Review

Effect of probiotics on glucose metabolism in patients with type 2 diabetes mellitus: A meta-analysis of randomized controlled trials

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A B S T R A C T

Objective: Our aim was to investigate the effects of probiotics on glucose metabolism in patients with type 2 diabetes mellitus using a meta-analysis of randomized, controlled trials.

Materials and methods: Online databases Embase, Web of Science, and PubMed were searched until August 2014 to identify eligible articles. Finally, 7 trials were included.

Results: Probiotic consumption significantly changed fasting plasma glucose (FPG) by −15.92 mg/dL (95% confidence interval [CI], −29.75 to −2.09) and glycosylated hemoglobin (HbA1c) by −0.54% (95% CI, −0.82 to −0.25) compared with control groups. Subgroup analysis was conducted to trials with non-yogurts control. Meta-analysis of trials with multiple species of probiotics found a significant reduction in FPG (weighted mean difference [WMD]: −35.41 mg/dL, 95% CI: −51.98 to −18.89). The duration of intervention for ≥8 weeks resulted in a significant reduction in FPG (WMD: −20.34 mg/dL, 95% CI: −35.92 to −4.76). Subgroup analysis of trials with species of probiotics did not result in a significant meta-analysis effect. Furthermore, the duration of intervention <8 weeks did not result in a significant reduction in FPG. The results also showed that probiotic therapy significantly decreased homeostasis model assessment of insulin resistance (HOMA-IR) and insulin concentration (WMD: −1.08, 95% CI: −1.88 to −0.28; and WMD: −1.35 mL/l, 95% CI: −2.38 to −0.31, respectively).

Conclusions: The present meta-analysis suggests that consuming probiotics may improve glucose metabolism by a modest degree, with a potentially greater effect when the duration of intervention is ≥8 weeks, or multiple species of probiotics are consumed.

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1. Introduction

Type 2 diabetes mellitus is one of the most common metabolic disorders across the world. It is an established major independent risk factor for several chronic diseases such as ischemic heart disease and stroke [1]. Both pharmacologic and non-pharmacologic interventions can reduce the levels of glucose [2–4]. Previous studies have also found that dietary constituents and supplements such as green tea and garlic can improve glucose [5–7].

Recently, the health benefits of probiotics have attracted increased attention. Probiotics are defined as live microorganisms which play an important role in health and disease [8,9]. Probiotics are well studied for their health benefits in improving immune system function and preventing diarrhea [10,11]. It has also been demonstrated that probiotics can decrease the blood glucose through improved inflammation and prevented β-cell destruction in animal models [12]. However, human clinical studies using various probiotics have yielded mixed results, with some studies finding no effect [13], while others have identified a significant glucose-lowering effect [14]. In addition, sample size of those studies are small. Therefore, the current meta-analysis of randomized, controlled trials (RCTs) has been conducted to assess the efficacy of probiotic therapies in glucose metabolism.

2. Materials and methods

2.1. Literature search

Online databases Embase, Web of Science, and PubMed were searched until August 2014 for studies that investigated the effects of probiotics supplementation on glucose metabolism in patients with type 2 diabetes mellitus. The following search terms were used: (probiotic OR lactobacillus OR streptococcus OR saccharomyces OR enterococcus OR bifidobacteria) AND (diabetes OR glycemia OR glucose). Additional studies were also identified by a hand search of all the references of retrieved articles. Our search was restricted to studies published in the English language.

2.2. Eligibility criteria

Articles were eligible for meta-analysis if they met the following inclusion criteria: (1) were human RCTs; (2) used probiotic products with live bacteria; and (3) subjects were patients with type 2 diabetes mellitus [4]. The FPG, HbA1c, insulin concentration or homeostasis model assessment of insulin resistance (HOMA-IR) changes, along with standard deviation (SD), were reported for the intervention and control groups.

2.3. Statistical analysis

Before meta-analysis, the FPG levels in mmol/L were converted to mg/dL and insulin levels in ng/mL were converted to mIU/mL prior to computations. The mean net changes (mean values ± SD) in the FPG, HbA1c, insulin concentration and HOMA-IR for each study were calculated. The mean net changes (mean values ± SD) for the outcomes listed above were calculated as the weight mean difference (probiotic diet minus control diet) of the changes (endpoint minus baseline) in mean values. Statistical analysis was conducted using Review Manager 5.2 (The Cochrane Collaboration, Oxford, UK). The heterogeneity among studies was evaluated by the Q statistic test and I² statistic test. P values of <0.05 or I² of >50% indicated that heterogeneity existed among studies. Otherwise, homogeneity of those studies was indicated. And the pooled WMD of each study was calculated by the random effects model regardless of heterogeneity. A P value of <0.05 was considered statistically significant.

