Randomized Control Trials

The effects of probiotic and selenium co-supplementation on mental health parameters and metabolic profiles in type 2 diabetic patients with coronary heart disease: A randomized, double-blind, placebo-controlled trial

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SUMMARY

Background and aims: The objective of this investigation was to assess the effects of probiotic and selenium co-supplementation on indicators of mental health and metabolic profiles in diabetic people with coronary heart disease (CHD).

Methods: This randomized, double-blind, placebo-controlled trial was conducted among 54 diabetic people with CHD. Patients were randomly allocated into two groups to receive either 200 μg/day selenium plus 8×10^9 CFU/day probiotic (n = 27) or placebo (n = 27) for 12 weeks.

Results: Probiotic and selenium co-supplementation significantly decreased Beck Depression Inventory index (β −1.46; 95% CI, −2.61, −0.31; P = 0.01) and Beck Anxiety Inventory index (β −1.23; 95% CI, −2.33, −0.12; P = 0.02) compared with the placebo. Consuming probiotic plus selenium lowered fasting plasma glucose (β −10.80 mg/dL; 95% CI, −17.68, −3.92; P = 0.003), serum insulin levels (β −3.42 μIU/mL; 95% CI, −4.93, −1.90; P < 0.001), insulin resistance (β −0.96; 95% CI, −1.45, −0.47; P < 0.001), and enhanced insulin sensitivity (β 0.01; 95% CI, 0.007, 0.01; P < 0.001) compared with the placebo. Additionally, co-supplementation reduced triglycerides (β −34.45 mg/dL; 95% CI, −56.18, −12.72; P = 0.003), VLDL- (β −6.89 mg/dL; 95% CI, −11.23, −2.54; P = 0.003), total cholesterol (β −18.13 mg/dL; 95% CI, −23.42, −2.83; P = 0.02) and high sensitivity C-reactive protein (β −1043.28 ng/mL; 95% CI, −1929.67, −156.89; P = 0.02), and increased nitric oxide (β 7.86 μmol/L; 95% CI, 5.63, 10.09; P < 0.001), total antioxidant capacity (β 119.30 mmol/L; 95% CI, 63.04, 175.57; P < 0.001) and total glutathione (β 154.16 μmol/L; 95% CI, 82.57, 225.74; P < 0.001) compared with the placebo.

Conclusions: Probiotic and selenium co-supplementation to diabetic people with CHD improved indicators of mental health and metabolic profiles.

Registered under Clinical Trials.gov Identifier no. http://www.irct.ir: IRCT20170513033941N28.

1. Introduction

Type 2 diabetes mellitus (T2DM) and obesity are risk factors for coronary heart disease (CHD) and stroke [1]. Diabetic patients compared with nondiabetic people bear up to six-fold higher risk of future CHD [2]. Various factors including obesity, insulin resistance, dyslipidemia and hypertension in diabetic patients may affect vascular risk [3]. Disorders related to mental health such as depression, and T2DM and CHD occur together and this status can cause a vicious circle [4]. Approximately, 30% of the people with T2DM and/or CHD has subthreshold depression and higher than 40% of those will develop major depressive disorder within two years [5]. Moreover, increased inflammatory markers and oxidative damage play important roles in the progress of diabetes and atherosclerosis [6].

It was reported that selenium levels were low in diabetic patients with peripheral artery disease [7]. In addition, the gut microbiota plays an important function in host metabolism and has been associated with metabolic disorders and mental health [8]. However, the beneficial effects of only selenium or probiotic

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supplementation on metabolic profiles in patients with T2DM and/ or CHD were previously reported, data on combined selenium and probiotic supplementation on metabolic profiles in these patients are limited. In two meta-analyses studies, the beneficial effects of selenium on inflammation and oxidative damage [9] and probiotic on lipid profiles among people with CHD [10] were reported. Combined selenium and probiotic administration may reduce complications of people with T2DM and CHD by improving their metabolic profiles and attenuating oxidative stress and inflammation. Nido et al. [11] demonstrated that selenium-enriched probiotic than only selenium or probiotic improved metabolic profiles in an animal study.

Both probiotics and selenium have antidiabetic, antioxidant and anti-inflammatory effects, therefore we hypothesized that co-administration of probiotic and selenium might benefit diabetic patients diagnosed with CHD. To address the hypotheses, this study was aimed to determine the effects of probiotic and selenium co-supplementation on mental health and metabolic status of diabetic patients with CHD.

