Probiotic supplementation in diabetic hemodialysis patients has beneficial metabolic effects

see commentary on page 274

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This study determined the effects of probiotic supplementation on glycemic control, lipid concentrations, biomarkers of inflammation and oxidative stress in 60 diabetic patients on hemodialysis in a parallel randomized double-blind placebo-controlled clinical trial. Participants were initially matched based on sex, duration of dialysis and diabetes, body mass index and age. Subsequently, they were randomly divided into two groups to take either a capsule containing the probiotics *Lactobacillus acidophilus*, *Lactobacillus casei* and *Bifidobacterium bifidum* or placebo for 12 weeks. Based on three-day dietary records throughout the trial, there was no significant change in dietary macro- and micro-nutrients or total dietary fiber to confound results. After the 12 weeks, analysis of patients who received probiotic supplements compared with the placebo showed they had significantly decreased fasting plasma glucose (–22.0 vs. +6.6 mg/dl), serum insulin (–6.4 vs. +2.3 μIU/ml), homeostasis model of assessment-estimated insulin resistance (–2.9 vs. +2.5), homeostasis model of assessment-estimated beta-cell function (–14.1 vs. +6.1) and HbA1c (–0.4 vs. –0.1%,), and improved quantitative insulin sensitivity check index (+0.03 vs. –0.02). Additionally, compared with the placebo, probiotic supplementation resulted in significant reductions in serum high-sensitivity C-reactive protein (–1933 vs. +252 ng/ml), plasma malondialdehyde (–0.3 vs. +1.0 μmol/l), subjective global assessment scores (–0.7 vs. +0.7) and total iron binding capacity (–230 vs. +33 μg/dl), and a significant increase in plasma total antioxidant capacity (+15 vs. –88 mmol/l). Thus, probiotic supplementation for 12 weeks among diabetic hemodialysis patients had beneficial effects on parameters of glucose homeostasis, and some biomarkers of inflammation and oxidative stress.

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Received 3 July 2016; revised 19 September 2016; accepted 22 September 2016; published online 4 December 2016

Kidney International (2017) **91,** 435–442; http://dx.doi.org/10.1016/j.kint.2016.09.040

KEYWORDS: hemodialysis; metabolic status; probiotic supplementation

Diabetes is still among the most frequent reasons for end-stage renal failure.[1] More than 20% of hemodialysis (HD) patients are diabetic,[2] and malnutrition and inflammation are the most prevalent consequences in HD patients.[3] In addition, HD is associated with other metabolic complications, including dyslipidemia and oxidative stress.[4] Microvascular, macrovascular, and neurological complications, including retinopathy-related impairment and peripheral neuropathy, that develop among diabetic patients, especially those with HD, adversely influence the quality of life.[5] Previous studies have shown that both malnutrition and inflammation are associated with atherosclerosis progression and with an increased risk of all-cause and cardiovascular morbidity and mortality in dialysis patients.[6,7]

A few human clinical trials were conducted to determine whether daily probiotic bacterial treatment is beneficial for HD patients. Only surrogate endpoints have been studied, such as changes in serum concentrations or urinary excretion of biomarkers (e.g., uremic toxins or cytokines). A study by Simenhoff *et al.*[8] observed that HD patients who were fed *Lactobacillus acidophilus* had significantly lower blood dimethylamine and nitrodimethylamine concentrations. In addition, reduced levels of toxins, including dimethylamine and a carcinogen, nitrosodimethylamine, were seen after supplementation of *L. acidophilus* in patients on dialysis who had end-stage kidney failure.[9] Studies investigating the impact of probiotics on clinical endpoints, including cardiovascular diseases (CVD) or mortality, have not yet been conducted. Moreover, the quality, size, and design of trials are not sufficient enough to justify the widespread use of probiotics. In contrast, the beneficial effects of probiotic supplementation on glycemic control, lipid concentrations, biomarkers of inflammation, and oxidative stress among patients without

HD have been previously reported.[10,11] Furthermore, a significant decrease in biomarkers of inflammation among HIV-infected patients for 4 weeks[12] and oxidative stress among patients with major depressive disorder for 8 weeks[10] was observed after supplementation with probiotics. However, probiotic supplementation in patients with rheumatoid arthritis for 8 weeks did not influence biomarkers of oxidative stress.[13]

Improvement of insulin resistance, lipid profiles, biomarkers of inflammation, and stress by probiotics might be due to their effects on scavenging superoxide and hydroxyl radicals,[14] reduced inflammatory signaling,[15] and decreasing adiposity.[16] To our knowledge, no study is currently available that evaluates the effects of taking probiotics on metabolic status in diabetic HD patients. In addition, data on the effects of probiotic supplementation on metabolic profiles are conflicting. Therefore, the present study was done to investigate the effects of probiotic supplementation on glycemic status, lipid concentrations, biomarkers of inflammation, and oxidative stress in diabetic HD patients.

