Can probiotics be used as an adjuvant therapy for diabetes - hope or hype? Narrative review of the literature

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Abstract

Diabetes is a metabolic disorder that is characterized by inadequate insulin secretion by the pancreas or the lack in ability of the existing insulin to function properly. So, diabetes forms a fertile media for many diseases and embodies a risk to human-being's health. Unfortunately, the incidence of diabetes is increasing every year. Over decades, several strategies have been tried by specialists to control diabetes, some of which are medical and herbal.

Although diabetes mellitus represents a growing global epidemic disease, at the moment there is no absolute solution at the molecular level that targets the disease. Despite the fact that bacterial functions, such as gut barrier stability and butyrate production, are crucial for preserving normal blood sugar and insulin levels, a growing body of evidence suggests that some naturally occurring gut bacteria are underrepresented in the intestinal tracts of people with type 2 diabetes (T2D){Sharma, 2019 #8}.

In fact, we need to look at the possibility of using probiotics in the outpatient clinic. Probiotics have been demonstrated to be helpful for patients with diabetes mellitus, particularly at the cellular level, based on clinical trials and animal research, as well as their high tolerability. In preclinical investigations and human trials{Kocsis, 2020#7}, probiotics have shown that they can lower insulin and fasting blood glucose levels in people with diabetes. Recently, probiotics have been used to treat a range of ailments, such as autoimmune conditions, allergic reactions, and inflammation. However, there was a lot of heterogeneity in these trials. Examples include the kind of species used, how many probiotics are used, and the level of effectiveness.

In our review, we focused on reviewing the role of using probiotics as an adjuvant therapy for lowering blood levels of sugar and troubled metabolism of our body sugar.

Keywords: probiotics; diabetes; type 2 DM; inflammation; adjuvant therapy.

Introduction

Currently, 90–95 percent of all people with diabetes worldwide have diabetes mellitus (DM) type 2. one in five people are diagnosed with the chronic progressive disease type 2 diabetes Patients with insulin resistance and relative insulin insufficiency are included in this percentage (1). The percentage of diabetic patients was found to be 7 million of the population are diabetic and almost around 3 million have pre-diabetes{Galicia-Garcia, 2020 #9}.

As a result of hyper-insulinemia, insulin resistance and deficiency, and obesity, DM usually presents with other devastating illnesses such as dyslipidemia, hypertension, and cardiovascular (CVD) consequences (4). Also, the elevated lipid profiles among diabetic patients can lead to severe CVD disease and death (5). Also, hepatic and renal disease has been recorded (6).

There are some well established management strategies It includes weight loss by lowering caloric intake and glycemic index in diet and increasing physical activity as the first line for patients with type 2 DM (7).

Moreover, other strategies for lowering lipid parameters in diabetic patients have been advocated. They include using antioxidants, agents that lower the cholesterol, and mineral supplements (8). In recent times, limited studies (mainly on animals) have also concluded that expenditure of probiotics can improve the metabolic profiles (9). But these effects were noticed on animals and non-diabetic models.

Additionally, recorded data illustrating the effects of probiotics on serum lipid profiles are contradictory. Intake of a probiotic containing Lactobacillus acidophilus, fructo-oligosaccharide, inulin and mannitol for 8 weeks resulted in decreased serum triglycerides (TAG), total cholesterol (TC) and LDL-C levels as well as increased HDL-C concentrations in hypercholesterolemic pigs (10). A study conducted on a healthy pregnant women showed decreased serum TAG and VLDL-C levels following consumption of probiotic food containing heat-resistant Lactobacillus sporogeneses and 0.04 g inulin as prebiotic per one g after nine weeks (11).

The enzymatic deconjugation of bile acids (12), assimilation of cholesterol in the gastrointestinal tract, production of short chain fatty acids (SCFA), carbon disulfide, and methyl acetate, and conversion of cholesterol into coprostanol in the gut could all contribute to the positive effects of probiotics and probiotics on lipid profiles (13).

There are no obvious trials studying the effects of daily usage of probiotic on lipid profiles in diabetic patients. Although, some clinical trials on human samples using various probiotics have shown a mixed result. Some of these studies found no effect (14), while other studies have found obvious evidence of probiotics on lowering blood glucose(15).