2. Methods

2.1. Trial design and participants

This study was a randomized, double-blinded, placebo-controlled trial registered with Iranian Clinical Trials website (http://www.irct.ir: IRCT20170513033941N28). Study participants aged 45–85 years old had been diagnosed with both T2DM and CHD. The criteria of the American Diabetes Association and American Heart Association were used to diagnose T2DM and 2- and 3-vessel CHD, respectively. Study protocol was approved by the research ethics committee of Kashan University of Medical Sciences (KAUMS) and informed consent was signed by all participants. The study was conducted from December 2017 through March 2018. Participants reported selenium, probiotic and/or synbiotic consumption within the last 3 months, patients with thyroid disorders, severe renal insufficiency and hepatic failure, and those experiencing an acute myocardial infarction and cardiac surgery within the past 3 months were excluded from the study.

2.2. Study procedures

Initially, study participants were stratified according to their age and BMI. Then, they were randomly allocated into intervention groups to receive either 200 μg/day selenium as selenium yeast (Webber Naturals Company, Coquitlam, Canada) plus 8×10^9 CFU/ day probiotic (LactoCare®, Zisttakhmir Company, Tehran, Iran) containing Lactobacillus acidophilus, Lactobacillus reuteri, Lactobacillus fermentum and Bifidobacterium bifidum (2×10^9 CFU/g each) or placebo (Barij Essence, Kashan, Iran) (n = 27 each group) for 12 weeks. Computer-generated random numbers were used for randomization. Randomization and allocation were concealed from both researchers and participants until the completion of final analyses. All process of randomization, enrollment, and participants' assignment into the intervention groups were conducted by a trained nutritionist. Compliance rate was estimated by counting the pills of placebo, selenium and probiotics in the returned containers. A 3-day dietary intake record was completed by study participants at week 1, 4, 8 and 12. Nutritionist IV software (First Databank, San Bruno, CA), adopted for Iranian food pattern, was applied to determine participants' macro- and micro-nutrient intakes. The same nutritionist also measured anthropometric parameters (Seca, Hamburg, Germany) at the beginning and end of the intervention in cardiology clinic.

2.3. Assessment of outcomes

The homeostasis model of assessment-insulin resistance (HOMA-IR) was considered as the primary outcome, but indicators of mental health and other metabolic parameters were considered as secondary results. Fasting blood (10 mL) were taken at baseline and after the 12-week intervention. ELISA kits were used to determine insulin (DiaMetra, Milano, Italy) and high sensitivity C-reactive protein (hs-CRP) (LDN, Nordhorn, Germany). HOMA-IR and the quantitative insulin sensitivity check index (QUICKI) were assessed in accordance with the standard formulas. Enzymatic kits (Pars Azmun, Tehran, Iran) were applied to estimate fasting plasma glucose (FPG) and lipid profiles. Nitric oxide (NO) [12], total antioxidant capacity (TAC) [13], total glutathione (GSH) [14] and malondialdehyde (MDA) levels [15] were determined by the spectrophotometric test. Inter-assay and intra-assay coefficient variances (CVs) of metabolic profiles were lower than 7%

2.4. Clinical assessment

Beck Depression Inventory (BDI) and Beck Anxiety Inventory (BAI) developed by Beck et al. were assessed. Quality of sleep was determined using Pittsburgh Sleep Quality Index (PSQI).

2.5. Statistical methods and sample size

Sample size formula for randomized clinical trial were used, where type one (α) and type two errors (β) were 0.05, and 0.20 (power = 80%), respectively. In a previous study [16], 1.61 as the SD and 2.30 as the change in mean (d) of HOMA-IR were used. According to the formula, in each group 25 individuals were required; after the attrition rate 20% in every group, the sample size was 30 persons in each group.

The Kolmogorov–Smirnov test was used for checking the normality of data. Differences in anthropometric measures and dietary intakes between the two groups were tested using the independent-samples t-test. To evaluate treatment impacts on study variables, we used multiple linear regression models. Differences in proportions were evaluated by Chi square test. Statistical significance was set at P-value <0.05. The Statistical Package for Social Science version 18 (SPSS Inc., Chicago, Illinois, USA) was used for statistical analyses of this trial.

3. Results

Three subjects in the supplements (n = 3) and placebo (n = 3) groups dropped out for personal reasons (Fig. 1). Finally, 54 patients [selenium plus probiotic (n = 27) and placebo (n = 27)] finished the trial. Overall, the compliance rate was high, such that more than 90% of capsules were consumed throughout the study in both groups. No adverse effects were recorded in diabetic patients with CHD after the intake of selenium and probiotic.

