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Probiotics improve insulin resistance status in an experimental model of Alzheimer's disease

Somayeh Athari Nik Azm[1], Abolghassem Djazayeri[1], Majid Safa[2], Kian Azami[3], Mahmoud Djalali[4], Mohammad Sharifzadeh[5]*, Mohammadreza Vafa[6]*

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Abstract

Background: Nowadays, Alzheimer's disease (AD) is considered as Type 3 diabetes in which insulin resistance is the common cause of both diseases. Disruption of insulin signaling cascade and insulin resistance can induce AD; and central insulin resistance causes systemic alterations in serum insulin, FBS levels, and lipid profile. Studies have shown that probiotics (Lactobacillus and *Bifidobacterium* species) can be used as a nutritional approach to improve these metabolic changes. We assessed the probiotic effect (4 species of *Lactobacillus* and *Bifidobacterium*) on insulin resistance biomarkers in an experimental model of AD.

Methods: A total of 60 rats were divided into 5 groups: (1) a control group without surgical and dietary intervention; (2) a control-probiotics group receiving probiotics for 8 weeks, but not receiving any surgical intervention; (3) a group receiving a sham operation in which PBS was injected intrahippocampus but without dietary intervention; (4) an Alzheimer group for which Amyloid-ß (Aß) 1-42 was injected intrahippocampus but without dietary intervention; (5) and an Alzheimer-probiotics group for which Aß1-42 was injected intrahippocampus and given 2g probiotics for 8 weeks. The FBS levels and lipid profile were measured by a calorimetric method, insulin levels were detected by an ELISA kit, and HOMA-IR was calculated using a formula. ANOVA (one way analysis of variance followed by Bonferroni comparisons post hoc) was used to compare all the variables between groups.

Results: Serum glucose, insulin levels, and HOMA-IR index increased in the Alzheimer group compared to the control ($p<0.001$), while probiotics decreased only insulin level and HOMA-IR index in AP group compared to Alzheimer group ($p<0.001$). Also, TG levels increased in the Alzheimer group ($p<0.001$), but no significant difference was detected between Alzheimer and Alzheimer-probiotics group.

Conclusion: It seems that probiotics play an effective role in controlling glycemic status of Alzheimer's disease.

Keywords: Alzheimer Disease, *Lactobacillus*, *Bifidobacterium*, Insulin, HOMA

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Introduction

Alzheimer's disease (AD), as a neurodegenerative disease, causes impaired cognition function and memory loss (Tillisch et al. 2013). Nowadays, the number of patients with AD is estimated to be 36 million worldwide, and it is estimated that the number will be quadrupled in 2050 (Ríos et al. 2014, Saxena et al. 2011). Although less than 5% of AD cases are the inherited familial type, the sporadic type (late-onset) is the most common type of AD, and environmental factors affect its prevalence (Saxena et al. 2011). Observations have revealed that amyloid cascades, oxidative stress, neuroinflammation, insulin resistance, and apoptosis are involved in AD pathogenesis; nevertheless, the exact mechanism of AD is not known (Li et al. 2010).

Amyloid-β (Aβ) Aβ (1-42), produced by Amyloid protein precursor (APP), has a neurotoxicity effect and is

Corresponding author: *Dr Mohammadreza Vafa, rezavafa@yahoo.com*
Dr Mohammad Sharifzadeh, msharifzadeh@sina.tums.ac.ir

1. Department of Community Nutrition, School of Nutritional Science and Dietetics, Tehran University of Medical Sciences, Tehran, Iran.
2. Cellular and Molecular Research Center and Hematology Department, School of Allied Medical Science, Iran University of Medical Sciences, Tehran, Iran.
3. Department of Pharmacology, Pharmaceutical Science Research Center, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran.
4. Department of Cellular-Molecular Nutrition, School of Nutritional Science and Dietetics, Tehran University of Medical Sciences, Tehran, Iran.
5. Department of Pharmacology and Toxicology, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran.
6. Department of Nutrition, School of Public Health, Iran University of Medical Sciences, Tehran, Iran.

