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The beneficial effects of *Lactobacillus reuteri* ADR-1 or ADR-3 consumption on type 2 diabetes mellitus: a randomized, double-blinded, placebo-controlled trial

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Probiotics have been reported to ameliorate symptoms of type 2 diabetes mellitus (T2DM) in animal models and human studies. We previously demonstrated that oral administration of *Lactobacillus reuteri* ADR-3 reduced insulin resistance in high-fructose-fed (HFD) rats. In the present study, we first identified another *L. reuteri* strain, ADR-1, which displayed anti-diabetes activity that reduced the levels of serum HbA1c and cholesterol and that increased antioxidant proteins in HFD rats. We further performed a randomized, double-blinded, placebo-controlled trial with a total of 68 T2DM patients to examine the beneficial effects of oral consumption of *L. reuteri* strains ADR-1 and ADR-3 and to investigate the associated changes in intestinal flora using a quantitative PCR method to analyze 16S rRNA in fecal specimens. Significant reductions in HbA1c and serum cholesterol were observed in participants in the live ADR-1 consumption group (n = 22) after 3 months of intake when compared with those in the placebo group (n = 22). Although there was no significant difference in the HbA1c serum level among participants who consumed heat-killed ADR-3 (n = 24), the systolic blood pressure and mean blood pressure were significantly decreased after 6 months of intake. There was no obvious change in serum inflammatory cytokines or antioxidant proteins in participants after intaking ADR-1 or ADR-3, except for a reduction in IL-1 β in the ADR-3 consumption group after 6 months of intake. With the analysis of fecal microflora, we found that *L. reuteri* or *Bifidobacterium* spp. were significantly increased in the ADR-1 and ADR-3 consumption groups, respectively, after 6 months of intake. Interestingly, a significant reduction in HbA1c was observed in the ADR-1 and ADR-3 consumption participants who displayed at least an 8-fold increase in fecal *L. reuteri*. We also observed that there was a significantly positive correlation between *Bifidobacterium* spp. and *Lactobacillus* spp. in participants with increased levels of fecal *L. reuteri*. In the ADR-1 intake group, the fecal *Lactobacillus* spp. level displayed a positive correlation with *Bifidobacterium* spp. but was negatively correlated with *Bacteroidetes*. The total level of fecal *L. reuteri* in participants in the ADR-3 consumption group was positively correlated with *Firmicutes*. In conclusion, *L. reuteri* strains ADR-1 and ADR-3 have beneficial effects on T2DM patients, and the consumption of different strains of *L. reuteri* may influence changes in intestinal flora, which may lead to different outcomes after probiotic intake.

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