3. Results

The literature search yielded 381 citations. We retrieved 60 articles, of which 7 met eligibility criteria [13–19]. A flow chart on article selection for the meta-analysis is shown in Fig. 1.

3.1. Characteristics of included studies

Table 1 contains specific information on sample size, age, intervention, dosages and duration of treatment, and intervention and control baseline measures (changes from baseline).

Seven studies with 8 trials, with 386 participants in total, were included in the final meta-analysis. Six studies were double-blind and one was single-blind. Six studies used parallel design and one used cross-over design. The study duration varied from 4 to 8 weeks. All studies reported changes in FPG, 4 studies reported changes in insulin concentration, and only 3 studies reported changes in HbA1c and HOMA-IR levels. The probiotic species and dose used varied between studies. Five studies used combination of more than 2 strains, whereas only 2 studies used a single species of probiotics. The total daily dose of probiotic consumption varied from 10^6 colony-forming units (CFU) to 10^8 CFU, except for one study using 1500 mg probiotic capsules twice daily. The subjects of two studies in the intervention group consumed probiotic yogurt and subjects in the control group consumed conventional yogurt which contained Lactobacillus delbrueckii and Streptococcus thermophilus. The subjects of two studies in the intervention group consumed probiotic capsules and those in the control group consumed placebo capsules. The subjects of one study were randomly assigned to consume either synbiotic (containing both probiotics and prebiotics) or control shake. The subjects of one study in the intervention group consumed synbiotic food and those in the control group consumed placebo food. And the subjects of one study were assigned to consume either synbiotic, probiotic or control bread, which was analyzed as two trials in this meta-analysis. Only two studies mentioned the duration of diabetes, one of which was less than 15 years and the other was at least 1 year.

3.2. Fasting glucose

FPG changes were reported in all studies. The meta-analysis of 8 trials showed a significant reduction of FPG by 15.92 mg/dL
(95% CI, −29.75 to −2.09; P = 0.02) compared with control groups. The forest plot of the effect is presented in Fig. 2. The included studies were not homogeneous ($I^2 = 64\%$, $P < 0.05$). Limiting analysis to trials with non-yogurts control did not show a meaningful reduction compared with control groups (Table 2). Subgroup analysis was conducted to trials with non-yogurts control groups. Meta-analysis of trials with multiple species of probiotics found a significant reduction in FPG ($WMD: −35.41 \text{ mg/dL}, 95\% \text{ CI: } −51.93 \text{ to } −18.48$), with high homogeneity ($I^2 = 12\%$, $P > 0.05$). Those trials using single species of probiotics as the treatment did not show a meaningful reduction compared with control groups. The duration of intervention for $\geq 8$ weeks resulted in a significant reduction in FPG ($WMD: −20.34 \text{ mg/dL}, 95\% \text{ CI: } −35.92 \text{ to } −4.76$, $P < 0.05$), with high homogeneity ($I^2 = 0\%$, $P > 0.05$). Subgroup analysis to those interventions with the duration of intervention for $< 8$ weeks did not show a significant reduction compared with control groups.