↑What is "already known" in this topic:
Studies have shown that probiotics can be a nutritional approach to improve metabolic markers such as FBS and lipid profile in patients with diabetes.

→What this article adds:
Disruption of insulin signaling cascade and insulin resistance can induce AD that causes systemic alterations in serum insulin, FBS levels, and lipid profile; however, probiotics can improve these markers.

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deposited in extracellular senile plaque composed of β-amyloid and following the aggregation of Aβ, microglial cells lose their protective function and cannot clear Aβ, which causes synaptic function loss, neurons apoptosis, oxidative stress, neuroinflammation, and memory loss (Butterfield et al. 2007, Cioanca et al. 2013, El Khoury and Luster. 2008). Since all these mechanisms are involved in pathogenesis of diabetes mellitus, many studies have shown that AD is associated with diabetes and AD is considered as Type 3 diabetes in which insulin resistance is the common cause of both diseases (Ríos et al. 2014). Aβ can compete with insulin or decrease insulin receptors binding affinity. It can also cause insulin signaling impairment and increase the susceptibility of neurons to oxidative stress and cause insulin resistance and disruption in memory (Kim and Feldman. 2015). Insulin signaling cascades have a neuroprotective role in the central nervous system (CNS) and improve synaptogenesis and synaptic remodeling against apoptosis and oxidative stress. Thus, disruption of insulin signaling cascade can induce AD. Central insulin resistance can lead to systemic alterations in insulin level (Burns et al. 2012) and other biomarkers including fasting blood sugar (FBS) and lipid profile (Schiffrin et al. 2010, Solfrizzi et al. 2006).

Many studies have found that using components such as nutrients or bioactive components of foods can improve oxidative stress and insulin resistance, and thus, they are useful and effective in improving pathological markers in AD (Hashimoto et al. 2009, Kumar et al. 2011, van der Beek and Kamphuis. 2008).

If probiotics, as a group of gastrointestinal microbiota bacteria, are consumed in adequate amounts, they can show useful effects in the host (Dinan and Cryan. 2012, Quigley. 2010). Although studies on microbiota and diversity of gut bacteria in those with Alzheimer's disease are limited, the results of one study have shown the increased gram-negative bacteria of microbiota in a transgenic rat model of Alzheimer's disease (Mayer et al. 2014). Observations have revealed that oxidative stress and inflammation in the Alzheimer's disease can lead to the increased gram-negative bacteria and the decreased gram-positive bacteria, or probiotics (Lye et al. 2009). Also, germ free mice showed cognitive dysfunction (Bhattacharjee and Lukiw. 2013). On the other hand, studies have demonstrated that aging as a risk factor of AD can cause a decrease in probiotics bacteria, especially in *Bifidobacterium* and *Lactobacillus* (Leung and Thuret. 2015, Marques et al. 2014) that have anti-inflammatory and antioxidative properties (Ruan et al. 2015). Probiotics such as Lactobacillus and *Bifidobacterium* have beneficial effects on the metabolic profile and insulin resistance biomarkers (Shimizu et al. 2015). Moreover, specific species of lactic acid bacteria such as *L.acidophilus* improve glucose intolerance, hyperglycemia, and hyperinsulinemia (Ruan et al. 2015). Thus, the present study aimed at evaluating the probiotics effect on improving Aβ-induced insulin resistance in a rat model of Alzheimer's disease.

Methods

Study Design

In this study, 60 male Wistar rats (weight: 180-220 g, 8 weeks) were purchased from the Faculty of Pharmacy at Tehran University of Medical Sciences. Each rat was housed in one cage and all cages were kept at 25±2 ^{0}C temperature and on a 12- hour light/ dark cycle. All the rats had accessed to adlibitum food (chow) and water. Our experiments were approved by the ethical committee for the care and use of laboratory animals at Tehran University of Medical Sciences (code: 902-1324001) and council of graduated students of Iran University of Medical Sciences (code: 93-01-27-24403).

