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ORIGINAL

The effect of Familact probiotic supplement in patients with diabetes

(Evaluation of Blood Glucose Parameters, Lipid Profile)

El efecto del suplemento probiótico Familact en pacientes con diabetes
(Evaluación de glucosa en sangre y perfil lipídico)

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Abstract

Due to the increasing prevalence of this disease, the present study was performed to investigate the effect of pure probiotic supplement Familact on fasting blood glucose and insulin indices and lipid profile of patients with type 2 diabetes. This double-blind randomized controlled clinical trial was performed on 60 patients with type 2 diabetes. The subjects in the Moore intervention group received 7 probiotic capsules containing 7 strains of a mixture of Lametobacillus and Bifidobacterium, at a dose of 1010 CFU, and the placebo group received 4 placebo capsules containing magnesium stearate daily for 6 weeks. Dietary intake, anthropometric indices including weight, body mass index, waist circumference, waist circumference and hip circumference, along with biochemical indices including fasting blood sugar, fasting blood insulin and lipid profile were measured and evaluated at the beginning and end of the study. Statistical analysis was performed using SPSS software using chi-square test, t-test and analysis of variance. Finally, it was observed that the mean fasting blood sugar in the probiotic group was significantly lower than before the intervention (P = 0.001). Also, at the end of the study, the amount of HDL cholesterol in the probiotic group was significantly increased compared to the amount before the intervention (P = 0.006), but this increase was not significant in comparison between groups. Minor and intragroup increases in blood insulin and cholesterol, decrease in LDL cholesterol and insulin and triglyceride resistance were also not significant.

Keywords: Probiotics, type 2 diabetes, fasting blood sugar, insulin, lactobacillus.

Resumen

Debido a la creciente prevalencia de esta enfermedad, el presente estudio se realizó para investigar el efecto del suplemento probiótico puro Familact en los índices de glucosa e insulina en sangre en ayunas y en el perfil lipídico de los pacientes con diabetes de tipo 2. Este ensayo clínico controlado y aleatorizado a doble ciego se realizó en 60 pacientes con diabetes de tipo 2. Los sujetos del grupo de intervención Moore recibieron 7 cápsulas de probióticos que contenían 7 cepas de una mezcla de Lametobacillus y Bifidobacterium, a una dosis de 1010 UFC, y el grupo de placebo recibió 4 cápsulas de placebo con estearato de magnesio al día durante 6 semanas. Al principio y al final del estudio se midieron y evaluaron la ingesta dietética, los índices antropométricos, como el peso, el índice de masa corporal, el perímetro de la cintura y el perímetro de la cadera, y los índices bioquímicos, como la glucemia en ayunas, la insulina en ayunas y el perfil lipídico. El análisis estadístico se realizó con el programa informático SPSS mediante la prueba de chi-cuadrado, la prueba t y el análisis de la varianza. Se observó que la media de azúcar en sangre en ayunas en el grupo probiótico era significativamente menor que antes de la intervención (p= 0.001). Asimismo, al final del estudio, la cantidad de colesterol HDL en el grupo probiótico aumentó significativamente en comparación con la cantidad anterior a la intervención (P = 0.006), pero este aumento no fue significativo en la comparación entre grupos. Tampoco fueron significativos los aumentos menores e intragrupo de la insulina y el colesterol en sangre, la disminución del colesterol LDL y la resistencia a la insulina y los triglicéridos.

Palabras clave: Probióticos, diabetes de tipo 2, glucemia en ayunas, insulina, lactobacillus.

Introduction

Today, diabetes is one of the most common diseases in the world, affecting half of the world's population. Treatment for diabetes varies depending on the type[1-3]. In type 1 diabetes, the main treatment is based on insulin intake as the most important chemical drug, while in type 2 diabetes, due to environmental factors, the main and various treatments, including drug and chemical treatments, lifestyle changes (increased physical activity, reduced stress) [4-6]. And smoking cessation) and diet changes and natural remedies. Therefore, in type 2 diabetes, today, most efforts are made to reduce the number of chemical drugs used in this disease by using lifestyle changes and natural remedies, including herbal remedies and other natural substances[7-10].

Even prevented the disease. Because doctors are increasingly emphasizing the diagnosis of latent diabetes as a way to prevent type 2 diabetes, as well as its complications, including cardiovascular, eye and kidney problems[11-13]. For this reason, in this study, the effect of probiotics as a natural substance that can have therapeutic or preventive properties on type 2 diabetes is investigated. Therefore, in this project, in order to investigate the possibility of prescribing probiotics as a dietary supplement to help treat or reduce the complications of diabetes along with diet and medication and in the next stage, its use in the production of probiotic dairy and non-dairy products, its effect on patients with type 2 diabetes will be discussed. research questions:

1. Is the mean and difference of mean lipid profile (plasma concentration of HDL-C, LDL-C, Total Cholesterol, TG) between the two groups of patients with type 2 diabetes receiving probiotics and placebo, before and after the intervention and in each Are the two groups different before and after the intervention?
2. Are the mean and mean differences in fasting plasma glucose levels between the two groups of patients with type 2 diabetes receiving probiotics and placebo, before and after the intervention, and in each of the two groups, before and after the intervention?
3. Is the mean and mean difference in plasma insulin levels between the two groups of patients with type 2 diabetes receiving probiotics and placebo, before and after the intervention, and in each of the two groups, before and after the intervention?