### 3.3. Glycosylated hemoglobin

Three RCTs assessed the effect of probiotics on the level of HbA1c and showed a significant change of $−0.54\%$ (95% CI, $−0.82 \text{ to } −0.25$; $P < 0.001$) in mean difference of HbA1c compared with control groups (Fig. 3), with high homogeneity ($I^2 = 4\%$, $P > 0.05$).
<table>
<thead>
<tr>
<th>Ref.</th>
<th>Intervention/control (sample size)</th>
<th>Duration (weeks)</th>
<th>Age (years)</th>
<th>Probiotics</th>
<th>Dose (CFU)</th>
<th>Intervention baseline measures (changes from baseline)</th>
<th>Control baseline measures (changes from baseline)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asemi et al. 2013 [16]</td>
<td>Probiotic capsules/placebo capsules (27/27)</td>
<td>8</td>
<td>35–70</td>
<td>L. acidophilus</td>
<td>0.2–20 × 10⁶</td>
<td>FPG: 143.8 ± 55.60 (1.60 ± 31.18) HbA1c: 7.71 ± 1.92 (0.3 ± 1.92) Insulin: 5.7 ± 4.16 (2.04 ± 4.26) HOMA-IR: 1.98 ± 1.71 (0.78 ± 1.61)</td>
<td>FPG: 134.5 ± 49.88 (28.80 ± 44.17) HbA1c: 6.35 ± 1.56 (0.18 ± 1.61) Insulin: 5.82 ± 5.20 (4.11 ± 4.73) HOMA-IR: 2.03 ± 2.29 (2.38 ± 3.38)</td>
</tr>
<tr>
<td>Asemi et al. 2014 [18]</td>
<td>Symbiotic food/placebo food (62/62)</td>
<td>6</td>
<td>35–70</td>
<td>L. sporogenes</td>
<td>1 × 10⁷</td>
<td>FPG: 147.9 ± 66.14 (22.3 ± 62.20) Insulin: 8.80 ± 5.51 (–1.75 ± 4.72) HOMA-IR: 3.05 ± 2.20 (–0.14 ± 2.36)</td>
<td>FPG: 168.4 ± 63.78 (4.2 ± 55.12) Insulin: 8.08 ± 4.65 (0.95 ± 8.58) HOMA-IR: 3.27 ± 1.97 (0.69 ± 4.09)</td>
</tr>
<tr>
<td>Ejtehed et al. 2012 [14]</td>
<td>Probiotic yogurt/conventional yogurt (30/30)</td>
<td>6</td>
<td>30–60</td>
<td>L. delbrueckii S. thermophilus B. lactis</td>
<td>6.04–7.23 × 10⁶</td>
<td>FPG: 145.89 ± 45.07 (–12.67 ± 28.08) HbA1c: 7.29 ± 1.21 (–0.12 ± 0.76) Insulin: 7.47 ± 4.89 (–0.5 ± 2.99)</td>
<td>FPG: 133.04 ± 23.17 (3.26 ± 14.90) HbA1c: 6.87 ± 0.81 (0.3 ± 0.49) Insulin: 6.31 ± 3.72 (0.19 ± 2.31)</td>
</tr>
<tr>
<td>Mazloom et al. 2013 [13]</td>
<td>Probiotic capsules/placebo capsules (16/18)</td>
<td>6</td>
<td>25–65</td>
<td>L. acidophilus L. bulgaricus L. bifidum</td>
<td>–</td>
<td>FPG: 158.56 ± 54.80 (0.13 ± 39.38) Insulin: 10.14 ± 15.82 (–1.48 ± 9.66) HOMA-IR: 2.47 ± 1.61 (–0.71 ± 3.36)</td>
<td>FPG: 149.83 ± 59.65 (12.84 ± 99.57) Insulin: 6.18 ± 2.10 (0 ± 3.91) HOMA-IR: 1.93 ± 1.29 (0.13 ± 1.15)</td>
</tr>
<tr>
<td>Mohamadshahi et al. 2014 [19]</td>
<td>Probiotic yogurt/conventional yogurt (22/22)</td>
<td>8</td>
<td>–</td>
<td>L. delbrueckii S. thermophilus B. lactis</td>
<td>3.7 × 10⁶</td>
<td>FPG: 175.24 ± 46.63 (–17.96 ± 28.68) HbA1c: 8.24 ± 1.68 (–1.15 ± 1.01)</td>
<td>FPG: 187.42 ± 55.13 (–2.23 ± 38.40) HbA1c: 8.33 ± 1.46 (–0.24 ± 0.97)</td>
</tr>
<tr>
<td>Shakeri et al. 2014 [17]</td>
<td>Probiotic bread/control breads (26/26)</td>
<td>8</td>
<td>35–70</td>
<td>L. sporogenes</td>
<td>1 × 10⁸</td>
<td>FPG: 129.7 ± 37 (–6.00 ± 38.3)</td>
<td>FPG: 168.1 ± 78.90 (0.30 ± 76.4)</td>
</tr>
<tr>
<td>Shakeri et al. 2014 [17]</td>
<td>Symbiotic bread/control breads (26/26)</td>
<td>8</td>
<td>35–70</td>
<td>L. sporogenes</td>
<td>1 × 10⁸</td>
<td>FPG: 142.7 ± 58.7 (–15.6 ± 52.4)</td>
<td>FPG: 168.1 ± 78.90 (0.30 ± 76.4)</td>
</tr>
</tbody>
</table>
Table 2 – Results of subgroup analysis of included randomized, controlled trials with non-yogurts control in meta-analysis of probiotics and FPG.

<table>
<thead>
<tr>
<th>Subgroup analysis</th>
<th>Weight mean difference (95% confidence interval)</th>
<th>No. of study</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention duration ≥8 weeks</td>
<td>-20.34 (−35.92, −4.76)</td>
<td>3</td>
<td>0.01</td>
</tr>
<tr>
<td>Intervention duration &lt;8 weeks</td>
<td>-14.29 (−65.83, 37.26)</td>
<td>3</td>
<td>0.59</td>
</tr>
<tr>
<td>Single species of probiotics</td>
<td>2.67 (−18.78, 24.13)</td>
<td>3</td>
<td>0.81</td>
</tr>
<tr>
<td>More than 1 species of probiotics</td>
<td>-35.41 (−51.93, −18.89)</td>
<td>3</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>All trials with non-yogurts control</td>
<td>-15.80 (−38.83, 7.22)</td>
<td>6</td>
<td>0.18</td>
</tr>
</tbody>
</table>

3.4. Insulin concentration

Only four RCTs reported the effects of probiotics on insulin concentration. The meta-analysis result showed a significant change of −1.35 mIU/L (95% CI, −2.38 to −0.31; P < 0.05) in mean difference of insulin concentration compared with control groups (Fig. 4), with high homogeneity ($I^2 = 0\%$, $P > 0.05$).