No difference in mean age, anthropometric parameters and METs was seen between the two groups (Table 1).

We observed no significant changes in dietary intake of macro- and micronutrients between the two groups (Data not shown).

Probiotic and selenium co-supplementation decreased BDI (β −1.46; 95% CI, −2.61, −0.31; P = 0.01) and BAI (β −1.23; 95% CI, −2.33, −0.12; P = 0.02) compared with the placebo (Table 2). Consuming probiotic plus selenium lowered FPG (β −10.80 mg/dL; 95% CI, −17.68, −3.92; P = 0.003), insulin levels (β −3.42 μIU/mL; 95% CI, −4.93, −1.90; P < 0.001), HOMA-IR (β −0.96; 95% CI, −1.45, −0.47; P < 0.001), and enhanced QUICKI (β 0.01; 95% CI, 0.007, 0.01; P < 0.001) compared with the placebo. Additionally, co-
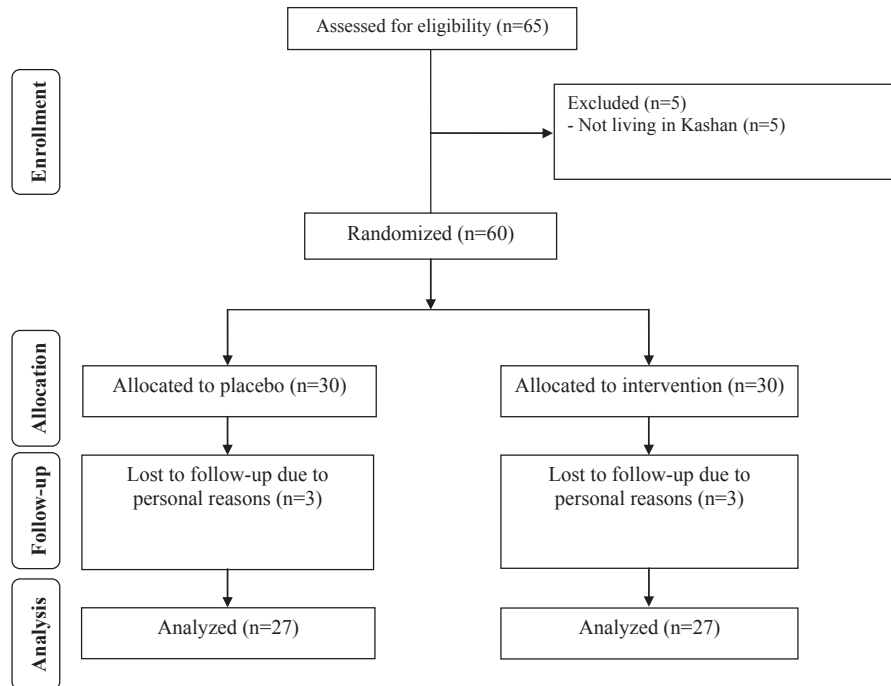
Fig. 1. Summary of patient flow diagram.

Table 1
General characteristics of study participants.

	Placebo group (n = 27)	Probiotic plus selenium group (n = 27)	P[a]
Age (y)	62.4 ± 13.1	64.8 ± 8.3	0.45
Gender			
Female	17 (63.0)	16 (59.3)	0.78[b]
Male	10 (37.0)	11 (40.7)	
Height (m)	160.7 ± 8.8	158.9 ± 10.4	0.46
Weight at study baseline (kg)	77.1 ± 13.1	78.7 ± 12.7	0.65
Weight at end-of-trial (kg)	77.3 ± 13.0	78.7 ± 12.7	0.68
Body weight change (kg)	0.2 ± 1.3	0.1 ± 0.6	0.61
BMI at study baseline (kg/m^2)	29.9 ± 5.0	31.4 ± 5.8	0.31
BMI at end-of-trial (kg/m^2)	30.0 ± 5.0	31.4 ± 5.7	0.33
BMI change (kg/m^2)	0.1 ± 0.5	0.02 ± 0.3	0.56

Data are means± SDs.
BMI, body mass index.
[a] Obtained from independent samples *t*-test.
[b] Obtained from Pearson Chi-square test.

supplementation reduced triglycerides (β −34.45 mg/dL; 95% CI, −56.18, −12.72; P = 0.003), VLDL- (β −6.89 mg/dL; 95% CI, −11.23, −2.54; P = 0.003), total cholesterol (β −18.13 mg/dL; 95% CI, −23.42, −2.83; P = 0.02) and hs-CRP (β −1043.28 ng/mL; 95% CI, −1929.67, −156.89; P = 0.02), and increased NO (β 7.86 μmol/L; 95% CI, 5.63, 10.09; P < 0.001), TAC (β 119.30 mmol/L; 95% CI, 63.04, 175.57; P < 0.001) and GSH (β 154.16 μmol/L; 95% CI, 82.57, 225.74; P < 0.001) compared with the placebo. Probiotic and selenium co-supplementation did not affect PSQI, other metabolic profiles and blood pressures.