Research Hypotheses

1. Mean and difference of mean lipid profile levels (plasma concentrations of HDL-C, LDL-C, Total Cholesterol, TG), between two groups of patients with type 2 diabetes receiving probiotics and placebo, before and after the intervention and in each It differs from the two groups.
2. Mean and difference of mean fasting plasma glucose levels between the two groups of patients with type 2 diabetes receiving probiotics and placebo, before and after the intervention and in each of the two groups, before and after the intervention.
3. Mean and difference of mean plasma insulin level between the two groups of patients with type 2 diabetes receiving probiotics and placebo, before and after the intervention and in each of the two groups, before and after the intervention. Mean and difference of mean level of insulin resistance index (HOMA-IR) between the two groups of patients with type 2 diabetes receiving probiotics and placebo, before and after the intervention and in each of the two groups, before and after the intervention. Mean and difference of mean level of anthropometric indices (weight, body mass index, abdomen circumference and hip circumference) between two groups of patients with type 2 diabetes receiving probiotics and placebo, before and after the intervention and in each of the two groups, before is different from after the intervention.

A review of Studies

Despite the wide range of animal studies around the world, most of the studies conducted in Iran to measure the effect of probiotics on blood parameters of people with type 2 diabetes have been human studies[14-18].

However, these studies make up the bulk of human studies available worldwide. The first human study conducted in Iran was conducted in Shiraz in 2010 by Ms. Mazloum et al in their study, they examined the effect of daily intervention on a number of probiotic capsules containing 1,500 mg of L. bacteria. acidophilus L. bulgaricus, L. bifidum, and L. casei or placebo capsules, containing 1000 mg of magnesium stearate, in 40 diabetic patients (20 in the intervention group and 20 in the placebo group), for 6 weeks they paid. Finally, despite a significant reduction in waist circumference of the intervention samples compared to the placebo group, no significant changes were observed in the patients' blood sugar, blood insulin and other blood factors[19-22].

It should be noted that after measuring the quality of human articles through the Jadad scale, this study did not obtain a sufficient and desirable score in terms of the quality of clinical studies[23].

Ms. Ijtihad et al. they intervened. Unlike Mazlum et al, they were able to report a significant reduction in fasting blood sugar levels as well as glycosylated hemoglobin in patients. But they did not see a significant difference in blood insulin levels and insulin resistance at the end of their study[24-28].

In several animal studies, the effect of probiotics on the control of fasting blood sugar has been found to have

a significant effect on lowering fasting blood sugar in various ways[29-31].

Most of the strains used were Lactobacillus and Bifidobacterium. The intervention period of these studies varied from 3 to 8 weeks, except for two studies that Hsieh et al[32] and Andersson et al[33] respectively. Finished at 14 and 18 weeks. The results of this study showed significant and positive effects on lowering blood sugar in diabetic rats without any side effects. It is also noteworthy that these significant effects were seen from the sixth week of the study until the end of the intervention period.

The results of a study by Honda et al in 2012[34] showed that the use of Lactobacilus GG strain in diabetic rats in 2 stages of 3 and 6 weeks, separately and in daily doses of y% and 0.5%, respectively. 0% of the solution enriched with the mentioned bacteria causes a significant decrease in the levels of Nasha blood sugar, 5-hour blood sugar and glycosylated hemoglobin, while the use of Lactobacillus Bulgricus strain during these two stages showed a significant result in none of the indicators. This study showed that Lactobacilus GG was more potent than L. Bulgaricus and had a greater effect on intestinal metabolic activity. In a 2013 study, Huang et al examined the effect of Lactobacillus Plantarum on four distinct groups. These 4 groups included the control group, the group receiving Lactobacillus Plantarum pure and at a daily dose of 108 CFU, the group receiving fermented vegetables and the group receiving a mixture of Lactobacillus Plantarum and fermented vegetables. They found that the intervention of these substances separately for 8 weeks significantly reduced blood sugar and significantly increased blood insulin in diabetic rats[35].

In fact, this study showed that probiotics can play a positive role in glycemic control even without the presence of prebiotics as a carrier and adjuvant effect. In a study, Tomaro et al found that high doses of L. fermentum (1010 CFU) significantly decreased blood sugar levels in diabetic and hypercholesterolemic mice only 11 days after the start of the intervention, which remained at the end of 8 weeks of intervention. Remaining and even at the end of this period, fasting blood sugar levels of diabetic rats showed a significant decrease.

However, they did not report significant changes in blood insulin levels, insulin resistance, and glycosylated hemoglobin[36].

On the other hand, Hsieh et al in a study conducted in 2013, stated that the daily intervention of high dose of L. reuteri (109 2 CFU) for 14 weeks increases the beneficial intestinal flora of Bifidobacteria (Lactobacilli) and Lactobacilli) and reduces harmful bacteria. It becomes the gastrointestinal tract (Clostridia) and therefore can have beneficial effects on controlling blood sugar in diabetics. At the end of their intervention period, they observed a significant decrease in fasting blood sugar, glycosylated hemoglobin, 5-hour blood sugar and insulin resistance, as well as a significant increase in blood insulin levels in diabetic mice receiving probiotics compared to the healthy or placebo group[37].