RESULTS

Two participants in the probiotic group and 3 participants in the placebo group withdrew due to personal reasons, and were excluded from the study (Figure 1). Fifty-five participants (probiotic [n = 28] and placebo [n = 27]) completed the trial. However, because the analysis was done based on the intention-to-treat principle, all 60 participants (30 in each group) were included in the final analysis. On average, the rate of compliance in our study was high, such that >90% of probiotic and placebo capsules were consumed throughout the study in both groups. No significant gastrointestinal symptoms were reported because of the probiotics. However, this was not assessed routinely in the study, but the patients were asked to report any complications of taking the supplements. No side effects were reported after the administration of probiotics in diabetic HD patients throughout the study.

Distribution of sex, mean age, height, baseline weight, and body mass index (BMI), as well as their means after intervention, and years of dialysis of the study participants were not statistically different between the two groups (Table 1).

Based on the 3-day dietary records obtained throughout the trial, we found no significant change in dietary macro- and micronutrient intakes, and total dietary fiber (data not shown).

After 12 weeks of intervention, patients who received probiotic supplements compared with placebo had significantly decreased fasting plasma glucose (FPG) levels (−22.0 ± 48.2 mg/dl vs. +6.6 ± 27.4 mg/dl; $P = 0.006$), serum insulin levels (−6.4 ± 6.8 μIU/ml vs. +2.3 ± 7.1 μIU/ml; $P < 0.001$), homeostasis model of assessment–estimated insulin resistance (HOMA-IR) (−2.9 ± 3.5 vs. +1.0 ± 2.5; $P < 0.001$), HOMA-estimated β-cell function (HOMA-B) (−14.1 ± 36.9 vs. +6.1 ± 30.5; $P = 0.02$), and glycosylated hemoglobin (HbA_{1c}) (−0.4 ± 0.8% vs. −0.1 ± 0.4%; $P = 0.02$), and had an improved quantitative insulin sensitivity check index (QUICKI) (+0.03 ± 0.02 vs. −0.02 ± 0.04; $P < 0.001$) (Table 2). In addition, compared with placebo, probiotic supplementation resulted in significant reductions in serum high-sensitivity C-reactive protein (hs-CRP) (−1933.3 ± 4530.7 ng/ml vs. +252.4 ± 3190.8 ng/ml; $P = 0.03$), plasma malondialdehyde (MDA) (−0.3 ± 0.4 μmol/L vs. +1.0 ± 2.4 μmol/L; $P = 0.007$), subjective global assessment (SGA) scores (−0.7 ± 2.2 vs. +0.7 ± 1.8; $P = 0.01$), and total iron binding capacity (TIBC) (−230.3 ± 397.2 μg/dl vs. +33.3 ± 266.1 μg/dl; $P = 0.004$), and caused a significant increase in plasma total antioxidant capacity (TAC) concentrations (+15.3 ± 143.3 mmol/L vs. −88.4 ± 207.6 mmol/L; $P = 0.02$). Supplementation with probiotics had no significant effects on lipid profiles, biomarkers of inflammation, and oxidative stress compared with placebo.

There was a significant difference in the baseline levels of QUICKI ($P = 0.03$), TAC ($P = 0.009$), MDA ($P = 0.01$), blood urea nitrogen (BUN) ($P = 0.03$), and albumin ($P = 0.009$) between the 2 groups. Therefore, we adjusted the analysis for baseline values of biochemical parameters, age,

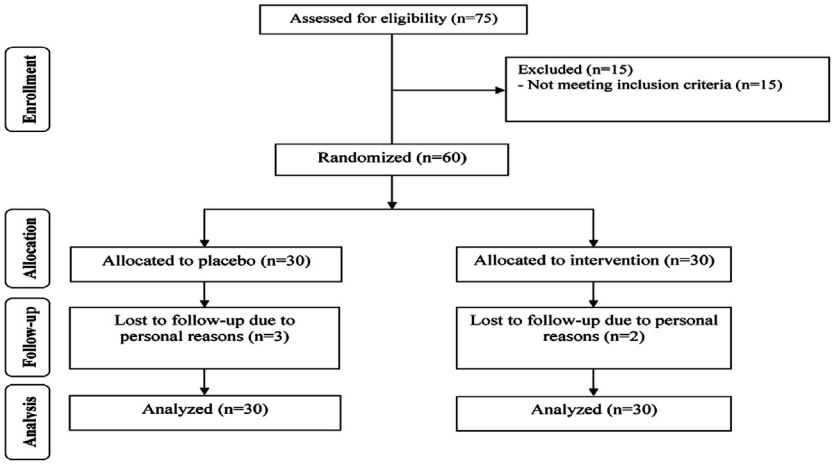

Figure 1 | Summary of patient flow diagram.