3.5. HOMA-IR

Three RCTs reported the change in HOMA-IR. The meta-analysis result showed a significant change of −1.08 (95% CI, −1.88 to −0.28; $P < 0.01$) in mean difference of HOMA-IR compared with control groups (Fig. 5). A high level of statistical homogeneity was observed for the meta-analysis of HOMA-IR ($I^2 = 0\%$, $P > 0.05$).

4. Discussion

Previous studies have analyzed the effect of probiotics on glucose metabolism in different mice models and appropriate human epithelial cell lines [20–22], with all reporting a reduction in fasting and postprandial glucose and decreasing HbA1c after consuming probiotics. Some previous studies on probiotics have reported that consumption of probiotic yogurt can significantly improve glucose metabolism, whereas other studies showed no benefit. This review systematically analyzed RCTs to clarify the effects of probiotic consumption on glucose metabolism. Overall, the results showed that consuming probiotics could significantly reduce FPG by 15.92 mg/dL and HbA1c by 0.53%. In especial, duration of intervention for ≥8 weeks resulted in a significant reduction in FPG by 20.34 mg/dL, and multiple species of probiotics found a significant reduction in FPG (WMD: −35.33 mg/dL).

Another important finding of this meta-analysis was the variation in the effect of probiotics on HOMA-IR, which showed a significant reduction of HOMA-IR by 0.98. Similar findings were reported in a meta-analysis by Ma and Li, where a greater impact of multiple species of probiotics on HOMA-IR in patients with nonalcoholic fatty liver disease (NAFLD) was observed [23]. Previous study using neonatal STZ-induced diabetic (n-STZ) rats, feeding of diet containing probiotics have reported that the serum insulin level at 30 min after glucose loading was significantly higher in probiotic group compared with control group [24]. However, in our study, the level of fasting insulin was significantly decreased in the probiotic treatment compared with placebo treatment, which was contrary to expectation. It is possible that the effect of probiotic on the secretion of insulin was based on dining. Probiotics may promote the secretion of postprandial insulin, while no effect on the secretion of fasting insulin. In addition, there are other mechanisms which have not been explored. To be noted, previous study showed that no significant effect of symbiotic group consumption on FPG was seen compared to the probiotic group [17], so we did not distinguish between the two.

Fig. 4 – The effect of probiotics on insulin concentration.

Fig. 5 – The effect of probiotics on HOMA-IR.
The impact of probiotics on glucose metabolism may work through several different mechanisms. Firstly, current researches suggested that the oxidative damage and antioxidative ability played an important role in the pathogenesis of diabetes [25, 26]. The antioxidant activity of probiotics has been confirmed in previous experiments [27]. Yadav et al. showed that probiotics decreased oxidative damage by inhibiting the lipid peroxidation and increasing the antioxidant content of glutathione, superoxide dismutase, catalase and glutathione peroxidase in diabetic rats [28, 29]. Secondly, probiotic has been reported to exert anti-diabetic effects against insulin resistance by increasing liver natural killer T (NKT) cells. Probiotic treatment also improved insulin resistance and inflammation by modulating TNF-α expression and reducing NF-κB binding activity [30]. In addition, probiotics may improve glucose metabolism by increasing the bioavailability of gliclazide, inhibiting or delaying the intestinal absorption of glucose and changing the activity of autonomic nervous [31–33].

There are several limitations to this review. All of the studies were lacking in the dietary restrictions, exercise, and physical activities or reporting the evaluation of the successfulness of blinding. There are only 7 published reports available that is difficult to analyses the effect of different strains and dosages of probiotic treatment on glucose metabolism. More RCTs with larger sample groups and longer durations of conditions trials are needed to confirm the effect of probiotic on glucose metabolism in patients with type 2 diabetes mellitus.

5. Conclusions

The present meta-analysis suggests that consuming probiotics may improve glucose metabolism by a modest degree, with a potentially greater effect when the duration of intervention is ≥8 weeks, or multiple species of probiotics are consumed. The effect of probiotics on glucose metabolism, especially patients with type 2 diabetes mellitus, as well as the mechanisms by which probiotics can affect glucose metabolism and health need further investigation.

Conflict of interest

The authors declare no conflict of interest.

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REFERENCES