Alsalami et al. Also stated that daily intervention of a mixture of L. acidophilus, L. rhamnosus and B. lactis at a dose of 75 mg / kg body weight in mice for only 3 days had significant hypoglycemic effects, especially in early-stage diabetes develops in diabetic rats and decreases serum glucose sub-graph (AUC)[38]. In this study, they showed that probiotic intervention after administration of glycilazide (a hypoglycemic drug) increased the bioavailability of this drug in mice with type 1 diabetes compared to non-diabetic mice.

Research Method

In the simple random method of this study, the Balanced Block method is also used to reduce possible errors. In fact, in this method, patients are divided into m groups and in each group, they are randomly selected so that they are randomly assigned to treatment A and B and finally each group is randomly selected. This method assigns the same treatment to each group.

Research Community

With inclusion and exclusion criteria Patients with type 2 diabetes referred to Metabolism Research Center who were willing to cooperate were invited to study. Main criteria for inclusion in the study and sample selection: Patients whose blood sugar is defined according to WHO or ADA index (non-insulin dependent diabetes due to non-response of the body to secretory insulin and often due to obesity and inactivity) and less It takes 15 years for them to develop diabetes and they will be in the age range of 25 to 65 years. Selected individuals, in addition to taking medications prescribed by a physician, should be at a controlled level in terms of blood sugar and lipids, and during the study can use these drugs without changing the previous dosage[39].

Selected individuals should not use hormone replacement therapy or vitamin supplements. Also, people who smoke and drink alcohol or who have chronic kidney, liver, lung, and chronic or acute inflammatory diseases (especially acute pancreatitis and endocarditis), heart valve disease, short bowel syndrome, and allergies. People with low immune systems (autoimmune) and pregnant and lactating women were removed from the list of eligible people. (These conditions were confirmed by the clinical consultant in the case of the subjects).

Exclusion Criteria

People who become allergic to probiotic or placebo capsules during the study, or become pregnant during the study, or develop one of the above-mentioned diseases, or have to change the dosage of medications, will be excluded from the study. Also, people who took less than 10% of probiotic capsules or placebo were excluded from the study.

Sampling method and sample size: Specifications of the studied samples (entry and exit criteria) along with sampling method and sample size.

Determining the sample size and how to calculate it (Sample Size): Considering α error of 0.05 and 80% power and considering Total Cholesterol = 0.25 = mmol / yr, standard deviation of 2.5 and variance of 6.25, and considering drop of 32 samples per drop in each group and in total 64 people were studied. The sample size is calculated based on the above assumptions and using STATA software and considering the equal volume in each of the groups. Formula 1, the desired formula in calculating the sample size.

$$n = \frac{2\delta^2\left(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta}\right)^2}{(\mu_1 - \mu_2)^2}$$

$Z_{1-\alpha/2}$ =96/1 95% δ = 2.5
$Z_{1-\beta}$ = 84/0 80% μ-1 μ2 =2

Sampling

After approval by the Medical Ethics Committee and determination of 64 patients (32 in each group) participants who were willing to cooperate and signed the informed consent, using the Balanced Block method (division of individuals into equal groups) with the same size, random selection of individuals in each group to receive capsule or placebo treatment) were included in the study and were divided into one of two intervention groups (probiotic capsule recipient) and placebo (placebo recipient). Data were collected through interviews, anthropometrics, and biochemical tests.

Data Collection Tools

The questionnaire used in collecting and evaluating the food consumed by the participants was a 24-hour feed questionnaire as well as a food frequency questionnaire (FFQ) and a questionnaire to measure their physical activity, each before and after the intervention by the facilitator and separately for each participant was completed. After collecting the food information of the participants, the average information in the mentioned questionnaires was converted into home units in terms of grams and entered into the Nutritionist 4 software to calculate the calories consumed micronutrients and macronutrients.

Then, the information obtained from this software along with other information and findings were entered into EndNote software version 16 for final analysis of information. To measure the weight before and after the intervention of each participant from a digital scale with an accuracy of 1.0 kg. The German model "Ska" was used. Also, to measure their height, a portable height gauge with an accuracy of 0.1 cm (Ska model, made in Germany) was used. The size of their breasts, abdomen and hips were also measured using a plastic meter before and after the intervention. For the intervention capsules, the strains used per gram of Familact supplement capsules are as follows:

- Lactobasillus casaei 2×10^8 cfu/g
- Lactobasillus Acidofilus 2×10^8 cfu/g
- Lactobasillus Bulgarigus 2×10^9 cfu/g
- Lactobasillus rhamnosus 3×10^8 cfu/g
- Bifidobacterium Breve 2×10^8 cfu/g
- Bifidobacterium Longum 1×10^9 cfu/g
- Streptococus Thermophilus 3×10^8 cfu/g

The total dose for each of the 7 strains is 1010 CFU per. Capsule. Patients' venous blood samples at the beginning and end of the study, which were taken at a rate of 5 cc each time for 10 hours of fasting, were poured into 1 ml microtubes and stored in a freezer at -70 ° C until the experiments. Serum glucose, total cholesterol and triglyceride levels were measured by calorimetric method (based on enzymatic method (Glucose Kit, Pars Azmoun Company, USA-France), Alcyon Iran) and autoanalyzer 300 (HDL and LDL cholesterol concentration using Photometric method, Pars Azmoun Company, USA-France and Alcyon Iran) and autoanalyzer (300 were measured).

