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Clinical and metabolic response to probiotic administration in patients with major depressive disorder: A randomized, double-blind, placebo-controlled trial

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ABSTRACT

Objective: We are aware of no study examining the effects of probiotic supplementation on symptoms of depression, metabolic profiles, serum high-sensitivity C-reactive protein (hs-CRP), and biomarkers of oxidative stress in patients with major depressive disorder (MDD). The present study was designed to determine the effects of probiotic intake on symptoms of depression and metabolic status in patients with MDD.

Methods: This randomized, double-blind, placebo-controlled clinical trial included 40 patients with a diagnosis of MDD based on DSM-IV criteria whose age ranged between 20 and 55 y. Patients were randomly allocated into two groups to receive either probiotic supplements (n = 20) or placebo (n = 20) for 8 wk. Probiotic capsule consisted of three viable and freeze-dried strains: *Lactobacillus acidophilus* (2×10^9 CFU/g), *Lactobacillus casei* (2×10^9 CFU/g), and *Bifidobacterium bifidum* (2×10^9 CFU/g). Fasting blood samples were taken at the beginning and end of the trial to quantify the relevant variables. All participants provided three dietary records (two weekdays and one weekend) and three physical activity records during the intervention.

Results: Dietary intake of study participants was not significantly different between the two groups. After 8 wk of intervention, patients who received probiotic supplements had significantly decreased Beck Depression Inventory total scores (-5.7 ± 6.4 vs. -1.5 ± 4.8, $P = 0.001$) compared with the placebo. In addition, significant decreases in serum insulin levels (-2.3 ± 4.1 vs. 2.6 ± 9.3 μIU/mL, $P = 0.03$), homeostasis model assessment of insulin resistance (-0.6 ± 1.2 vs. 0.6 ± 2.1, $P = 0.03$), and serum hs-CRP concentrations (-1138.7 ± 2274.9 vs. 188.4 ± 1455.5 ng/mL, $P = 0.03$) were observed after the probiotic supplementation compared with the placebo. Additionally, taking probiotics resulted in a significant rise in plasma total glutathione levels (1.8 ± 83.1 vs. -106.8 ± 190.7 μmol/L, $P = 0.02$) compared with the placebo. We did not find any significant change in fasting plasma glucose, homeostatic model assessment of beta cell function, quantitative insulin sensitivity check index, lipid profiles, and total antioxidant capacity levels.

ZA. contributed to conception, design, statistical analysis, and drafting of the manuscript. G.A., Z.K.-P., M.T.-E., P.J., H.A., M.T., M.R.M., and A.E. contributed to data collection and manuscript drafting. Z.A. supervised the study. All authors approved the final version for submission. Clinical trial registration number: IRCT2014060717993 N1 (www.irct.ir). The present study was supported by a grant (no. 9344) from the vice chancellor for research, Kashan University of Medical Sciences, Iran. The authors would like to thank the staff of Kargarneghad Hospital (Kashan, Iran) for their assistance in this project. None of the authors had any personal or financial conflict of interest.

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Conclusions: Probiotic administration in patients with MDD for 8 wk had beneficial effects on Beck Depression Inventory, insulin, homeostasis model assessment of insulin resistance, hs-CRP concentrations, and glutathione concentrations, but did not influence fasting plasma glucose, homeostatic model assessment of beta cell function, quantitative insulin sensitivity check index, lipid profiles, and total antioxidant capacity levels.

Introduction

Major depressive disorder (MDD) is a complex and multifactorial disorder that involves marked disabilities in global functioning, anorexia, and severe medical comorbidities [1]. It affects around 20% of the population at some point during their lifetime [2]. Previous studies have shown a link between metabolic profiles, biomarkers of inflammation, oxidative stress, and MDD [1,3,4]. Depression or depressive episodes may affect cortisol dysregulation, which might in turn result in the development of insulin resistance in patients with depression [5]. In addition, recent studies have reported that decreased antioxidant levels, especially of glutathione (GSH), are associated with increased anhedonia severity, which subsequently might lead to involvement of neuroinflammation and oxidative stress in patients with MDD [6].

Probiotics are proposed to have a range of health benefits. Their beneficial impacts on a wide range of symptoms have been examined, including relief of irritable-bowel syndrome and inflammatory bowel disease, as well as the amelioration of lactose intolerance, and the prevention of bowel cancer [7,8]. Moreover, emerging research has reported that the microflora of the intestines may affect the immune system and functioning beyond the gut [9]. Probiotics might have favorable effects on mood and psychological problems [10]. In a study by Mohammadi et al. [11], consumption of probiotic yogurt or a multispecies probiotic capsule for 6 wk had beneficial effects on mental health parameters in petrochemical workers. Other studies have also reported the favorable effects of probiotic administration in healthy subjects [12] and patients with chronic fatigue syndrome [13]. In a study by Benton et al. [14], consumption of probiotic yogurt improved the mood of those whose mood was initially poor. In addition, improved metabolic status, biomarkers of inflammation, and oxidative stress were observed after a 2-mo supplementation with probiotics in pregnant women and patients with type 2 diabetes mellitus [15,16]. However, probiotic supplementation containing *Lactobacillus rhamnosus* strain GG and *Bifidobacterium* had no beneficial effects in people with schizophrenia after 14 wk [17].