Rats were divided into 5 groups: (1) a control group (C) without surgical and dietary interventions; (2) a control-probiotics (CP) group that received probiotics in drinking tap water for 8 weeks but received no surgical intervention; (3) a group receiving a sham operation (S) for which phosphate buffered saline (PBS), as the solvent of Aβ, was injected intrahippocampus, but without any dietary intervention; (4) an Alzheimer group (Aβ) for which 50 ng/μL/side β-amyloid was injected intrahippocampus, but without dietary intervention; and (5) an Alzheimer-probiotics (AP) group that received 2 g probiotics with drinking tap water during 8 weeks (with 4 weeks interval before and after Aβ injection) in addition to surgical intervention (Aβ injection).

Beta- amyloid (1-42) preparation

Aβ (1-42) (sigma-Aldrich, USA) was dissolved in PBS (the solvent of Aβ). The solution was incubated for 5 days at 37°C and diluted by PBS to 50 ng/μL concentration on the test day. (Aβ dosage was selected based on previous studies (Asadi et al. 2015, Eftekharzadeh et al. 2012, Shariatpanahi et al. 2015) and our pilot study).

Probiotics preparation

Powdered preparation probiotics was obtained from Tak-Gen Company (Tehran, Iran). Based on the results of our pilot study, water volume was calculated (30 mL) and 2 g of probiotics (probiotics dosage was selected based on a previous study (Davari et al. 2013) and our pilot study) including lactobacillus acidophilus, fermentum, Bifidobacterium lactis, and longum (10^{10} colony forming units (CFU)/g) were dissolved in an amount of calculated drinking tap water every morning. Water intake was monitored in all groups. Probiotics were selected based on antioxidative and anti-inflammatory effects, which have been reported in the past studies (Fijan. 2014, Hamaji et al. 2007, Messaoudi et al. 2011, Pang et al. 2012). Probiotics powder was colorless and odorless; at first, probiotics are inactive in water due to their special formulation, which includes a carrier compound that bonds to probiotics and allows probiotics activation in gut. Thus, the environmental factors do not affect probiotics in water.

Surgery procedure

Rats were anesthetized with an intraperitoneal injection of ketamine (90 mg/kg) and Xylazine (5 mg/kg) and were

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put in stereotaxic apparatus (Stoelting, wood Dale, IL, USA). For intrahippocampal injection of Aβ, using atlas of Paxinos and Watson (anterior-posterior, 3.08 mm; lateral, ± 2.2 mm; dorsal-ventral 2.7 mm from bregma), CA1 areas of hippocampus were detected, and injection was performed using a Hamilton syringe (50ng/µL/side). Every injection lasted for 1 minute; and to facilitate diffusion of Aβ, injection in the left side was performed after 60 seconds. Finally, the head of the rats was darned and they were returned to cages; probiotics intake began again in the next day.

Glucose, Insulin levels, and Lipid profile detection

After 12 hours of fasting, 5 mL blood was collected from all rats. The samples were kept for 30 minutes for clotting and were then centrifuged at 1500 rpm for 10 minutes. Clear serum was collected and kept in -80. Serum Glucose, triglyceride, total cholesterol, LDL, and HDL levels were detected by a calorimetric method with commercial kits (Dialab GmbH, Austria). Insulin level was detected by ultrasensitive rat insulin ELISA kit (Mercodia, Sweden). Insulin resistance was determined using homeostasis model assessment of insulin resistance (HOMA-IR) using the following formula: fasting serum glucose (mg/dl) × fasting serum insulin (MU/dl) /405.

Statistical analysis

Data were analyzed using SPSS 23.0. Results were presented as Mean±SD. ANOVA (one way analysis of variance followed Bonferroni comparisons post hoc) was used to compare all the variables between groups.

Results

Weight changes

At baseline and at the end of the study, weight was not significantly different between groups. During the intervention, only weight showed a significant difference on the third week in AP group compared to C, CP, and S groups (Fig. 1).