4. Discussion

We found that co-supplementation with probiotic and selenium to diabetic people with CHD improved indicators of mental health and metabolic profiles.

4.1. Effect on clinical symptoms

We demonstrated that consuming probiotic plus selenium by diabetic people with CHD significantly improved BDI and BAI scores, but did not affect PSQI. Intervention studies of selenium administration in humans and its effects on depression have proposed inconsistent findings. In a study by Mokhber et al. [17], 100 μg/day selenium administration for 2 months to pregnant women prevented postpartum depression. Moreover, probiotic administration for 12 weeks to people with multiple sclerosis improved mental health parameters [18]. Selenium intake may affect mental health parameters through modulating thyroid function, which in turn play a role in the reduction of depression [19]. The main mechanisms by which probiotic intake may improve metal health symptoms include the modulation of neurotransmitters and inflammation [20].

4.2. Effect on metabolic parameters

In a study by Wang et al. [21], higher dietary selenium intake significantly reduced insulin resistance. We have previously showed that 200 μg/day selenium intake for 2 months to women with polycystic ovary syndrome improved insulin resistance, triglycerides and VLDL-cholesterol levels, while did not affect other metabolic profiles [22]. Insulin resistance and dyslipidemia lead to peripheral arterial disorder and endothelial cell dysfunctions, thus increasing risk factors for heart failure [23]. Selenium intake may improve glycemic status and lipid profiles through enhancing gene expression of very long chain dehydrogenase and enzymes related to β-oxidation [24]. In addition, probiotic intake by increasing β-oxidation of long-chain fatty acids in liver and muscle tissues and decreasing lipid synthesis in liver may decrease insulin resistance and dyslipidemia [25].

4.3. Effect on inflammation and oxidative stress

This study documented that taking probiotic plus selenium decreased hs-CRP, and increased NO, TAC and GSH levels, but did

Table 2
The effect of probiotic and selenium co-supplementation on mental health parameters, cardio-metabolic risk and biomarkers of oxidative stress in type 2 diabetic patients with coronary heart disease.

