A Single-Blinded, Randomized Controlled Study - Role of Probiotics on Glucose and Lipid Metabolism in Patients with Type - 2 Diabetes Mellitus in a Tertiary Care Hospital, Odisha

Santosh Kumar Swain[1], Aswini Kumar Rout[2], Sriprasad Mohanty[3], Prabhat Kumar Padhi[4], Roma Rattan[5], Ashok Kumar Behera[6]

[1, 2, 3, 4, 6] Department of General Medicine, SCB Medical College & Hospital, Cuttack, Odisha, India.
[5] Department of Biochemistry, SCB Medical College & Hospital, Cuttack, Odisha, India.

ABSTRACT

BACKGROUND

Diabetes mellitus (DM) is a metabolic disorder, characterized by hyperglycaemia, insulin deficiency and insulin resistance. Along with diet, exercise, and oral antidiabetic drugs (OADs), probiotic intervention in novel food formulations enriched with specific bacterial strains could also be effective. In patients with type 2 DM and obesity, there is alteration in composition of the gut microbiota resulting in moderation of intestinal permeability and increasing endotoxin secretion. The utility of probiotic therapy in the management of type 2 DM has not been fully explored. Probiotics also regulate gut microflora and plasma lipids. The study was designed with a purpose of assessing the role of probiotics in glucose and lipid metabolism and its effectiveness in controlling blood sugar and lipid profile in type 2 DM.

METHODS

The single-blind randomized controlled study was conducted from February 2019 to January 2020 in the Department of Medicine, SCB Medical College and Hospital, Cuttack, in patients of type 2 DM. A total of 80 patients were included in the study with 40 as cases and another 40 as controls. Statistical analysis was performed using SPSS version 20. The mean ± standard deviation, median and ranges were calculated using chi square test and independent t-test. The level of significance was considered as $P < 0.05$.

RESULTS

The FBS and HbA1C levels were decreased by 16 mg / dl and 0.5 % respectively after consuming probiotics ($P < 0.001$). The total cholesterol, triglyceride, low density lipoprotein was decreased and high density lipoprotein level was increased after taking probiotics which was significant ($P < 0.001$). Probiotics help in cholesterol reduction through different mechanisms.

CONCLUSIONS

Probiotics have a definite role in improving glycaemic status and lipid levels in type 2 DM.

KEYWORDS

Glycosylated Haemoglobin, Type 2 DM, Probiotics, Intestinal Permeability

Corresponding Author:
Dr. Ashok Kumar Behera,
Assistant Professor,
Department of General Medicine,
SCB Medical College & Hospital,
Cuttack, Odisha, India.
E-mail: bdr.ashok@yahoo.com

DOI: 10.18410/jebmh/2021/339

How to Cite This Article:
Swain SK, Rout AK, Mohanty S, et al. A single-blinded, randomized controlled study - role of probiotics on glucose and lipid metabolism in patients with type -2 diabetes mellitus in a tertiary care hospital, Odisha. J Evid Based Med Healthc 2021;8(22):1797-1802. DOI: 10.18410/jebmh/2021/339

Submission 29-10-2020,
Peer Review 10-11-2020,
Acceptance 09-04-2021,
Published 31-05-2021.

BACKGROUND

Diabetes mellitus (DM) is a multifactorial disorder caused by genetic, epigenetic, environmental and lifestyle related factors resulting in the development of pathophysiological manifestation such as beta cell dysfunction, relative deficiency of insulin, insulin resistance, hyperglycaemia, hypercholesterolemia, metabolic endotoxemia, systemic inflammation, intestinal permeability, defective incretin secretion, ectopic fat storage and oxidative stress.[1,2]

Abnormal glucose metabolism is causally related to a greater risk of several chronic disorders, including obesity, dyslipidaemia, and cardiovascular disease. Deadliest part of diabetes is its various complications which affects many organ systems and responsible for majority of morbidity and mortality associated with disease. Microvascular complications such as Neuropathy, Retinopathy, Nephropathy and macrovascular complications such as stroke, coronary artery disease (CAD), peripheral vascular disease (PVD) can occur. An estimated 463 million adults aged 20 – 79 years are currently living with diabetes. This represents 9.3 % of the world's population in this age group. The International diabetes federation has predicted a rise in case to 578 million (10.2 %) by 2030 and to 700 million (10.9 %) by 2045.[3]

