**Bifidobacterium** species lower serum glucose, increase expressions of insulin signaling proteins, and improve adipokine profile in diabetic mice

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ABSTRACT

This study, using C57BL/6J mice with streptozotocin (STZ)-induced diabetes, aimed to determine whether *Bifidobacterium* species (spp.) both induces the expressions of proteins in the insulin signaling pathway and enhances the expressions of certain adipocytokines. The protein expressions of IκB kinase alpha (IKKα), IκB kinase beta (IKKβ), nuclear factor-kappaB inhibitor alpha (IκBα), and the mitogen-activated protein kinase (MAPK) pathway were also investigated. Oral administration of *Bifidobacterium* spp. reduced blood glucose levels significantly and increased the protein expressions of insulin receptor beta, insulin receptor substrate 1, protein kinase B (Akt/PKB), IKKα, and IκBα. Extracellular-signal-regulated kinase 2 (ERK2) showed increased expression. *Bifidobacterium* spp. also induced the adiponectin expression and decreased both macrophage chemotactrant protein-1 (MCP-1) and interleukin-6 (IL-6) expression. In addition, IKKβ, c-Jun NH2-terminal kinase (JNK) and p38 MAP kinase expressions showed no significant changes in both groups. In conclusion, *Bifidobacterium* spp. may be the promising bacteria for treating diabetes.

Strains including *B. bifidum*, *B. longum*, *B. infantis*, and *B. animalis* are *Bifidobacterium* spp., which comprise genus of gram-positive, non-motile, often branched anaerobic bacteria. *Bifidobacteria* are used as probiotics for supporting digestion in many countries. To date, several studies have demonstrated the benefits of probiotics in managing metabolic disorders including diabetes. At present, there are research groups focusing on this novel concept. Dietary supplementation with multiple probiotic strains, including *L. acidophilus*, *L. casei*, *L. rhamnosus*, *L. bulgaricus*, *B. breve*, *B. longum*, and *S. thermophilus*, has been shown to prevent elevations of fasting plasma glucose in diabetic patients (3). The insulin signaling pathway controls glucose transport in muscle and fat cells. Insulin binds to insulin receptors on the surfaces of target cells. This binding activates insulin receptor beta (IR-β), and then activates insulin receptor substrate 1, protein kinase B (Akt/PKB), IKKα, and IκBα. Extracellular-signal-regulated kinase 2 (ERK2) showed increased expression. *Bifidobacterium* spp. also induced the adiponectin expression and decreased both macrophage chemotactrant protein-1 (MCP-1) and interleukin-6 (IL-6) expression. In addition, IKKβ, c-Jun NH2-terminal kinase (JNK) and p38 MAP kinase expressions showed no significant changes in both groups. In conclusion, *Bifidobacterium* spp. may be the promising bacteria for treating diabetes.

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exerts effects on those pathways remains as yet unknown.

The mixture of *Bifidobacterium infantis* and *Lactobacillus acidophilus* reportedly decreased the interleukin-6 (IL-6) mRNA level in primary intestinal epithelial cells isolated from resected ileum with necrotizing enterocolitis (11). *Bifidobacterium longum* significantly down-regulated levels of macrophage chemotactrant protein-1 (MCP-1) and IL-6 in porcine intestinal epithelial cells challenged with heat-killed enterotoxigenic *Escherichia coli* (34). The mixture that contained *B. longum* and *B. animalis* inhibited MCP-1 production in colitis of BALB/c mice (25). *B. bifidum* was shown to suppress MCP-1 expression in an *in vitro* co-culture of intestinal epithelial cells and T cells (18). However, only one recent study focused on the anti-diabetic effect of *Bifidobacterium* spp. and its molecular mechanism (13). Infection with Kilham rat virus leads to increased *Bifidobacterium* spp. in the intestine, which raises the possibility that virus-induced type 1 diabetes may involve alterations in the balance among bacterial groups, resulting in the down-regulation of protective mechanisms or, conversely, the up-regulation of pro-inflammatory innate pathways culminating in anti-islet T cell responses (13).