Insulin resistance biomarkers

Figure 2 illustrates serum FBS levels. Aβ injection led to an increase in serum FBS level and indicated statistical difference in Aβ group (156.83±19.39) compared to C (113.17±9.94; P< 0.001), S (115.67±12.68; p< 0.001), and CP (127.75±26.32; p< 0.001) groups. In the AP group, probiotics intake decreased serum FBS level (147.40± 17.49) compared to Aβ group, but it was not significant, but it was higher than C, CP, and S (p< 0.001) groups. Aβ injection led to a statistically remarkable increase in serum insulin level (1.46±0.21) (Fig. 3), and insulin resistance index was defined as HOMA-IR (0.56±0.11) (Fig. 4) in Aβ group compared to C (0.78±0.32 and 0.22±0.01), CP (0.79±0.29 and 0.25±0.12), and S (0.78±0.15 and 0.22±0.05) groups (p< 0.001). In AP group, probiotics intake considerably reduced serum insulin level (0.93±0.14) and HOMA index (0.33±0.05) compared to Aβ group (p< 0.001).

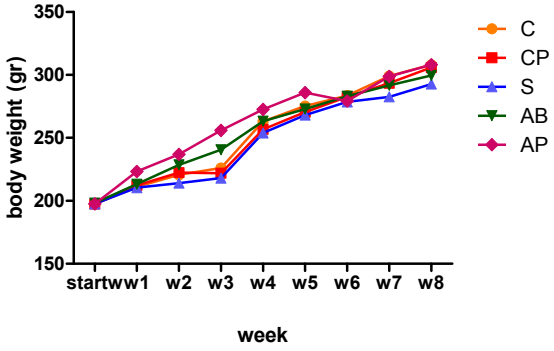

Fig. 1. The changes of body weight
At the baseline and at the end of study, weight did not show any significant difference between groups. During the intervention, except for difference in the third week, results did not show any statistical difference between the groups (p> 0.05). C: control; CP: control-probiotics; S: sham operation; Aβ: Alzheimer; AP: Alzheimer-probiotics.

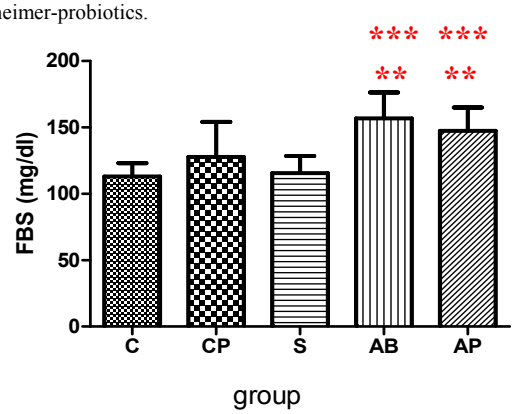

Fig. 2. The effect of intrahippocampal injection of Aβ and Aβ+probiotics intake on FBS level
The results have been presented as Mean±SD. ***P< 0.0001 significant difference between Aβ vs C, Aβ vs S and AP vs C. **P< 0.01 significant difference between Aβ vs CP, AP vs CP and AP vs S. C: control; CP: control-probiotics; S: sham operation; Aβ: Alzheimer; AP: Alzheimer-probiotics.

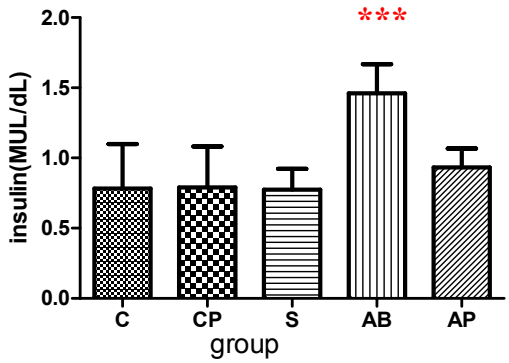

Fig. 3. The effect of intra hippocampal injection of Aβ and Aβ+probiotics intake on insulin level
The results have been presented as Mean±SD. ***P< 0.0001 significant difference between Aβ vs C, Aβ vs CP, Aβ vs S and Aβ vs AP. C: control; CP: control-probiotics; S: sham operation; Aβ vs: Alzheimer; AP: Alzheimer-probiotics.