Table I: Summary of application descriptions.

Name of equipment or materials	Consumption or non-Consumption	Required number
Familact probiotic supplement	Consumption	210
Placebo capsules	Consumption	150
single-use glove	Consumption	100
Microtube 1.5 cc	Consumption	25
5 ml blood collection syringe	Consumption	140
Insulin Kit	Consumption	1
Glucose kit and lipid profile	Consumption	y
Blue sampler head	Consumption	3
Yellow sampler head	Consumption	3000
Disposable test tube	Consumption	280
Micro tube	Consumption	3
Micro tube	Consumption	1000
Small packet milk	Consumption	144

Data Analysis Method

Numerical indicators and frequency tables were used to display the data, so that the data is shown as an average (standard deviation) for quantitative variables and as a frequency (percentage) for qualitative variables. In general, SPSS software version 16 was used for data analysis. The normality of data distribution was assessed using Kolmogorov-Smirnov test. Chi-square test and Fisher's exact test were used to analyze the qualitative data. T test and paired T test were used to compare quantitative traits. Analysis of variance with repetitive data was used to investigate the trend of quantitative trait changes between the two groups by controlling confounders. Significant level was considered P <0.05 in all cases.

Place and Time of Study

The sampling of this project started, from patients with type 2 diabetes, and having the conditions for inclusion in the study mentioned in the proposal, was performed from Taleghani Hospital. On Saturday, Tuesday, and Wednesday, patients were referred to Taleghani Hospital in Tehran, Velenjak St., Yemen St.

Therefore, the facilitator was present at the hospital on the mentioned days and talked orally with the patients about the free probiotic supplement intervention plan and its possible benefits in reducing the complications of diabetes.

Some people participated in the project voluntarily. Patients referred to clinic department, on Sundays,

Table II: Basic information of individuals.

*P	Medicine	Probiotic group	
P=0/020	61,3± 5,2	57/3±7/5	Age (years)
P=0/438	Woman(n=14) 46%/7 man(n=16) 53%/3	Woman(n=13) 43%/3 man(n=17) 56%/7	man / Woman (percentage and number)
P=0/612	154/4 ±9/08	164/89 ±9/29	Height (Sunni meters)
P=0/697	5/8 ±2/8	6/16 ±3/05	Period of diabetes (year)
P=0/712	7% 47% 46%	5% 45% 50%	Physical activity (percentage) Top · medium · Low
P=0/186	41%/7 53%/3 5%	44%/7 51%/3 4%	Medications received (percentage) · Matt Fermin · Glybine glamide · Other medicines

Table III: Comparison of the effect of probiotics on biochemical parameters before and after the intervention in the groups.

The value of P between groups †	Placebo group			Probiotic group			Variables
	Intragroup P value*	After the intervention	Before intervention	Intragroup P value*	After the intervention	Before intervention	
P=0/610	P=0/910	147/0±36/3	146/8±35/1	P=0/001	132/7±33/6	146/5±4/3	Fasting blood sugar (mg /dl)
P=0/811	P=0/713	153/8±38/5	155/1±33/9	P=0/510	151/4±35/y	149/3±36/3	Total cholesterol (mg/dl)
P=0/521	P=0/423	153/8±38/5	151/1±33/9	P=0/100	135/3±61/3	141/8±62/3	Triglyceride (mg/dl)
P=0/823	P=0/832	44/5±6/9	44/6±6/0	P=0/006	46/3±10/8	44/y±11/7	HDL cholesterol (mg/dl)
P=0/715	P=0/810	81/9±36/0	82/5±31/1	P=0/812	77/5±31/y	79/4±39/y	LDL cholesterol (mg/dl)
P=0/412	P=0/931	10/5±5/0	10/5±5/6	P=0/913	10/5±5/1	10/3±6/5	Fasting insulin µU/ml
P=0/410	P=0/641	3/7±1/8	3/6±1/7	P=0/112	3/3±1/6	3/7±2/7	Insulin resistance (/U/ml/mg/dl)

HDL: High Density of Lipoprotein
LDL: Low Density of Lipoprotein

*Comparison within the group at the end of the intervention, the value of P is less than 0.05. (Fasting blood glucose unit is mg / dL.) The mean fasting blood glucose before intervention in the probiotic group was 146.5 43 43.6 mg / dL and after the intervention in this group was 33.6, reached 132.7 mg / dL. While the mean of this index before and after the intervention in the placebo group was 146.8 35 35.1 and 147 36 36.3 mg / dl, respectively.
Based on analysis of variance, comparing the mean blood sugar after the intervention, it was found that the mean of this index decreased in the probiotic group compared to the placebo group, but this decrease did not reach a significant level (P = 0.1).
In contrast, the intragroup comparison showed that this decrease reached a significant level after the probiotic intervention compared to before the intervention in the intervention group. Also, the mean HDL cholesterol before the intervention in the probiotic group was 44.1 1 1.1 mg / dl and the mean in this group after the intervention reached 46.29 mg/dl.
While the mean of this index before and after the intervention in the placebo group was 44.6 0 0.6 and 45.4 9 6.9 mg / dl, respectively. Based on analysis of variance, comparing the mean HDL cholesterol after the intervention, it was found that the mean of this index increased in the probiotic group compared to the placebo group, but this increase did not reach a significant level (P = 0.4). In contrast, the intragroup comparison showed that this increase reached a significant level after the probiotic intervention compared to before the intervention in the intervention group.