Therefore, we examined whether oral administration of *Bifidobacterium* spp. ameliorates diabetes, possibly via effects on the insulin signaling pathway and inflammatory adipocytokines, in a lean insulin-depleted murine diabetic model; mice with streptozotocin (STZ)-induced diabetes. This murine model of diabetes is not influenced by obesity which is related to insulin resistance. We evaluated the effects of *Bifidobacterium* spp. on the mRNA expressions of adiponectin, MCP-1 and IL-6, as well as the protein levels of IRS-1, IR-β and Akt in adipose tissues from mice with diabetes induced by STZ. Furthermore, the protein expressions of IκB kinase alpha (IKKa), IκB kinase beta (IKKβ), nuclear factor-kappa B inhibitor alpha (IxBα) and MAP kinase pathway proteins, such as extracellular-signal-regulated kinase 2 (ERK2), JNK, and p38 MAP kinase, were also investigated.

**MATERIALS AND METHODS**

**Antibodies.** Mouse anti-mouse IR-β monoclonal antibody was purchased from Abcam (Cambridge, UK). Rabbit anti-mouse IRS-1 polyclonal antibody, rabbit anti-mouse Akt polyclonal antibody, mouse anti-mouse β-Actin monoclonal antibody, rabbit anti-mouse IKKa polyclonal antibody, rabbit anti-mouse IKKβ polyclonal antibody, rabbit anti-mouse 1αBα polyclonal antibody, rabbit anti-mouse JNK polyclonal antibody, rabbit anti-mouse p38 MAP kinase polyclonal antibody, horseradish peroxidase (HRP)-conjugated anti-mouse and anti-rabbit antibodies were from Sigma-Aldrich (St. Louis, MO, USA). All other reagents used were of analytical grade.

**Preparation of Bifidobacterium spp. strains for administration.** *Bifidobacterium* spp. strains including *B. bifidum* ATCC 15700, *B. longum*, *B. infantis*, and *B. animalis* were obtained from DVS Biolife Limited (Hyderabad, India). *Bifidobacterium* spp. strains were cultured overnight in MRS broth (Merck, Germany) added to 0.25% L-cysteine (Sigma) in anaerobic condition at 37°C. Concentrations of the cultured strains were counted by culturing on MRS agar (Merck) containing 0.25% L-cysteine and incubated at 37°C for 72 h in an anaerobic chamber containing an atmosphere of 85% N₂, 10% H₂ and 5% CO₂. The cultured strains in MRS broth were collected and then washed three times with phosphate buffered saline (PBS) by centrifugation at 9,000×g for 30 min at 4°C. Mixing of freshly prepared live bacteria was performed daily for administration to each mouse just prior to use. The mixture of *Bifidobacterium* spp. included 10⁹ colony-forming units (CFU) of *B. longum*, 10⁸ CFU of *B. bifidum*, 10⁹ CFU of *B. infantis*, and 10⁸ CFU of *B. animalis*. This mixture was prepared in 0.4 mL of PBS and fed to the mice once a day.

**Experimental design.** Ten male C57BL/6j mice of seven-week-old were obtained from the Jackson Laboratory (Bar Harbor, ME, USA) for this study. All mice were maintained and treated in accordance with the Guidelines and Regulations for Experiments on Vertebrate Animals of the National Institute for Food Control in Testing, Research, and Training. The mice were housed individually in plastic cages in a room with controlled light (08 : 30–20 : 30), temperature (25 ± 1°C) and humidity (60 ± 5%) under conventional conditions.

Diabetes was induced in normal mice by five sequential daily intraperitoneal injections of a freshly prepared solution of Streptozotocin (STZ) in citrate buffer (pH 4.5) at 45 mg/kg of body weight (31, 33). The mice were supplied with 10% sucrose water to avoid sudden post-injection hypoglycemia. The mice were tested to assure sufficient levels of hyperglycemia at 4 weeks post-injection. After all of the mice had been confirmed to be in a diabetic
state (blood glucose greater than 16.7 mmol/L) within 1 week (26), they were randomly assigned to trial and control groups. The trial group (n = 5) received a normal diet (Oriental Yeast Tokyo, Japan) with the mixture of *Bifidobacterium* spp. for 5 weeks by oral gavage while the control group (n = 5) was given only the normal diet with saline at an equivalent volume by oral gavage for 5 weeks. The normal diet (AIN-93M) contained (per 100 g of the diet) 14.00 g of milk casein, 0.18 g of L-cysteine, 46.57 g of corn starch, 15.50 g of α-corn starch, 10.00 g of sucrose, 4.00 g of soybean oil, 5.00 g of powdered cellulose, 3.50 g of AIN-93M mineral mixture, 1.00 g of AIN-93M vitamin mixture, 0.25 g of choline bitartrate, and 0.0008 g of tert-butylhydroquinone. At the end of the experimental period, all mice were fasted for 6 h, anesthetized with diethyl ether and then exsanguinated from the heart. The blood of each mouse was collected to measure glucose levels. The mesenteric fat of each mouse also was collected and weighed. Total RNA and protein of adipose tissue were isolated from adipose tissue of both the trial and the control group.