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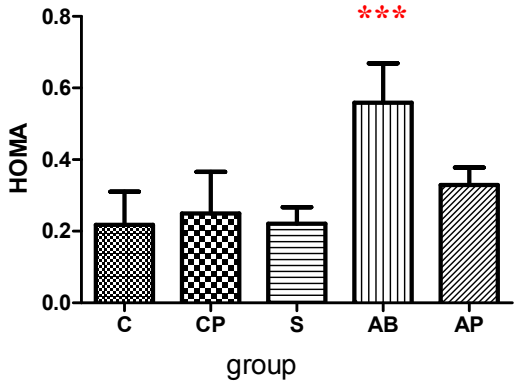

Fig. 4. The effect of intrahippocampal injection of Aβ and Aβ+probiotics intake on HOMA-IR index
The results have been presented as Mean±SD. ***P< 0.0001 significant difference between Aβ vs C, Aβ vs CP, Aβ vs S and Aβ vs AP. C: control; CP: control-probiotics; S: sham operation; Aβ: Alzheimer; AP: Alzheimer-probiotics.

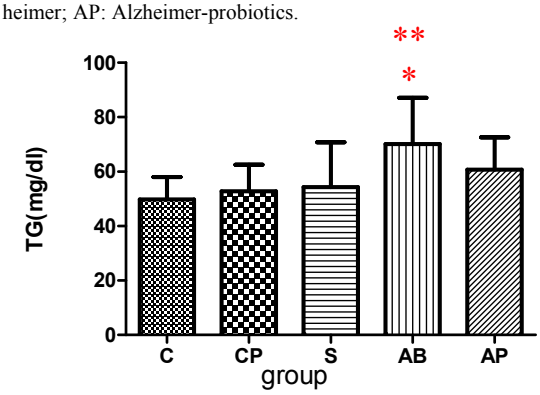

Fig. 5. The effect of intrahippocampal injection of Aβ and Aβ+probiotics intake on TG level
The results have been presented as Mean±SD. ** P< 0.01 significant difference between Aβ vs C; * P< 0.05 significant difference between Aβ vs CP and Aβ vs S. C: control; CP: control-probiotics; S: sham operation; Aβ: Alzheimer; AP: Alzheimer-probiotics.

Lipid profile

According to lipid profile, Aβ injection only increased serum TG level (Fig. 5) in Aβ group (79.08±17.03) compared to C (49.83±8.21; p< 0.001), CP (52.83±9.73) and S (54.25±16.55) groups (p= 0.03). In the AP group, probiotics intake reduced serum TG level (60.70±11.92), but it was not significant compared to Aβ group and other groups. Total cholesterol, LDL, and HDL levels were not significantly different between groups (Table 1).

Discussion

In this study, we assessed insulin resistance biomarkers. Our results revealed higher serum FBS, insulin levels, and HOMA-IR index in the Alzheimer group compared to the control group. In the AP group, probiotics intake decreased FBS level, but it was not significant compared to the Alzheimer group; moreover, FBS level was higher than the control group. Nevertheless, fasting insulin level and HOMA-IR index considerably declined and returned to the optimal level in the AP group. With respect to lipid profile, only serum TG level dramatically increased in the Alzheimer group compared to the control, but TG level did not show any significant differences between the Alzheimer and AP groups.