Recent studies have shown that there is alteration in the gut microbiota composition in patients with obesity and type 2 DM which modulates intestinal permeability and increases metabolic endotoxin secretion that leads to chronic low level of inflammation, the pathogenesis of insulin resistance and type 2 DM.[4,5] Along with diet, exercise, and OAD, probiotic intervention in the form of novel food formulations enriched with specific bacterial strains could be very effective dietary strategy to manage chronic intestinal diseases and lifestyle metabolic disorders such as type 2 DM, obesity and cardio vascular diseases.

Probiotics are defined as live microorganisms, which when administered in adequate amounts confer a health benefit on the host.[6,7] Health benefits have mainly been demonstrated for specific probiotic strains of the following genera lactobacillus, bifidobacterium, saccharomyces, enterococcus, streptococcus, pediococcus, leuconostoc, bacillus, *Escherichia coli*. Many research demonstrated that alteration of microbiota causing dysbiosis may be corrected by consuming probiotics. As probiotic properties are strain specific, accurate identification of particular strain is important. lactobacilli and bifidobacteria, the two key members of this group, used extensively in the development of different food formulations are now being explored as biotherapeutics in the management of several diseases such as diarrhoea, ulcerative colitis, inflammatory bowel syndrome, crohn's disease and colon cancer.[8]

However, the prospects of probiotic therapy in the management of lifestyle diseases particularly type 2 DM have not been fully explored and there are limited studies in this regard. In spite of that, some recent studies clearly point towards the antidiabetic and cholesterol lowering effect of probiotics based intervention.[9,10] Probiotics also regulate gut microflora and plasma lipids mainly by decreasing serum triglycerides, LDL-cholesterol and by increasing HDL-cholesterol, therefore having a beneficial effect on patients with type 2 DM.[11]

Objectives

To study the role of probiotics in glucose and lipid metabolism and its effectiveness in controlling blood sugar and lipid profile in patients with type 2 DM.

METHODS

Single-blinded randomized controlled study was conducted from February 2019 to January 2020 in the Department of Medicine, S.C.B Medical College and Hospital, Cuttack in patients of type 2 DM attending the Out-patient as well as the In-patient departments. Patients of type 2 DM with FBS ≥ 126 mg / dl, total cholesterol > 200 mg / dl, triglyceride > 150 mg / dl, LDL > 100 mg / dl, aged from 30 to 70 years with less than 15 years' history of DM and not on any antibiotics during the study period were included. Patients on non-steroidal anti-inflammatory drugs (NSAIDs), on multivitamins, hormone replacement therapy, change or modifications of OAD doses during the study, patients on insulin therapy, current smokers and diabetic complications involving lungs, liver, kidney and heart were excluded. The study was approved by the Institutional Ethical Committee (IEC) and written informed consent both in English and local Odia language was obtained from all patients prior to the study.

Patients in the case group were given probiotic capsules containing genus lactobacillus (*L. acidophilus*, *L. paracasei, L. plantarum)* and genus bifidobacterium (*B. breve, B. infantis*, *B. longum).* The daily dose of strain was 10^6 - 10^8 CFU twice daily in the morning and evening after meal for a period of 6 weeks and the controls were given multivitamins without any lactobacillus for same period of 6 weeks. A total of 80 patients were taken for the study which was divided into two groups, consisting of 40 cases and same number of age and sex matched patients were selected as control group. After detailed clinical history and complete physical examination patients underwent routine blood investigations like complete haemogram (CBC), urine routine and microscopic examination, fasting blood glucose, blood urea and serum creatinine, lipid profile (serum TC, TG, LDL, VLDL, HDL) and HbA1C. Auto analyser biosytem A-25 was used to estimate the FBS, lipid profile. HbA1C was estimated by high-performance liquid chromatography (HPLC) method. All the measurements were taken at baseline and after 6 weeks of intervention. The patients were asked to report any adverse event by phone calls or by face to face in follow up visit. Based on the outcome of the study statistical analysis was done.