We aim in the current review to inspect the effects of regular expenditure of probiotics and their effect on lipid profiles in patients with T2DM.

Methods

We conducted a thorough literature search till April 2022 using PubMed dataset. We used the subheadings and the following keywords accordingly, “Probiotics; Bifidobacterium; bifidum, Fructo-oligosaccharide; Lactobacillus acidophilus; Microbiota; Diabetes; Glucose; Review

History of probiotics

Live, non-pathogenic organisms are considered probiotics. Health advantages can be conferred on the host when consumed in the proper dosages. Probiotics and humans have a long history of interaction. They are frequently utilised commercially as a functional food and are well recognised as “health-friendly bacteria.” Probiotics have become significantly more popular as a result of the growing body of clinical research demonstrating their positive effects. Numerous in vivo and in vitro experimental studies have shown that probiotics can prevent and treat a variety of diseases, including ulcerative colitis and diarrhoea brought on by antibiotics. Additionally, a number of recent studies have suggested that probiotics may be effective in treating a wide range of metabolic, lifestyle, and diet-related illnesses, such as obesity, type 2 diabetes, metabolic syndrome, and irritable bowel syndrome. The most popular probiotic strains are those of Bifidobacterium, Lactobacillus, and Saccharomyces boulardii.

Pathophysiology

The effect of probiotics on glucose metabolism could be mediated in a variety of ways. According to several researchers, oxidative damage and antioxidative activity play an essential role in the etiology of diabetes (16, 17). The capability of probiotics has been established in earlier experiments (18). In diabetic rats, Yadav et al. discovered that probiotics reduced oxidative damage by preventing lipid peroxidation and boosting the antioxidant content of glutathione, superoxide dismutase, catalase, and glutathione peroxidase (19). Secondly, probiotics have been shown to have anti-diabetic effects against insulin resistance by boosting natural killer T (NKT) cells in the liver. By regulating TNF-expression and decreasing NF-B binding activity, probiotic therapy decreased insulin resistance and inflammation (20). Furthermore, probiotics may improve glucose metabolism by boosting gliclazide bioavailability, blocking or delaying glucose absorption in the intestine, and altering autonomic nervous system activity(21, 22).

Probiotics are live microorganisms that have a significant impact on healthy and diseased cases (23, 24). They have been investigated for their potential health advantages in terms of immune system function and diarrhea prevention (25, 26). Probiotics have also been shown in animal models to lower blood glucose levels by improving inflammation and preventing cell death (27).

Evidence of probiotic use for diabetic patients

Ten articles using varied methodologies and comparative groups were examined. The conclusive evidence is still debatable and questionable. The majority of studies used animal models and showed no statistically significant difference between actual results and projected results. These results, however, cannot be regarded as conclusive evidence for the beneficial role of probiotics in the treatment of diabetes because of variations in the groups tested in each trial. Zheng 2019 conducted a systematic review and meta-analysis study (28) which concluded that probiotics and synbiotics have a positive impact on diabetic patients, according to a study that looked at sixteen randomized control trials with a total of 1060 cases. All inflammatory markers were decreased (hs-CRP and MDA with the P-value equal to 0.000 for both), and oxidative stress was increased as follows (TAC with the P-value equal 0.006, NO with the P-value equal 0.001, GSH with the P-value equal 0.000). These findings concurred with those of Tabrizi et al (29).

An update of Meta-Analysis by Liang et-al 2021 (30) discovered that using various probiotic supplements raised insulin resistance and decreased FBS. This study, involved 818 diabetes individuals from 8 different nations, age, body mass index (BMI), and the length of time a probiotic supplement was taken, to show its effectiveness. On HbA1c, Jafarabadi et al. 2021 provided insight. Probiotics were discovered to have a P-value of 0.01 for lowering HbA1c, FBG, and insulin levels. Probiotics with selenium can lower fasting blood sugar (FBS), insulin concentration, and insulin resistance with P-values of 0.004, 0.002, and 0.001 correspondingly, according to an RCT by Amirani et al. 2022 done on 60 cases evaluating the effect of probiotic and selenium vs. placebo, where insulin sensitivity was significantly increased with P-value 0.002. Another SR and MA study by Pan et al (31) found that probiotics can reduce fasting serum insulin (P-value 0.00001) but, fasting plasma glucose wasn't reduced (p-value 0.09). Other systematic reviews and meta-analyses (32-35) support the role of probiotics in patients with diabetes especially at cellular level. We summarized some of these studies in Table 1.