Consistent with the results of our study, many studies have suggested increased level of serum glucose, insulin, and HOMA in AD patients without diabetes (Burns et al. 2012, Li et al. 2015, Qiu and Folstein. 2006). Some studies have indicated that insulin resistance index (HOMA-IR) is mostly correlated with senile plaque and that AD patients are highly likely to develop diabetes. For example, the results of one study indicated that 80% of AD patients suffer from Type 2 diabetes or an impaired fasting glucose level (Kim and Feldman. 2015). It is possible that increased peripheral insulin level suggested in AD is compensatory for decreased insulin level in CNS and insulin signaling impairment. Also, results of some studies have suggested that pathological alterations of the brain related to AD commonly happen in regions regulating metabolism and satiety and could lead to systemic alterations of insulin level (Burns et al. 2012). On the other hand, oxidative stress and inflammation observed in AD can affect systemic biomarkers. Various studies have found increased inflammatory and oxidative markers in the serum of AD patients. Inflammatory factors such as TNFα lead to increased level of glucose and triglyceride production in the liver and decrease the peripheral glucose uptake, which causes insulin resistance (Mushtaq et al. 2015). Also, oxidative stress biomarkers can elevate FBS and HOMA-IR index (Salim et al. 2010). The elevated glucose level can affect the glucose uptake and may increase denevo lipogenesis and TG synthesis (Yadav et al. 2007).

Probiotics such as lactobacillus and *bifidobacterium* have beneficial effects on metabolic profile (Shimizu et al. 2015). Specific species of lactic acid bacteria such as *L.acidophilus* improve glucose intolerance, hyperglycemia, and hyperinsulinemia (Ruan et al. 2015). One Study shows that consumption of capsules containing *L.acidophillus*, *L.casei*, and *B.bifidum* decreases serum

Table 1. The serum lipid profile biomarkers

Group	Total Cholesterol (mg/dl)	LDL (mg/dl)	HDL (mg/dl)
Control	68.5 ± 9.85	34.17 ± 5.81	27.08 ± 3.89
CP	75.33 ± 10.56	35.42 ± 5.29	27.08 ± 3.92
S	67.25 ± 8.58	33.92 ± 5.5	25.75 ± 4.20
Aβ	69.25 ± 9.21	32.67 ± 5.23	26.08 ± 3.96
AP	66.70 ± 6.5	30.10 ± 2.88	25.00 ± 3.05

The results are in Mean±SD.
There was no significant difference between the groups (P>0.05). CP: control-probiotics, S: sham operation; Aβ: Alzheimer; AP: Alzheimer-probiotics.

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insulin level and HOMA-IR, but it does not show any effect on FBS level and lipid profile in patients with major depressive disorder (Akkasheh et al. 2016). Another study suggests that intake of probiotics including *L.acidophillus*, *L.fermentum*, and *B.lactis* have resulted in a decreased level of FBS and insulin in STZ-induced diabetic rats (Davari et al. 2013).The results of a meta-analysis suggest that decreased level of glucose following probiotics intake is significantly higher in hyperglycemic objects. Interventions with duration over 8 weeks reveal a remarkable effect on FBS level; however, in interventions with durations of less than or equal to 8 weeks, a slight trend of glucose reduction have been observed. Also, amount of bacteria $\geq 10^{11}$ CFU is related to significant effects (Desbonnet et al. 2010). So, alteration in FBS, insulin levels, and HOMA-IR are confirmed in our study.

Also, probiotics cause PPARα (peroxisome proliferator-activated receptor) and CPT2 (carnitine-palmitoyl-transferase) expression up-regulation, β-oxidation activation, and lipogenesis suppression that eventually lead to decreased TG level, as observed in our study (Park et al. 2013). Another meta-analysis demonstrated that probiotics significantly reduce the total cholesterol and LDL levels and they do not have any effect on HDL or TG levels. It is noted that when the baseline cholesterol and LDL levels are optimal, probiotics do not show any effects. The hypocholesterolemic effect of probiotics is stronger in trials over than or equal to 8 weeks. Also, bacterial strains and dosage are important factors (Cho and Kim. 2015). Since there were fewer baseline levels of cholesterol and LDL in our study, these parameters did not change.

Nevertheless, there were some limitations in our study. Given the costs associated with such undertaking, it was not possible to prolong the study. Also, it was better to study genetically modified mice as AD phenotype to avoid additional inconsistencies.

Conclusion

Overall, our study results indicate that probiotics can decrease insulin resistance markers such as serum insulin levels and HOMA-index, which have raised following intrahippocampal Aβ injection in an experimental model of Alzheimer's disease.

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Conflict of Interests

The authors declare that they have no competing interests.

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