Statistical Analysis

The statistical analysis was performed using statistical package for social sciences (SPSS) version 20. The mean ± standard deviation, median and ranges were calculated. chi square test and Independent t-test were used to compare

categorical and numerical variables. The level of significance was considered as P < 0.05.

RESULTS

Total eighty patients diagnosed of type 2 DM were considered for the final analysis. Majority of patients both from case and control group belonged to the age group of 51 - 60 years i.e. 11 patients and 13 patients respectively. With regards to gender wise distribution among the groups the P value was 0.36 which was not significant. The mean duration of diabetes among cases and controls were 5.15 years and 4.12 years respectively having P value of 0.65 which was not significant.

The mean FBS level among cases and controls at the beginning were 170.98 mg / dl and 157mg / dl respectively and there was no significant difference (P = 0.92). Among the cases the mean FBS level significantly decreased after probiotic intervention (P < 0.001) but in controls it was not significant (P = 0.077).

In the case group 36 (90 %) patients and 18 (45 %) patients from control group showed decrease in FBS level from initial value after probiotic and placebo intervention respectively. (Table - 1)

From the case group 35 (87.5 %) patients and 17 (42.5 %) patients from control group showed decrease in HbA1c level from initial value after probiotic and placebo intervention respectively.

The mean HbA1c level among cases and controls at the beginning of the study were 7.42 % and 7.28 % respectively which was not significant (P = 0.42). There was a significant difference in mean HbA1c level between the two groups (P = 0.004) after probiotics intervention. Among the cases the mean HbA1c level significantly decreased after probiotic intervention (P < 0.001) but in controls it was not significant (P = 0.169). (Table - 1)

Among the case group 35 (87.5 %) patients and 23 (57.5 %) patients from control group showed decrease in TC level after intervention respectively but 17 (42.5 %) cases showed increase in TC level.

At the beginning the mean TC level among cases and controls were 212.65 mg / dl and 212.78 mg / dl respectively which was not significant (P = 0.96) but was significant between the two groups (P < 0.001) after probiotic therapy. Among the cases the mean TC level significantly decreased after probiotic intervention (P < 0.001) but in controls it was not significant (P = 0.168). (Table - 2)

95 % (38) patients from case group and 60 % (24) patients of control group showed decrease in TG level after intervention. 37.5 % (15) from control group showed increase in TG level. At the beginning the mean TG level among cases and controls were 184.72 mg / dl and 177.28 mg / dl respectively which was not significant (P = 0.20) but was significant in the two groups (P < 0.001) after intervention.

Among the cases the mean TG level significantly decreased after probiotic intervention (P < 0.001) and in controls it was not significant (P = 0.194). (Table - 2)

After probiotics and placebo intervention, the decrease in LDL level among patients were 90 % (36) patients and 62.5 % (25) patients respectively. At the beginning the mean LDL level among cases and controls were 121.85 mg / dl and 122.42 mg / dl respectively which was not significant (P = 0.86). After the intervention the mean LDL level between the two groups was significant (P < 0.001) and also in case group the LDL level was significantly decreased (P < 0.001). (Table - 2)

	Fasting Blood Sugar (mg / dl)					HbA1c (in %)				
	Before		After		P Value	Before		After		P Value
	Mean	SD	Mean	SD		Mean	SD	Mean	SD	
Cases	170.98	45.49	154.15	40.79	< 0.001	7.42	0.93	6.86	0.82	< 0.001
Control	157.25	22.31	161.08	28.50	0.077	7.28	0.59	7.35	0.64	0.169
	P = 0.92		P = 0.33			P = 0.42		P = 0.004		
	FBS Variation after intervention in both groups (in number)					HbA1c variation (in number)				
	FBS Variation									
	Decrease		Increase				Decrease	No Change	Increase	
Cases	36 (90 %)		4 (10 %)			Cases	35 (87.5 %)	0 (0 %)	5 (12.5 %)	
Control	18 (45 %)		22 (55 %)			Control	17 (42.5 %)	2 (5 %)	21 (52.5 %)	
Total	**54 (67.5 %)**		**26 (33.5 %)**			**Total**	**52 (65 %)**	**2 (2.5 %)**	**26 (32.5 %)**	