RNA extraction and reverse transcription PCR. TRIzol reagent (Life Technologies, Carlsbad, CA, USA) was used to extract total RNA from adipose tissue of C57BL/6J mice. The RNA was treated with DNase I (Life Technologies), and 0.5 μg RNA was reverse transcribed using TaKaRa PrimeScript™ RT reagent kits according to the manufacturer’s instructions (Takara Bio, Kyoto, Japan).

Quantitative RT-PCR. Samples were prepared using TaKaRa SYBR Premix Ex Taq according to the manufacturer’s instructions (Takara Bio). Quantitative real-time reverse transcription PCR with 100 ng cDNA was performed using the CFX96 system (Bio-Rad Laboratories, Hercules, CA, USA). The following oligonucleotide primers were used: adiponectin 5'-TGTTGGAATGACAGGAGCTG-3' (forward) and 5'-CGAATGGGTACATTGGGAAC-3' (reverse); IL-6 5'-ACAACCACGGCCCTCCCTACTT-3' (forward) and 5'-CAGATTTCGCCAGAAGATGTCG-3' (reverse); MCP-1 5'-CCCAATGAGTAGGCTGGAGA-3' (forward) and 5'-TCTGGACCATTCCCTTTCGTG-3' (reverse); 18S ribosomal RNA 5'-AAACGGCTACCACATCCAAG-3' (forward) and 5'-GGCTCGAAAGAGTCCTGTA-3' (reverse). The annealing temperature for the PCR reactions was 60°C, product sizes ranged from 172 to 225, and the total reaction mixture volume was 20 μL. After the reaction, each PCR product was verified for its single amplification by melting curve analysis. Data were normalized by the 18S ribosomal RNA expression levels in each sample and shown as the means ± SE of 3 independent quantitative-RT-PCR analyses.

Western blot analysis. At the end of the experimental period, adipose tissues were taken from mice and then rinsed three times with ice-cold PBS and lysed in RIPA buffer (50 mM Tris, 150 mM NaCl, 1 mM EDTA, 0.5% sodium deoxycholate, 1% NP-40, 0.1% SDS, 1 μM aprotinin, 10 μM leupeptin, 0.1 μM phenylmethylsulfonyl fluoride, 20 mM sodium fluoride, 20 mM beta glycerophosphate and 1 mM sodium orthovanadate, pH 7.4). The supernatants were obtained by centrifugation at 13,000 rotations per minute at 4°C for 20 min, and the protein content was determined for each sample employing the Nanodrop 1000 system (Thermo Scientific, USA). Equal amounts of protein (100 μg) were subjected to sodium dodecyl sulfate-polyacrylamide gel electrophoresis. Gels were transferred to an Immobilon-P membrane (Millipore, Bedford, MA, USA). Immunoblotting was performed with an enhanced chemiluminescence kit (Pierce, Thermo Scientific, USA) according to the manufacturer’s instructions. Densitometric analyses were performed using Image J1.38 x software (NIH, Bethesda, MD, USA).

Statistical analysis. The values obtained are presented as means ± SE. Significant differences (*P < 0.05 or **P < 0.01) between means were evaluated by applying the unpaired Student’s t-test.

RESULTS

*Bifidobacterium* spp. improved adipose insulin signaling sensitivity in diabetic mice

Blood glucose testing is the gold standard for subclinical diagnosis of diabetes. Mice with blood glucose levels higher than 16.7 mmol/L one week after STZ injection were considered to have diabetes (33). The insulin concentrations in these mice could not be measured due to the insufficient sensitivity of the enzyme-linked immune sorbent assay (ELISA) used. All of the diabetic mice were randomly divided into 2 groups. After 5 weeks with (trial group) or without (control group) probiotic administration, blood glucose levels of the trial group were significantly lower than those of the control group (P < 0.01) (Table 1). Neither body nor adipose tissue weights differed significantly between the trial and control groups of mice (Table 1). To elucidate the role of *Bifidobacterium* spp. in the expressions of insulin
**Bifidobacterium** spp. treatment increased the adiponectin mRNA level and reduced MCP-1 and IL-6 mRNA levels in adipose tissue of mice with STZ-induced diabetes