Table 1: GDM; gestational diabetes mellitus, T2DM; type 2 diabetes mellitus, CRP; C - reactive protein, NO; nitric oxide, FBG; fasting blood glucose.

ID	Disease	Number of patients treated	Design	Main outcomes	Main finding
Zheng 2019	Diabetic patients	1060 cases were randomly distributed into probiotic and/or synbiotic (n = 533) or into control (n = 527) groups.	Systematic review and meta-analysis	Inflammatory markers in diabetic patients	Probiotics and synbiotics had a positive effect on serum hs-CRP and MDA levels, which were significantly decreased And increased oxidative factors like TAC, NO, and GSH.
Liang 2021	Cases with type 2DM	818 of cases from 8 countries	An update of MA	glycemic, lipid, blood pressure and inflammatory biomarkers	Probiotics improve glycemic and inflammatory markers in diabetic patients especially those with age less than 50 and BMI less than 30
Jafarabadi 2021	Diabetic patients	-	Update of evidence	Glycemic control	HbA1c and insulin level could be decreased when using probiotic supplements rather than foods
Ding 2021	Patients with type 2DM	423 diabetic patients	SR&MA	Inflammatory markers in diabetic patients	Probiotics can improve inflammatory biomarkers and glucose level in patients with T2DM. Probiotics could be used as adjuvant therapy for T2DM
Pan 2017	Patients with GDM	830 Patients with GDM	SR&MA	Gestational DM	Probiotics could reduce serum insulin but not FBG
Amirani 2022	GDM	60 cases with GDM divided into 30 in the intervention group and 30 in the control group	Randomized control trial	Glycemic control and lipid profile in patients with GDM	Probiotics and selenium can reduce both FBS and insulin. Also, can increase insulin sensitivity in patients with GD

Limitations

The research featured used various approaches, which may have resulted in information bias. Some trials reviewed synbiotics instead of probiotics alone, and there was non-uniformity in the comparisons made across the investigations of the different groups. Furthermore, many routing factors, such as impaired nutritional condition (36) unquestionably affect outcomes and complications in diabetic patients. It is also difficult to establish clinical practice recommendations due to the wide diversity of probiotic strains, time spent using probiotics, and daily doses used in the studies (28).

Recommendations

While, no definite conceptual proof of the effect of probiotic therapy on diabetic patients has been properly demonstrated, the cause-effect association that may be created by the supplementations, as an example, was not visible in the most critical investigation till now. Furthermore, records that could explain the biological mechanics of such supplements are unavailable.

Due to the relatively recent approval of probiotics in clinical practice, the database, which includes biological agents with various action mechanisms, is still in its early years in global literature. More clinical trials, as presented in this review, are needed to address concerns about probiotic bacterial species, treatment course, and daily dosage of therapy (37). Neither the included studies nor the evaluation of the impact of active probiotics on the regulation of gut hormones profiled changes in gut microbiota (38). Consuming live bacteria, particularly those present in fermented foods, may improve the harmony between intestinal permeability and barrier performance. A current focus of scientific and medical research is the microbiome (39). A larger panel of stool and serum surrogate markers should be used in well-designed RCTs to uncover explanations and processes.

In order to design an effective study that will produce more meaningful results to resolve the controversy and aim for more reliable and high-quality evidence, we also advise prospective analysis and trials enroll a significant case sample with strict details and more comparison groups than are currently used.

Conclusions

Probiotic usage appears to be beneficial for people with DM; nevertheless, further prospective interventional research, mostly using human models, is required to fully understand the impact of probiotic use in diabetic patients. Even if the majority of the cited research demonstrated a statistically significant reduction in patients' levels of diabetes and improvement in other inflammatory outcomes, a conclusive connection from the available data is still debatable. Each case should receive a unique, interdisciplinary assessment, and decisions should be made while modifying the molecular and cellular mechanism of action in humans.

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