Table - 1. FBS & HbA1c (in %) – Variation within and between the Two Groups and FBS & HbA1c (in %) Variation after Intervention in Both Groups (in Number)

	Total Cholesterol (mg / dl)					Triglyceride (mg / dl)					LDL (mg / dl)					
	Before		After		P Value	Before		After		P Value		Before		After		P
	Mean	SD	Mean	SD		Mean	SD	Mean	SD			Mean	SD	Mean	SD	Value
Cases	212.65	11.69	194.20	14.29	< 0.001	184.72	32.61	162.72	19.36	< 0.001	Cases	121.85	17.32	109.95	14.80	< 0.001
Control	212.78	11.63	210.22	11.96	0.168	177.28	16.79	175.22	13.08	0.194	Control	122.42	11.58	120.55	8.04	0.160
	P = 0.96		P < 0.001			P = 0.20		P < 0.001				P = 0.86		P < 0.001		
	TC Variation after intervention in both groups (in number)					TG variation after intervention in both groups (in number)					LDL Variation after intervention in both groups (in number)					
	TC Variation					TG variation					LDL Variation					
	Decrease		Increase				Decrease	No change	Increase			Decrease		Increase		
Cases	35 (87.5 %)		5 (12.5 %)			Cases	38 (95 %)	0	2 (5 %)		Cases	36 (90 %)		4 (10 %)		
Control	23 (57.5 %)		17 (42.5 %)			Control	24 (60 %)	1 (2.5 %)	15 (37.5 %)		Control	25 (62.5 %)		15 (37.5 %)		
Total	**58 (72.5 %)**		**22 (27.5 %)**			**Total**	**62 (77.5 %)**	**1 (1.25 %)**	**17 (21.25 %)**		**Total**	**61 (76.25 %)**		**19 (23.5 %)**		

Table 2. Total Cholesterol (TC), Triglyceride, LDL (in mg / dl) – Variation within and between the Two Groups and TC, Triglyceride, LDL (in mg / dl) Variation after Intervention in Both Groups (in Number)

Among the case and control groups there was an increase in HDL level in 35 (87.5 %) patients and 21 (52.5 %) patients respectively but there was a decrease in HDL after intervention in 19 (47.5 %) patients among control group. At the beginning of the study the mean HDL level among cases and controls were 38.92 mg / dl and 38.52 mg / dl respectively which proved non-significant (P = 0.73). There was a significant difference in mean HDL level between the two groups (P < 0.001). Among the cases the mean HDL level significantly increased after probiotic intervention (P < 0.001) whereas in controls it was not significant (P = 0.906). (Table - 3)

HDL (mg / dl)					
	Before		After		P Value
	Mean	SD	Mean	SD	
Cases	38.92	5.38	45.48	4.59	< 0.001
Control	38.52	4.84	38.60	3.80	0.906
	P = 0.73		P < 0.001		
HDL Variation after intervention (in number)					
HDL Variation					
	Decrease		No change		Increase
Cases	4 (10 %)		1 (2.5 %)		35 (87.5 %)
Control	19 (47.5 %)		0 (0 %)		21 (52.5 %)
Total	**23 (28.75 %)**		**1 (1.25 %)**		**56 (70 %)**

Table 3. HDL-Variation within and between the Two Groups and HDL Variation after Intervention in Both Groups (in Number)

DISCUSSION

A total of 80 patients were included in the study, out of them majority were males (60 %) and most of them were in the age group of 51 to 60 years (30 %). The prevalence of type 2 DM was more in adult males which may be due to increased incidence of sedentary lifestyle, smoking habits, abdominal obesity and insulin resistance.