Variables	Placebo group (n = 27)		Probiotic plus selenium group (n = 27)		Difference in outcome measures between probiotic plus selenium and placebo treatment groups[a]	
	Baseline	Week 12	Baseline	Week 12	β (95% CI)	P[b]
BDI	24.5 ± 4.1	23.5 ± 3.6	24.9 ± 4.5	22.2 ± 3.8	−1.46 (−2.61, −0.31)	0.01
BAI	17.9 ± 4.5	16.8 ± 4.7	18.1 ± 4.8	15.7 ± 4.3	−1.23 (−2.33, −0.12)	0.02
PSQI	8.2 ± 1.9	8.3 ± 2.2	7.9 ± 1.8	7.7 ± 2.1	−0.47 (−1.56, 0.61)	0.38
FPG (mg/dL)	134.7 ± 43.9	132.6 ± 43.1	142.0 ± 41.9	129.5 ± 45.5	−10.80 (−17.68, −3.92)	0.003
Insulin (μIU/mL)	11.5 ± 4.8	12.7 ± 4.9	12.9 ± 2.5	10.3 ± 2.7	−3.42 (−4.93, −1.90)	<0.001
HOMA-IR	3.8 ± 2.1	4.1 ± 1.9	4.5 ± 1.4	3.6 ± 1.4	−0.96 (−1.45, −0.47)	<0.001
QUICKI	0.32 ± 0.02	0.31 ± 0.01	0.30 ± 0.01	0.32 ± 0.01	0.01 (0.007, 0.01)	<0.001
Triglycerides (mg/dL)	179.9 ± 68.2	179.1 ± 67.9	176.8 ± 76.4	143.7 ± 62.8	−34.45 (−56.18, −12.72)	0.003
VLDL-cholesterol (mg/dL)	36.0 ± 13.6	35.8 ± 13.6	35.3 ± 15.3	28.7 ± 12.6	−6.89 (−11.23, −2.54)	0.003
Total cholesterol (mg/dL)	171.6 ± 41.4	174.9 ± 49.3	169.6 ± 29.8	154.6 ± 24.3	−18.13 (−23.42, −2.83)	0.02
LDL-cholesterol (mg/dL)	90.0 ± 42.7	91.9 ± 50.5	87.5 ± 24.5	79.7 ± 17.6	−8.69 (−22.09, 4.70)	0.19
HDL-cholesterol (mg/dL)	45.7 ± 8.3	47.3 ± 8.7	46.7 ± 10.7	46.2 ± 9.4	−2.22 (−5.20, 0.75)	0.14
Total-/HDL-cholesterol ratio	3.8 ± 1.0	3.8 ± 1.4	3.8 ± 0.9	3.4 ± 0.6	−1.48 (−0.68, 0.12)	0.17
hs-CRP (ng/mL)	2683.9 ± 1812.5	3321.6 ± 2667.4	2618.5 ± 1395.9	2133.3 ± 1127.6	−1043.28 (−1929.67, −156.89)	0.02
NO (μmol/L)	36.0 ± 8.7	35.4 ± 8.3	36.6 ± 5.7	43.6 ± 6.1	7.86 (5.63, 10.09)	<0.001
TAC (mmol/L)	959.6 ± 204.7	944.5 ± 194.0	1062.2 ± 98.3	1141.8 ± 102.9	119.30 (63.04, 175.57)	<0.001
GSH (μmol/L)	511.7 ± 117.7	491.9 ± 167.8	542.3 ± 73.9	669.5 ± 149.9	154.16 (82.57, 225.74)	<0.001
MDA (μmol/L)	2.4 ± 0.4	2.5 ± 0.4	2.7 ± 0.3	2.7 ± 0.2	0.10 (−0.04, 0.25)	0.17
SBP (mmHg)	136.7 ± 9.3	135.9 ± 7.6	134.2 ± 12.6	132.4 ± 9.6	−2.64 (−6.32, 1.02)	0.15
DBP (mmHg)	78.2 ± 5.1	78.5 ± 5.7	76.8 ± 6.1	77.5 ± 6.8	0.11 (−2.54, 2.77)	0.93

Data are mean ±SDs.
BDI, beck depression inventory; BAI, beck anxiety inventory; DBP, diastolic blood pressure; FPG, fasting plasma glucose; GSH, total glutathione; HOMA-IR, homeostasis model of assessment-estimated insulin resistance; hs-CRP, high-sensitivity C-reactive protein; MDA, malondialdehyde; NO, nitric oxide; PSQI, Pittsburgh Sleep Quality Index; QUICKI, quantitative insulin sensitivity check index; SBP, systolic blood pressure; TAC, total antioxidant capacity.
[a] "Outcome measures" refers to the change in values of measures of interest between baseline and week 12. β [difference in the mean outcomes measures between treatment groups (probiotic plus selenium group = 1 and placebo group = 0)].
[b] Obtained from multiple regression model (adjusted for baseline values of each biochemical variables, age and baseline BMI).

not affect MDA and blood pressures. Selenium-enriched probiotics intake for 42 days in an animal model significantly decreased biomarkers of oxidative stress [26]. Probiotic supplementation for 8 weeks to people with rheumatoid arthritis also decreased inflammatory cytokines [27]. Tissue inflammation and oxidative damage are main pathogenic factors for the progress of diabetic complications [28]. Therefore, selenium and probiotic intake due to their anti-inflammatory and antioxidative effects may reduce complications related to diabetes and CHD events. The anti-inflammatory and antioxidative effects of selenium may be due to blocking activation of nuclear factor-κB through modulating selenoprotein genes expression and inhibiting production of reactive oxygen species [29]. Moreover, probiotic may reduce inflammatory factors and oxidative damage through producing short chain fatty acids in the gut and the decreasing production of free radicals [30].

Our study had a number of limitations. We did not measure plasma and/or urine selenium levels and fecal bacteria loads. Moreover, we did not determine the effects of selenium and probiotic co-supplementation on gene expression related to metabolic status.

Overall, probiotic and selenium co-supplementation to diabetic people with CHD had beneficial effects on indicators of mental health and metabolic profiles.

Authors' contributions

ZA contributed in conception, design, statistical analysis and drafting of the manuscript. FR and VO contributed in conception and data collection.

Conflicts of interest

None.

Acknowledgments

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.clnu.2018.07.017.

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