*Comparison within the group at the end of the intervention, the value of P is less than 0.05. (The unit of fasting blood sugar is milligrams per deciliter.) Comparison between group and intragroup other biochemical parameters showed that blood insulin levels and insulin resistance in the probiotic group compared to the placebo group did not change significantly. Also, in relation to lipid profile levels, no significant intragroup and intergroup changes were reported for total cholesterol, triglyceride and LDL cholesterol indices.
Regarding anthropometric variables, weight, waist circumference and body mass index in both groups decreased slightly compared to the initial value, which did not reach a significant level. Also, changes in waist circumference and hip circumference did not change significantly. (All values are P <0.05).

Mondays, and sometimes Tuesdays. The day before each patient was referred, I reminded them by phone of the date of the test. The number of patients referred per day varied from 2 to 5 (due to limited admission conditions). The duration of intervention was 6 weeks for each patient.

The difference between groups at the beginning of the study was significant in terms of P <0.05. Numbers are expressed as "standard deviation mean" and "percentage". Measurement of basal food intake (before intervention) including energy intake, micronutrients and macronutrients in the intervention subjects, which was measured by N4 software, showed that there was no significant difference between the energy intake of individuals before the intervention. This comparison also showed that there was no significant difference between micronutrients and macronutrients, except for sodium, vitamin D, vitamin E, and PUFA, sodium and selenium intake (P <0.05).

Therefore, to compare the mean of the variables after the intervention, the distorting effect of age nodes, sodium, selenium, vitamin D and vitamin E intake and PUFA intake were adjusted. After comparing the diets of patients before and after the intervention, it was shown that there was no significant difference between energy intake, and all macronutrients and micronutrients (P <0.05). **Table III** lists the information related to the analysis of food intake of individuals before and after the intervention.

Discussion

The effect of probiotics on fasting blood sugar

The present experimental study showed that the intervention of probiotics without changing the diet or applying a special diet in individuals, can significantly reduce fasting blood sugar (FPG) in the probiotic group, while this reduction in comparison between the probiotic group and the placebo group Did not reach a significant level. Positive effects of probiotics on the control and improvement of FPG were seen in many animal studies. In several animal studies that examined only fasting blood sugar, significant effects on FPG reduction were observed within the intervention group and between the placebo and intervention groups. However, there are many differences between the study method and the groups tested in these studies. In fact, this effect was significant in the probiotic intervention group compared to the diabetic and non-diabetic groups receiving placebo[40], the fat-rich diet group[41], Huang et al or fructose[42], (used to cause diabetes), the group receiving a diet rich in fermented vegetables[43], and the group receiving skim milk[44], has been seen. In the present study, from 7 different strains including 3 species of Lactobacillus (Lactobasillus casaei, Lactobasillus acidophilus, Lactobasillus Bulgarigus, Lactobasillus rhamnosus), 2 strains of Bifidobacterium (Bifidobacterium Brev, Bifidobacterium longum) and 10 strains of Cocene 1 Each. Capsule was used. In all of these animal studies, a class of the same bacteria called Lactobacillus was used.

However, different species such as L. reuteri GMNL-, L. plantarum, L. fermentum, Lactococcus lactis, L. rhamnosus GG and L. bulgaricus have been used in each study; In only two studies, a mixture of L. fermentum, L. acidophilus and Bifidobaterium lactis or a mixture of Lactobacillus casei and Lactococcus lactis biovar diacetylactis was used. The dose of probiotics intervened in these studies varies from 108 to 1010 CFU per gram of body weight or ml of gavage per sample per day. The time of intervention also varied from 3 to 8 weeks, except for a study conducted by Hsieh et al at 14 weeks[44], and Andersson et al at 20 weeks[45].

In the study of Honda et al., 2 intervention sessions were performed separately; They believed that the effect of probiotics on diabetes control was not due to cellular components and immune factors, but to the type of bacterial strain and its ability to be active in the gut. In conclusion, in this study, they examined the effect difference between L.GG and L. bulgaricus for 6 weeks and at a daily dose of 0.5% and also the effect difference between active L. GG and L. ggar heated for 3 weeks and at a daily dose of 2%, and found that only active L. GG significantly reduced blood sugar in both groups[46].

In general, animal studies show that Lactobacillus strain intervention can have positive effects on lowering blood sugar in diabetic animals; Also, although in these studies the minimum daily dose of 108 CFU was reported in each mouse and the minimum duration of intervention was 3 weeks, it is not possible to determine the effects of the effective dose and period of intervention and the effect of different species.

However, the results of the present study also showed a significant decrease in the probiotic group before and after the intervention, although this reduction was not significant compared to the placebo group. In contrast, very few human studies are correct. Similar to the present study, among the 4 human studies that examined the effect of probiotics on FPG, **y** the study reported a significant difference in FPG levels and Andreasen et al. As well as the oppressed and colleagues could not achieve significant results[47].

Ijtihad and his colleagues in Tabriz used enriched yogurt with a daily dose of 300 g and 106 × 600 CFU per gram of L. acidophilus La and B. lactis Bb strains for 6 weeks and a significant reduction in group comparison. And reported between groups[48].

