	29	Parallel (Yes)	6	Synbiotic capsule (*Lactobacillus acidophilus*, *Lactobacillus casei* and *Bifidobacterium bifidum* (2×10^9 colony-forming units/g each) + 800 mg inulin) + lifestyle modification	3	Placebo capsule + lifestyle modification	TC, TG, LDL-C, HDL-C
Tajabadi-Ebrahimi (2016) [22]	Iran	30 M/30 F	T2DM	64	31	Parallel (Yes)	12	Synbiotic capsule (*Lactobacillus acidophilus* 2×10^9, *Lactobacillus casei* 2×10^9, *Bifidobacterium bifidum* 2×10^9 CFU/g + 800 mg inulin)	3	Placebo capsule	TC, TG, LDL-C, HDL-C
Ebrahimi (2017) [23]	Iran	42 M/28 F	T2DM	58	28	Parallel (Yes)	9	Synbiotic capsule (*Lactobacillus* family, *Bifidobacterium* family, *Streptococus thermophilus* + fructooligosaccharide)	3	Placebo capsule	TC, TG, LDL-C, HDL-C
Razmpoosh (2018) [24]	Iran	33 M/27 F	T2DM	60	27	Parallel (Yes)	6	Synbiotic capsule (*Lactobacillus acidophilus* [2×10^9 colony forming units (CFU)], *Lactobacillus casei* (7×10^9 CFU), *Lactobacillus rhamnosus* (1.5×10^9 CFU), *Lactobacillus bulgaricus* (2×10^8 CFU), *Bifidobacterium breve* (3×10^{10} CFU), *Bifidobacterium longum* (7×10^9 CFU), *Streptococcus thermophilus* (1.5×10^9 CFU + 100 mg fructooligosaccharide with lactose)	7	Placebo capsule	TC, TG, LDL-C, HDL-C
Nabhani (2018) [25]	Iran	90 F	GDM	30	27	Parallel (Yes)	6	Synbiotic capsule (*Lactobacillus acidophilus* (5×10^{10} CFU/g), *L. plantarum* (1.5×10^{10} CFU/g), *L. fermentum* (7×10^9 CFU/g), *L. gasseri* (2×10^{10} CFU/g) + 38.5 mg of FOS and lactose (300 mg), magnesium stearate, talc, colloidal silicon dioxide (each of them 5.5 mg)	4	Placebo capsule	TC, TG, LDL-C, HDL-C
Soleimani (2018) [26]	Iran	42 M/18 F	T2DM	62	26	Parallel (Yes)	12	Synbiotic capsule (2×10^9 CFU of *Lactobacillus acidophilus*, *Lactobacillus casei*,	3	Placebo capsule	TC, TG, LDL-C, HDL-C

Table 1. Characteristics of included trials.

First author (publication year)	Country	Total sample size (M/F)	Target population	Mean age (year)	Mean BMI (Kg/m^2)	RCT design (blinding)	Duration (weeks)	Intervention of experimental group (Dose)	Number of bacteria	Intervention of control group	Outcomes
Zare Javid (2020) [27]	Iran	21 M/23 F	T1DM	10	19	Parallel (Yes)	8	and *Bifidobacterium bifidum* + 0.8 g inulin) Synbiotic powder (*Lactobacillus sporogenesis* (1×10^9 CFU) + maltodextrin+ fructooligosaccharide)	1	2 g of starch powder with a glass of water once daily	TC, TG, LDL-C, HDL-C

4. Discussion

This review article presents evidence that synbiotic consumption may benefit lipid profile and improve dyslipidemia in patients with diabetes. Due to the synergic effect of probiotics and prebiotics in synbiotic supplements and foods, they may have greater potential in modulating the gut microbiota than either probiotics or prebiotics alone. It has been suggested that synbiotic supplementation may improve lipid metabolism, insulin resistance, inflammatory mediators, and liver enzymes markers by improving gut microbiota (28). The combination of probiotics and prebiotics may enhance the survival of bacteria passing the upper part of the gastrointestinal tract and reaching the large bowel, where they may colonies and change the balance of gut flora (29). The more pronounced effect observed on lipid profile from synbiotic supplements compared to synbiotic foods can also be explained by the potentially better survival rate of live cultures in the gastrointestinal tract in a form of supplement compared to food due to the extra protection provided by supplementation. The mechanism of the effect of synbiotic on lipid profile has remained largely unknown. Probiotics may improve serum lipid profile via their immunomodulatory properties (30). Probiotics may reduce inflammatory cytokines and Toll-like receptor 4 (TLR4) activation which may explain their beneficial impact on serum lipid profile (31). TLR4 is a transmembrane protein which when activated can lead to inflammatory cytokines production. These inflammatory cytokines are responsible for the activation of the innate immune system (32). Activation of the innate immune system through TLR4 is involved in the pathogenesis of insulin resistance, diabetes, and atherosclerosis (33). Also, probiotics are able to integrate cholesterol in their cellular membrane (34) or convert cholesterol into coprostanol (35) leading to a reduction in cholesterol absorption and serum TC levels. In addition, some probiotics can produce hydrolases that reduce cholesterol absorption via higher bile salt excretion (36, 37). Also, probiotics can produce short-chain fatty acids (SCFA) such as propionate and butyrate which are the product of prebiotics fermentation (38) SCFA prevent hydroxymethylglutaryl CoA reductase (HMG-CoA reductase) activation, which is a rate-limiting enzyme in the pathway of cholesterol synthesis, leading to lower cholesterol metabolism and better lipid metabolism (39). Another possible mechanism of the effect of synbiotics on lipid profile is by decreasing inflammation and insulin resistance, the storage of triglycerides in the liver, de novo lipogenesis driving by carbohydrate-responsive element-binding protein (ChREBP)/ sterol regulatory element-binding protein (SREBP), and very-low-density lipoprotein (VLDL) secretion. Synbiotics promote the secretion of fasting-induced adipose factor (FIAF), which in turn restrains endothelial lipoprotein lipase (LPL), which is responsible for releasing triglycerides from circulating chylomicrons and VLDL. Increased serum FIAF levels also lead to the deactivation of hepatic lipogenic enzymes by ChREBP and SREBP-1c, resulting in a reduction of triglyceride storage in adipocytes and the liver (40). Synbiotics may also increase circulating levels of glucagon-like peptide-1 (GLP-1). GLP-1 is involved in many metabolic pathways, including the stimulation of glucose-dependent insulin secretion, blockade of postprandial glucagon release, and induction of pancreatic beta-cell proliferation (41, 42). Literature suggests that GLP-1 directly hinders triglyceride absorption from the gut, potentially by inhibiting gastric lipases (43). There are some limitations in this study that should be taken into account when interpreting the results. First, a significant heterogeneity was detected between included studies. While the source of heterogeneity has been explored, other factors such as the dosage of synbiotic used, the health status of the included population, baseline age of participants, and study conditions may influence the heterogeneity. Second, most of the included studies were conducted in Iran. Therefore, it is difficult to generalize the results to the rest of the populations.

5. Conclusion

Conclusively, our systematic review and meta-analysis suggested that synbiotics consumption may be beneficial in reducing blood TC, TG, LDL-C and increasing HDL-C levels. More research with a larger sample size, different synbiotics dose, bacteria strains and prebiotics types are suggested to explore the effect and possible mechanism of the influence of synbiotics on lipid profile in diabetic patients.

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