To assess the role of **Bifidobacterium** spp. in improving the blood glucose levels of STZ-insulin-depleted mice, the mRNA levels of adiponectin, one of the adipokines influencing insulin sensitivity, in adipocytes were measured in both the trial and the control group. As shown in Fig. 3, the adiponectin mRNA level was markedly elevated in the trial group as compared to the control group (\(P < 0.01\)). In order to explore the role of **Bifidobacterium** spp. in the production of inflammatory adipokines, the mRNA expressions of IL-6 and MCP-1 were evaluated in both groups of mice with the STZ-induced diabetes. Both MCP-1 and IL-6 mRNA levels were markedly reduced in the trial group as compared to the control group (Fig. 4).

**Table 1**  
**Body weight, dietary intake and mesenteric fat weight in diabetic mice**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control (n = 5)</th>
<th>Trial (n = 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (initial) (g)</td>
<td>26.05 ± 1.02</td>
<td>27.44 ± 1.33NS</td>
</tr>
<tr>
<td>Body weight (final) (g)</td>
<td>32.21 ± 0.74</td>
<td>31.00 ± 1.66NS</td>
</tr>
<tr>
<td>Dietary intake (g/2 days)</td>
<td>3.96 ± 0.24</td>
<td>3.93 ± 0.41NS</td>
</tr>
<tr>
<td>Mesenteric fat weight (g)</td>
<td>0.46 ± 0.05</td>
<td>0.45 ± 0.06NS</td>
</tr>
<tr>
<td>Blood glucose (mmol/L)</td>
<td>17.9 ± 1.8</td>
<td>11.6 ± 1.0**</td>
</tr>
</tbody>
</table>

Twelve-week-old male C57BL/6J mice with diabetes (n = 10) were fed a normal diet with (trial group) or without (control group) a mixture of **Bifidobacterium** spp. for 5 weeks by oral gavage. The control group was given the same volume of saline for 5 weeks. Values are expressed as means ± SE (n = 5). N.S., no significant differences between control and **Bifidobacterium** spp. groups. (**P < 0.01 compared to the control)**

**Fig. 1**  
Expressions of insulin signaling pathway proteins in diabetic mice. Twelve-week-old mice with STZ-induced diabetes (n = 10) were treated with (trial group) or without (control group) a mixture of **Bifidobacterium** spp. for 5 weeks. Adipose tissue was harvested from the diabetic mice of both groups after a 6-hour fast. Total protein was extracted from adipose tissue and subjected to Western blot using IR-β, IRS-1, Akt, and β-Actin antibodies as described in Materials and Methods (Fig. 1A). Results were also quantified and the fold-increase from the trial group as compared to the control group was normalized by β-Actin (Fig. 1B). Data shown are the means ± SE (n = 5) (**P < 0.01 compared to the control group).

**Bifidobacterium** spp. increased IKKa, IκBa and ERK2 signals but did not affect JNK and p38 MAP kinase protein expressions

We examined the expressions of IKKa, IKKβ, and IκBa to investigate the impact of the mixture of **Bifidobacterium** spp. The levels of ERK2, JNK and p38 MAP kinase proteins involved in the MAPK pathway were also assessed. As shown in Fig. 2, expressions of IKKa, IκBa, and ERK2 were significantly increased in the trial group as compared to the control group. However, the expressions of IKKβ, JNK, and p38 MAP kinase were unchanged in both groups.

**Signaling pathway proteins, diabetic mice were assessed for the presence of IRS-1, IR-β and Akt. As shown in Fig. 1, the expressions of IR-β, IRS-1, and Akt were significantly increased in adipose tissue from the trial group as compared to that from the control after normalization by β-Actin expression.**

**Fig. 2**  
**Bifidobacterium** spp. increased IKKa, IκBa and ERK2 signals but did not affect JNK and p38 MAP kinase protein expressions
DISCUSSION