While Asemi et al in Kashan, similar to the present study, used capsules containing seven strains of bacteria (L.

acidophilus, L. casei, L. rhamnosus, L. Bulgaricus, B. breve, B. longum and Streptococcus thermophilus) with this difference. The dose and duration of the present study was 1010 CFU per day for 6 weeks, but in their study, one capsule containing 14 10 109 CFU per day for 8 weeks[49].

The important point in Asemi et al study is that the level of FPG in the placebo group has increased, while the level of this index in the probiotic group after the intervention was equal to its value before the intervention and had a very small increase and their study showed that Probiotic intervention significantly prevented fasting blood glucose compared with the placebo group, and they did not report any FPG-lowering effects in their study.

However, the present study reported a significant decrease in the probiotic group after the intervention of pure probiotic capsules, so the result of the present study is more important and more indicative of the therapeutic and prophylactic effects of probiotics.

In general, in previous studies, significant differences were found in the improvement of FPG levels in both high-dose interventions of several probiotic strains and interventions with lower doses of 2 bacterial strains at 6 and 8 weeks, respectively; From these results, it can be inferred that the duration of effective intervention, which is approved and effective by the FDA up to 8 weeks[50].

It is more important depending on the type of strain or their dose, because Andreasen et al. Intervened with L. acidophilus at a daily dose of 1010 CFU per tablet but for only 4 weeks and did not achieve significant results. Also, Mazlum and his colleagues, who used L. acidophilus, L. longum, L. bifidum and L. casei strains in a daily dose of 1500 mg in their study in Shiraz, did not report any decrease in fasting blood sugar in patients.

Honda and colleagues stated that preventing glucose uptake into the intestine through probiotic intervention is the main mechanism of 2-hour hypoglycemia and that the anti-diabetic effect of probiotics is due to this mechanism. The main mechanism of this finding was the reduction of hepatic glycogen storage and the changes in the 2K-dependent osteocalcin pathway by B. fragilis. In fact, they found that osteocalcin levels were significantly and positively correlated with B. fragilis levels in diabetic rats[60]; Osteocalcin is a protein dependent on vitamin 2K[51], and B. fragilis is one of the major bacteria producing vitamin K[52].

On the other hand, it has been shown that vitamin K together with osteocalcin can play an important role in improving the state of diabetes in humans, so this mechanism may indicate the cause of 2-hour hypoglycemia in diabetic rats.

Effect of probiotics on lipid profile

The present study also showed that probiotic intervention could lead to a significant increase in HDL levels in the intervention group, although this increase was not significant compared to the placebo group. In this regard, 5 animal studies also reported a significant increase in HDL and intragroup and HDL levels. Among these studies, El-khamisi et al stated that the mixed intervention of L.acidophilus and B. lactis has a better and more favorable effect on increasing the level of HDL than the intervention of each species alone.

They used a daily gavage dose of 108 CFU for 6 weeks. In their 3 studies, Yadav et al. Used a probiotic mixture called "Dahi" which includes 3 species of Lactobacillus in similar doses (73 8 108 CFU per day) but in different intervention periods of 8 weeks, 6 weeks and 4 weeks and in each Three studies showed a significant increase in HDL levels in diabetic rats compared to the control group at the end of the intervention, although they did not show any significant increase within the group.

Very few human studies have examined the effect of probiotics on HDL levels. Out of 3 human studies that have evaluated the effect of probiotics on HDL index so far, 2 studies reported a significant increase in the level of this index. Asemi et al in Kashan, who tested supplements containing probiotic strains, stated that HDL levels in the intervention group increased significantly compared to the placebo group after 8 weeks of 108-day daily intervention of bacteria. Similar to this study, the present study also evaluated the net supplementation of probiotic-like strains, with the difference that the interventional dose was higher at about 1010 CFU but for a shorter period of time (due to the absence of possible complications from the high dose of the intervention) and at about 6 weeks and only a significant increase within the group was reported. It is possible that increasing the time intervened will affect the outcome of the work.

In Another study conducted by Ijtihad et al. In Tabriz and Mohammad Shahi et al in Ahvaz, probiotic-enriched yogurt was used at a daily dose of 300 mg for 6 and 8 weeks of intervention. Out of these 2 studies, which had the same working method and only different intervention time, only Mohammad Shahi et al were able to report a significant increase after the intervention period in the probiotic group compared to the initial values in this group, which is similar to the present study. From these results, it can be inferred again that increasing the intervention period if lower doses can be used can have a positive effect on improving the results.

However, due to the limited human results in this field, more clinical studies are needed. Regarding other lipid profile indices, the present study did not achieve significant results at TG, LDL-C, and TC levels. In fact, a

very small decrease was observed in TG and LDL levels, but did not reach a significant level.

Studies have also reported contradictory effects in this regard. Studies that achieved significant results often used high doses or longer intervention periods. For example, Hsieh et al. [53], and Huang et al. [4], after 14 and 8 weeks of intervention, respectively, had a significant reduction in the total cholesterol of the group receiving 10 10 2 daily CFU probiotics. For each mouse of L. reuteri GMNL[5], and the group receiving daily received one ml containing 109 × 1 CFU probiotic per mouse of L. plantarum K[10]. These studies also reported a significant decrease in LDL and TG levels. However, a study by Andersson et al. On diabetic mice using a daily probiotic dose of about 40 g/kg body weight of L. plantarum DSM showed only a significant reduction in TC levels despite high doses. And their high intervention time did not report a decrease in other lipid parameters. On the other hand, in human studies conducted in this field, which is limited to 3 studies, different results have been expressed. Unlike the present study, Asemi et al who used probiotic capsules (mentioned above) were also able to report a significant decrease in LDL levels, although they did not report a significant change in TC levels similar to the present study?