There is a definite role of gut microbiota in pathogenesis of type 2 DM.[12] Probiotic intervention maintains the gut flora in healthy condition, prevents the metabolic endotoxemia and improves insulin resistance and helps to maintain a good glycaemic control in type-2 DM patients.[13,14] We found probiotic intervention significantly decreased FBS and HbA1C level among cases. 36 (90 %) patients in the case group showed decrease in FBS level from initial value. The mean ± SD of FBS variation among cases before and after probiotic intervention was significant (P < 0.001). 35 (87.5 %) patients out of 40 showed decrease in HbA1c level from initial value after probiotic intervention. The Mean ± SD of HbA1c variation among cases before and after probiotic intervention was significant (P < 0.001). The variation in mean HbA1c level in between the group was not significant (P = 0.42) before intervention but it became significant after intervention (P = 0.004) which may be due to good glycaemic control in patients receiving probiotics.

A study conducted by Ejtahed et al. in 2012[15] found that there were no statistically significant differences in blood glucose level and HbA1c between the two groups at the beginning (P > 0.05) but blood glucose level and HbA1C was significantly decreased (P = 0.009 and P = 0.019) respectively in the probiotic group compared with the control group. Another study conducted by Firouzi et al. in 2016[16] showed that glycated haemoglobin decreased by 0.14 % in the probiotics (P < 0.05). In this study, probiotics supplementation significantly improved HbA1c, while it had no effect on FBG. It can be assumed that improvements in postprandial blood glucose led to decreasing HbA1c in the probiotics group. Indeed, FBG is also influenced by several factors including physical activity,[17] durations since the last meal[18] and a range of other neuroendocrine factors.[19] Hence, any change in the FBG levels due to intervention might be difficult to be assessed. Similar study was conducted by Asemi et al. in 2013[20] they found that consumption of probiotic supplements in the intervention group prevented a rise in FPG, while in the placebo group they observed a significant increase in FPG (P = 0.002). When the mean changes in FPG were compared between the two groups, there was a statistically significant difference (+28.8 ± 8.5 for placebo vs. +1.6 ± 6 mg / dl for the probiotic group (P = 0.01).

Various meta-analysis studies taking different RCTs have shown a positive effect of probiotics on glycaemic control in patients of type 2 DM. Out of these meta-analysis studies, a study conducted by Qingging et al. 2016[21] involving 7 RCTs showed, probiotic consumption significantly changed FPG by 15.92 mg / dL (95 % confidence interval [CI], 29.75 to 2.09) and glycosylated haemoglobin (HbA1c) by 0.54 % (95 % CI, 0.82 to 0.25) compared with control groups which was in agreement with our study. Another meta-analysis by Sun J et al. 2016[22] involving 11 RCT with 614 subjects concluded that the glucose reduction was 9.36 mg / dL (95 % confidence interval [CI]: -0.92– [-0.11] p = 0·01) and the HbA1c reduction was 0.32 % (95 % CI: -0·57– [-0·07 %]; P = 0·01) which was similar to our study result with approximately 16 mg / dl reduction in FBS level and 0.5 % reduction in HbA1C level among cases after probiotic intervention.

In our study we found probiotic intervention significantly reduced total cholesterol (P < 0.001), Triglyceride (P < 0.001), LDL (P < 0.001) and increased HDL (P < 0.001). There were no significant differences of TC, TG, HDL, LDL level between cases and controls before intervention but there were significant differences after intervention, both within the group and in between the group (P < 0.001). 18 mg / dl in TC, 22 mg / dl in TG, 12 mg / dl reduction in LDL and 6 mg / dl rise in HDL was observed from the baseline after intervention with probiotics among cases.