Previous studies indicated that an IRS-1 knockout murine model showed mild insulin intolerance and ablation of the insulin receptor in adipose tissues, which resulted in diet-induced obesity and marked resistance to the development of glucose intolerance (35). In mice, homozygous knockout of the insulin receptor caused death at 3–7 days post parturition (1, 16). Other study indicated that null alleles of the insulin receptor and IRS-1 (IRS-1 null animals are mildly insulin intolerant) developed frank diabetes at 4–6 months of age (7). Although skeletal muscle accounts for more than 80% of postprandial glucose disposal, the ablation of the insulin receptor specifically in muscle resulted in normal glucose tolerance (6). Otherwise, probiotics may compensate for deficits in the insulin-like growth factor I receptor/P13K/Akt survival pathways and attenuate cardiac apoptosis in spontaneously hypertensive rats (21). As for the insulin signaling pathway, we demonstrated that oral administration of Bifidobacterium spp. increased the levels of IR-β, IRS-1, and Akt proteins in diabetic mice. In this study, Akt up-regulation may have improved glucose uptake as shown by reduced plasma glucose levels. Therefore, we can reasonably speculate that Bifidobacterium spp. promote the recovery of β-cells of pancreas or increase insulin sensitivity in mice with STZ-induced diabetes by enhancing the function of the insulin signaling pathway. Recovery of β-cell function in the trial group is even possible. However, serum insulin levels were not detectable by the ELISA method within the 5-week treatment period of this study.

Toll-like receptors are related to host immune responses (12). To date, three major MAPK pathways have been identified in mammals: ERK, stress-activated protein kinase/JNK, and p38 (12). Our observation that there were no changes in the levels of JNK and p38 MAP kinase under any of the study conditions, while expression of ERK2 was increased, raises the possibility of probiotics playing a
Adipose tissues produce leptin and adiponectin to regulate feeding behavior and generate pro- and anti-inflammatory adipokines which modulate inflammatory responses (9). Adiponectin enhances insulin sensitivity by increasing hepatic IRS-2 expression via a macrophage-derived IL-6-dependent pathway (4), while IL-6 and MCP-1 inhibit insulin sensitivity (17, 19). Adiponectin gene expression and secretion are inhibited by IL-6 in 3T3-L1 adipocytes (10). Insulin signaling may also be impaired by altered secretion of cytokines and chemokines (2). Children with type 1 diabetes reportedly have higher adiponectin levels than non-diabetic children (29) and this might be an autoimmune mechanism underlying insulin depletion. We showed adiponectin mRNA to be significantly higher in the trial group than in the control group ($P < 0.01$). This suggests that adiponectin may ameliorate the disease state in mice with STZ-induced diabetes. This mechanism may underlie one of the benefits of Bifidobacterium spp. ingestion. IL-6 was reported to reduce insulin-dependent hepatic glycogen synthesis (19, 28) and glucose uptake in adipocytes (27). Subjects with a high after-therapy IL-6 level showed poorer periodontal healing than those with lower levels (24). Significant expression of MCP-1 was documented in the myocardial tissues of cases with type 1 diabetes suffering from diabetic keto-acidosis, while smaller amounts of MCP-1 were expressed in the myocardial tissues of overweight/obese individuals (23). Another study involving 70 patients with type 1 diabetes showed that all indices of pro-inflammatory cytokines were higher in patients than in healthy control subjects. These observations suggest a positive correlation between blood pro-inflammatory cytokine levels and disease severity (20). In this study, we showed oral administration of a mixture of Bifidobacterium spp. to decrease the mRNA expressions of IL-6 and MCP-1.
Bifidobacterium species enhance insulin signaling

MCP-1 in diabetic mice. This may represent true benefit of Bifidobacterium spp. ingestion for eliminating the unwanted features of diabetes in mice.

In summary, oral administration of Bifidobacterium spp. enhances the expressions of proteins involved in the insulin-signaling pathway and increases levels of proteins related to innate immune responses. Moreover, the current study demonstrated that a mixture of Bifidobacterium spp. also decreased the blood glucose level and increased the expression of adiponectin mRNA while decreasing those of inflammatory adipokines (MCP-1 and IL-6) in insulin-depleted diabetic mice. Our findings may facilitate understanding the novel effects of Bifidobacterium spp. and suggest a newly-recognized benefit of Bifidobacterium spp. treatment for diabetes. It is necessary to elucidate the underlying mechanisms of action and to evaluate the efficacy of Bifidobacterium spp. treatment in diabetic patients.

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REFERENCES