Probiotics may result in reduced depressive symptoms, as well as improved metabolic status, biomarkers of inflammation, and oxidative stress, through their effect on neuronal circuits and the central nervous system mediated by the microbiota-gut-brain axis [18] and through affecting gene expression [19]. In addition, experimental studies in the animal model of depression have demonstrated that the oral administration of a probiotic can increase plasma tryptophan concentrations, decrease serotonin metabolite concentrations in the frontal cortex, and dopamine metabolite concentrations in the amygdaloid cortex [20]. However, whether probiotics have direct benefits on depressive symptoms and metabolic status in patients with MDD has to date not been assessed. The present study was therefore conducted to assess the favorable effects of probiotic supplementation on symptoms of depression, parameters of glucose homeostasis, lipid concentrations, biomarkers of inflammation, and oxidative stress in patients with MDD.

Materials and methods

Participants

Forty patients with MDD whose age ranged between 20 and 55 y were recruited for this randomized, double-blind, placebo-controlled trial from July 2014 to September 2014. To determine the sample size, we applied a randomized clinical trial sample size formula considering type I (α) and type II errors (β) of 0.05 and 0.20 (power = 80%), respectively. On the basis of a previous study [11], we used a standard deviation (SD) of 18.5 and a difference in mean (d) of 18, considering depression anxiety and stress scale as the key variable. This calculation indicated a total of 17 patients for each group. However, we recruited 40 patients with MDD in total (20 patients for each group) to compensate for the probable loss to follow-up. Patients with a diagnosis of MDD based on DSM-IV criteria and with a score of $\geq$15 on the 17-item Hamilton Depression Rating Scale were included in the study, and they were referred from Kargarneghad Hospital, Kashan University of Medical Sciences (KUMS), Kashan, Iran. Exclusion criteria were age <20 y or >55 y; a history of coronary infarction, angina pectoris, pregnancy or lactation, or substance abuse; and taking dietary supplements or probiotic supplements during the previous 2 mo. All procedures were followed according to the ethics standards of the responsible committee on human experimentation (institutional and national) and to the Declaration of Helsinki. In addition, the ethics committee of KUMS approved the study. All patients provided written informed consent. This study was registered in the Iranian website (www.irct.ir) for registration of clinical trials (IRCT Code: IRCT2014060717993 N1).

Study design

In the present study, patients were randomly allocated into two groups to receive either probiotic supplements (17 women and 3 men: n = 20) or placebo (17 women and 3 men: n = 20) for 8 wk. Patients in the probiotic group received daily one probiotic capsule containing *Lactobacillus acidophilus* (2×10^9 CFU/g), *Lactobacillus casei* (2×10^9 CFU/g), and *Bifidobacterium bifidum* (2×10^9 CFU/g). It would be more appropriate if the strains used in probiotic supplements for human consumption were derived from the human intestinal tract, well characterized, able to outlive the rigors of the digestive tract and possibly colonize, biologically active against the target, and stable and amenable to commercial production and distribution [21]. Because of the lack of evidence about the appropriate dosage of probiotics for patients with MMD, we used the above-mentioned doses based on a few previous studies in healthy subjects [11,14]. Subjects in the placebo group received the placebo that contained starch but no bacteria. The appearance of the placebo was indistinguishable in color, shape, size, packaging, smell, and taste from that of the probiotic supplement. All capsules were provided by Tak Gen Zist Pharmaceutical Company (Tehran, Iran) and were approved by the Food and Drug Administration of Iran. Random assignment was performed by the use of computer-generated random numbers. Randomization and allocation were concealed from the researchers and participants until the main analyses were completed. The randomized allocation sequencing, enrolling patients, and allocating participants to interventions were done by a trained nutritionist at a psychiatry clinic. At the beginning of the study, patients were requested not to change their routine physical activity or usual dietary intakes throughout the study; not to consume any supplements other than the one provided to them by the investigators; and not to take, during the 8-wk intervention, any medications that might affect findings. Compliance to probiotic and placebo capsules was monitored by asking participants to return the medication containers. All participants provided three dietary records (two weekdays and one weekend) and three physical activity records to ensure that they maintained their usual diet and physical activity during the intervention. Both dietary and physical activity records were taken at weeks 2, 4, and 6 of the intervention. To obtain nutrient intakes of participants based on the three-day food diaries, we used Nutritionist IV software (First Databank, San Bruno, CA, USA) modified for Iranian foods.