In a study conducted by Tahere et al. 2016[23] showed that consumption of probiotic supplement reduced lipid profile concentration in probiotic group. However, there was no significant difference between two groups. Probable mechanisms about the effect of probiotics in cholesterol reduction include: activating bile salt hydrolyses (BSH), de conjugating bile acids and stopping the circulation of intestinal bile acids,[24,25,26] reducing cholesterol absorption by combining cholesterol with bacterial cell membranes and reduction of synthesizing liver cholesterol by producing short-chain fatty acids in digestive system due to fermentation by probiotics.[27,28] Ataie Jafari et al. 2009[29] also showed that probiotic yogurt containing *Lactobacillus acidophilus* and *Bifidobacterium lactis* reduces serum total cholesterol, significantly.

Consumption of oral probiotics reduces blood cholesterol by 22 - 33 % proved in a study by Tomaro et al. 2014.[30]

These results are in agreement with the results of our study. But in a study by Hatakka et al. 2008[31] found that there was no effect on reduction of serum lipid level after probiotics consumption. These observations may be due to some differences in species, number and form of probiotic bacteria, duration of intervention, sample size, study design.

CONCLUSIONS

Recent evidences indicate the significant role of gut microbiota in the pathogenesis of metabolic syndrome. Different modulations which have been scientifically proven are regulation of pro-inflammation, decreased appetite, decreased blood glucose and serum lipids. The manipulation of gut microbiota by administration of specific bacterial strains containing probiotics help to achieve the goal in type 2 DM patients by reduction of blood glucose and serum lipids.

Limitations

Although different findings of research proved positive effect of probiotics in vitro, there is a need to conduct more research with a longer duration and different probiotic doses to confirm the ability of probiotics as an alternative for the treatment of different metabolic conditions in patients of type 2 DM.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.
Financial or other competing interests: None.
Disclosure forms provided by the authors are available with the full text of this article at jebmh.com.

REFERENCES

[1] Mengual L, Roura P, Serra M, et al. Multifactorial control and treatment intensity of type-2 diabetes in primary care settings in Catalonia. Cardiovasc Diabetol 2010;9:14.
[2] Cani PD. Crosstalk between the gut microbiota and the endocannabinoid system: impact on the gut barrier function and the adipose tissue. Clin Microbiol Infect 2012;(18 Suppl 4):50-53.
[3] IDF Diabetes Atlas, Ninth Edition. 2019. http://www.idf.org/diabetesatlas.org
[4] Diamant M, Blaak EE, de Vos WM. Do nutrient-gut-microbiota interactions play a role in human obesity, insulin resistance and type 2 diabetes? Obes Rev 2011;12(4):272-281.
[5] Everard A, Cani PD. Diabetes, obesity and gut microbiota. Best Pract Res Clin Gastroenterol 2013;27(1):73-83.
[6] Joint FAO/WHO Working Group Report on Drafting Guidelines for the Evaluation of Probiotics in Food. London, Ontario, Canada, April 30 and May 1, 2002.
[7] Fuller R. Probiotics in man and animals. J Appl Bacteriol 1989;66(5):365-378.
[8] Ritchie ML, Romanuk TN. A meta-analysis of probiotic efficacy for gastrointestinal diseases. PLoS One 2012;7(4):e34938.
[9] Yao K, Zeng L, He Q, et al. Effect of probiotics on glucose and lipid metabolism in type 2 diabetes mellitus: a meta-analysis of 12 randomized controlled trials. Med Sci Monit 2017;23:3044-3053.
[10] Mazloom Z, Yousefinejad A, Dabbaghmanesh MH. Effect of probiotics on lipid profile, glycemic control, insulin action, oxidative stress and inflammatory markers in patients with type 2 diabetes: a clinical trial. Iran J Med Sci 2013;38(1):38-43.
[11] Fooks LJ, Gibson GR. Probiotics as modulators of the gut flora. Br J Nutr 2002;(88 Suppl 1):S39-49.
[12] Cani PD, Amar J, Iglesias MA, et al. Metabolic endotoxemia initiates obesity and insulin resistance. Diabetes 2007;56(7):1761-1772.
[13] Tabuchi M, Ozaki M, Tamura A, et al. Anti-diabetic effect of Lactobacillus GG in streptozotocin-induced diabetic rats. Bioscience, Biotechnology and Biochemistry 2003;67(6):1421-1424.
[14] Le Chatelier E, Nielsen T, Qin J, et al. Richness of human gut microbiome correlates with metabolic markers. Nature 2013;500(7464):541-546.
[15] Ejtahed HS, Mohtadi-Nia J, Homayouni-Rad A, et al. Probiotic yogurt improves antioxidant status in type 2 diabetic patients. Nutrition 2012;28(5):539-543.
[16] Firouzi S, Majid HA, Ismail A, et al. Effect of multi-strain probiotics (multi-strain microbial cell preparation) on glycemic control and other diabetes-related outcomes in people with type 2 diabetes: a randomized controlled trial. Eur J Nutr 2017:56(4):1535-1550.
[17] Jensen TE, Richter EA. Regulation of glucose and glycogen metabolism during and after exercise. The Journal of Physiology 2012;590(5):1069-1076. https://doi.org/10.1113/jphysiol.2011.224972.
[18] Munsters MJ, Saris WH. Effects of meal frequency on metabolic profiles and substrate partitioning in lean healthy males. PLoS One 2012;7(6):e38632.
[19] Morton GJ, Schwartz MW. Leptin and the central nervous system control of glucose metabolism. Physiol Rev 2011;91(2):389-411.
[20] Asemi Z, Zare Z, Shakeri H, et al. Effect of multispecies probiotic supplements on metabolic profiles, HS-CRP, and oxidative stress in patients with type 2 diabetes. Ann Nutr Metab 2013;63(1-2):1-9.
[21] Zhang Q, Wu Y, Fei X. Effect of probiotics on glucose metabolism in patients with type 2 diabetes mellitus: a meta-analysis of randomized controlled trials. Medicina (Kaunas) 2016;52(1):28-34.
[22] Sun J, Buys NJ. Glucose- and glycaemic factor-lowering effects of probiotics on diabetes: a meta-analysis of randomised placebo-controlled trials. Br J Nutr 2016;115(7):1167-1177.
[23] Tofighiyan T, AkramKooshki A, Hoseini BL, et al. The effects of probiotic on serum lipid profiles in patients with type 2 diabetes mellitus: a randomized clinical trial. Journal of Food and Nutrition Research 2016;4(12):795-798.