On the other hand, Mohammad Shahi et al as well as ijtihad et al. could not mention a significant change in LDL level after the intervention of yogurt enriched with probiotics. In the meantime, only Ijtihad et al. Mentioned a significant decrease in TC level both at the intra-group and inter-group level. Many mechanisms have been suggested in these animal studies due to the reduction of probiotics on the lipid profile. Adherence of bacterial cell wall to cholesterol in the gastrointestinal tract, deconjugation of bile ducts, and production of short-chain fatty acids are important in these studies. However, this work needs more research.

Effect of Probiotics on Insulin

In the present study, no significant change in blood insulin levels was reported in diabetics. However, two animal studies measuring serum insulin alone reported both significant reductions in blood insulin levels after intervention with probiotics[20]. While 4 animal studies achieved significant results in reducing the level of this index[11], These significant results (at serum and blood plasma insulin levels) in the intervention with high doses of probiotics (daily 108, 109, 1010 CFU 50, per mouse, 1 mg or 2% of probiotics to for each mouse) was obtained in the medium duration (6, 8 69, and 9 weeks) or long (14 weeks).

Lactobacillus species were used in all significant studies, except for two studies in which a mixture of Lactobacillus and Bifidobacterium was used in one and Lactococcus in the other. The effect of probiotic reduction on blood insulin is debatable in human studies. Because among human studies, 3 studies examined the effect of probiotics on plasma insulin index and serum insulin and only Asemi et al despite the high intervention of several species of bacteria (L. acidophilus, L. casei, L. rhamnosus L. bulgaricus, Bifidobacterium breve, B. longum, Streptococcus thermophilus) for a long time (8 weeks)[9], or Andreasen et al. by intervening a bacterial species (L. acidophilus) for a short time (4 weeks), were able to increase Report significance at the level of this factor only in their intragroup comparison[7], and similar to the present study, no significant intergroup results were reported in all three studies. Most of the reported results on the effect of probiotics on plasma insulin are based on animal studies, and since there are few reports from human studies, more human studies are needed to better conclude on the effect of probiotics on insulin in diabetic specimens.

The role of probiotics in insulin resistance (IR) Chronic hyperglycemia in diabetics is usually due to long-term insulin resistance and is one of the most important pathophysiological factors in type 2 diabetes[18].

The present study could not report a significant change in the level of this index after 6 weeks of intervention of a mixture of beneficial bacteria. In this regard, despite the similarity of the results of other studies, some animal studies mentioned a significant change. Two studies reported a significant effect on improving insulin resistance[22], In these two studies, approximately equal doses of L. reuteri (109 2 F CFU per mouse) and L. plantarum (109 × 1 CFU per mouse) were used for 14 and 8 weeks of intervention, respectively. However, Tomaro et al did not achieve significant results with the intervention of L. fermentum NCIMB at a daily gavage dose of 1010 CFU per mouse for 8 weeks in hyperlipidemic and hyperglycemic mice[27].

Tanida et al. Also used the method of injection of Lactobacillus casei Shirota at a dose of 108 × 1 CFU for less than 150 minutes before blood insulin test, and did not achieve significant results[32]. Human studies did not show significant results along with the present study. Ijtihad et al. (2012) and Asemi et al evaluated insulin resistance using the HOMA-IR method, but did not observe any significant change in the level of this factor. Andreasen et al in their study also intervened with L. acidophilus NCFM at high dose (1010 CFU) for only 4 weeks, and also examined the insulin resistance index by measuring HOMA-IR2, but as a result No significance was reached at the level of this index[33]. Despite these results, these studies suggest that proinflammatory factors and hyperlipidemia play an important role in regulating insulin resistance and are themselves affected by probiotic intervention; Therefore, the use of probiotics

in interventions can have important effects on improving insulin resistance. The number of studies in this field is very limited and contradictory, so that human studies have not achieved significant results and among animal studies, only 2 studies using Lactobacillus strain for a long time were able to achieve the desired and significant results, using different subspecies. Bacteria and in different doses may be the reason for the different results. Therefore, due to the limited amount of animal and especially human information available, we need to conduct this group of studies with more accurate methods to obtain better results.

Effect of probiotics on body weight and food intake

The present study showed that receiving probiotics without changing the diet had no effect on weight loss after the intervention period. Most studies in this regard have been animal. Twenty animal studies[9-16], and only two human studies to date have examined changes in body weight of the test specimens[22-28], of which only 12 animal studies reported food intake along with weight changes. Although the present study did not report a significant change in the weight change process, but a slight weight loss trend was observed in the subjects after the intervention period.