[24] De Smet I, De Boever P, Verstraete W. Cholesterol lowering in pigs through enhanced bacterial bile salt hydrolase activity. Br J Nutr 1998;79(2):185-194.
[25] Klaver FA, van der Meer R. The assumed assimilation of cholesterol by Lactobacilli and Bifidobacterium bifidum is due to their bile salt-deconjugating activity. Appl Environ Microbiol 1993;59(4):1120-1124.
[26] Usman, Hosono A. Bile tolerance, taurocholate deconjugation and binding of cholesterol by Lactobacillus gasseri strains. J Dairy Sci 1999;82(2):243-248.
[27] Pereira DI, Gibson GR. Effects of consumption of probiotics and prebiotics on serum lipid levels in humans. Crit Rev Biochem Mol Biol 2002;37(4):259-281.
[28] Lay-Gaik O, Min-Tze L. Cholesterol-lowering effects of probiotics and prebiotics: a review of in vivo and in vitro findings. Int J Mol Sci 2010;11(6):2499-2522.
[29] Ataie-Jafari A, Larijani B, Majd HA, et al. Cholesterol-lowering effect of probiotic yogurt in comparison with ordinary yogurt in mildly to moderately hypercholesterolemic subjects. Ann Nutr Metab 2009;54(1):22-27.
[30] Tomaro-Duchesneau C, Jones ML, Shah D, et al. Cholesterol assimilation by Lactobacillus probiotic bacteria: an in vitro investigation. Biomed Res Int 2014;2014:380316.
[31] Hatakka K, Mutanen M, Holma R, et al. Lactobacillus rhamnosus LC705 together with Propionibacterium freudenreichii ssp shermanii JS administered in capsules is ineffective in lowering serum lipids. J Am Coll Nutr 2008;27(4):441-447.