Contrary to the present study, some studies have suggested that probiotic intervention increases the weight of diabetic specimens. Four studies more accurately stated that probiotics-maintained body weight in the samples and resulted in a continuous weight loss process induced by streptozotocin[3-6], or alloxan[4], high fat diet (HFD)[9], or high fructose diet (HFrD)[2]. This weight gain was demonstrated in the study of Marraza et al with the intervention of L. rhamnosus CRL along with soy milk. They found that soy milk intervention improved and increased the weight lost in streptozotocin-induced diabetic mice, and increased this amount with the intervention of L. rhamnosus CRL.

They stated that giving streptozotocin to mice caused DNA damage, protein loss, and hypoinsulinemia, which in turn prevented carbohydrates from being consumed as energy in the mice and ultimately reduced their weight.

On the other hand, the intervention of soy milk and probiotics, due to having micronutrients and macronutrients, proteins and salts, as well as isoflavone aglycone, leads to increasing and compensating for their lost weight. Marraza et al did not correlate this weight gain with energy intake because, similar to the present study, they did not observe a significant change in rat food intake[47]. Matsuzaki et al also reported a significant increase in weight after L. casei intervention compared to the control group in alloxan-induced diabetic rats and stated that probiotic intervention prevented the alloxan-induced weight loss process, which had an effect in the higher dose L. casei (0.1% daily) is more sensitive than lower dose (0.05% daily)[42].

Bejar et al[39], as well as Davari et al[16], initially observed weight loss in diabetic mice, while after intervention L. plantarum TN[52], and A mixture of L. acidophilus and B. lactis, L. fermentum[46], prevented continued weight loss and significant weight gain was seen in the probiotic group compared to the control group. Andersson et al. Stated that L. plantarum DSM intervention after HFD diet increased lean mass in the probiotic and HFD group compared to the control group (HFD recipient), which in turn led to greater glucose excretion and ultimately lower sugar. Samples and their body weight gain. They also cited another reason for weight gain as increased colonization due to L. plantarum DSM intervention, which leads to increased adipose tissue and improved functional mucosa of the gastrointestinal tract of mice. They stated that this significant increase in the weight of the samples was not due to the increase in energy intake[5]. While Huang et al attributed the weight loss and prevention of weight gain to the HFFrD diet by L. plantarum intervention and its association with probiotics, bacterial polypidemic properties, or changes in adiponectin ad leptin levels in the mice[1].

Zhang et al who studied the preventive and therapeutic effect of L. casei Zhang on type 2 diabetes in two different groups, observed that L. casei Zhang caused significant weight loss only. In the L. group, it was preventive compared to the control group, and had no effect on the L. treatment group. They attributed the weight loss to its association with the glucagon-like peptide (GLP-2) and said that the intervention of this bacterium reduced the effect of GLP-2 and reduced the absorption of carbohydrates and fats in mice and their body weight. They are also reduced[3].

In another experiment after the intervention of Lactobacillus casei, Matsuzaki and colleagues reported weight loss and prevention of continued weight gain in samples of mice with non-insulin dependent diabetes, and even declared this effect to be dose-dependent and stated that the rate of reduction Weight in the higher dose group (2 mg per day) was higher than in the lower dose group (0.05%). However, Matsuzaki and colleagues reported no change in the dietary intake of the samples, and therefore the main cause of weight loss was unknown and probably due to a change in their immune system after probiotic intervention. Among the 12 animal studies that examined changes in energy intake[36-42], all studies similar to the present study, except for two studies[3- 9], reported no significant change in changes in this index.

In fact, only Bejar et al 40, and Yun et al 10, both observed a significant decrease in food intake of the

probiotic group compared to the control group after the intervention. In contrast, very few human studies have been done in this regard. So, that only Asemi et al[7] and Ijtihad et al[9], measured the amount of weight changes and similar to the present study, both no group and intergroup changes in the weight of the samples after the intervention Announced. Therefore, more studies are needed in this field.

Conclusion

Overall, the present study stated that the intervention of a dietary supplement containing a pure mixture of probiotics for 6 weeks can lead to a decrease in fasting blood sugar in people with type 2 diabetes and also significantly improve their good cholesterol (HDL) cholesterol levels. Increase, so that other lipid parameters, especially total cholesterol in patients, do not change. However, it can be argued that both of these effects may prevent the progression of diabetes and its complications, such as insulin resistance and hyperglycemia, or prevent other comorbidities such as cardiovascular disease, hyperlipidemia, or heart attack and stroke. Be. Past animal studies have shown that safe and high-dose intervention in these strains over a relatively long and effective period of time can have beneficial effects on improving fasting blood sugar levels, lipid profiles, blood insulin, and even lowering the level of proinflammatory markers. Increased levels of antioxidant markers in diabetic patients. As mentioned, the type of probiotic intervention is very effective in changing the results because the present study used a probiotic dietary supplement, while some human studies used probiotic carriers that have macronutrients and micronutrients such as carbohydrates, protein and calcium. They are interfering agents and have a distinct role in lowering blood sugar or other biochemical parameters, even without probiotics. Therefore, the use of probiotic supplements as adjunctive therapy will be discussed separately from the consumption of probiotic carriers. However, other existing studies have shown that it does not significantly affect the blood counts of diabetes, although there may be an error in the method of their research or a difference in these methods has been used by the user. These supplements are used in some diseases such as autoimmune diseases including thyroid disease, type 1 diabetes, allergies and especially gastrointestinal diseases such as short bowel syndrome, or other diseases such as acute pancreatitis, chronic kidney and liver disease, heart valve disease.

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