Beneficial Effects of Bifidobacteria in a Gastroresistant Seamless Capsule on Hyperhomocysteinemia in Hemodialysis Patients

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Intestinal microflora is deranged in hemodialysis (HD) patients as an increase in aerobic bacteria such as Escherichia coli and a decrease in anaerobic bacteria such as Bifidobacterium. Bifidobacteria ferment carbohydrates to produce acetic acid and lactic acid, which inhibit the intestinal putrefaction. Thus, intake of Bifidobacteria effectively restores the disturbed microflora to normal. However, Bifidobacteria in most medical products and healthy foods cannot usually survive because of exposure to gastric juices before it reaches the intestines. A gastroresistant seamless capsule prevents Bifidobacteria from inactivation by acidic gastric juice and allows it to be active in the intestines. We showed that the oral administration of Bifidobacterium longum in a gastroresistant seamless capsule to HD patients is effective in decreasing the pre-HD serum levels of homocysteine, indoxyl sulfate, and triglyceride. The reduction in the serum level of homocysteine is mainly attributable to the supply of folate produced by Bifidobacterium longum in the human intestines.

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THE HUMAN GASTROINTESTINAL tract is a complex microbial system composed of about $10^{14}$ bacteria, comprising approximately 500 types.1-3 Intestinal microflora is deranged in hemodialysis (HD) patients as an increase in aerobic bacteria such as Escherichia coli and a decrease in anaerobic bacteria such as Bifidobacterium.4 A major source of fecal ammonia is the bacteria-mediated hydrolysis of urea that markedly accumulates in the blood of uremic patients and then diffuses into the intestinal tract. Such a high level of ammonia in uremic patients is responsible for elevation of the fecal pH value, and thus leads to promotion of aerobic bacterial growth. The intake of lactic acid bacteria, such as Bifidobacterium, effectively restores the disturbed microflora to normal.5 Bifidobacterium ferments carbohydrates to produce acetic acid and lactic acid, which inhibit intestinal putrefaction. Thus, Bifidobacterium plays an important role in human health by maintaining the balance of intestinal microflora.6

Bifidobacterium longum in a Gastroresistant Seamless Capsule

Bifidobacteria in most medical products and healthy foods cannot usually survive because of exposure to gastric juices before it reaches the intestines, imparting only a limited effect on the intestinal microflora. As shown in Figure 1, Bifidobacterium longum in powder formation could not survive at all in a solution of pH 1.2. However, Bifidobacterium longum in a gastroresistant seamless capsule could survive even in a solution of pH 1.2 (Fig 2). Thus, a gastroresistant seamless capsule prevents Bifidobacteria from inactivation by acidic gastric juice and allows it to be active in the intestines. Figure 3 shows the structure of Bifidobacterium longum in a gastroresistant seamless capsule.

Indoxyl Sulfate, a Uremic Toxin

Indoxyl sulfate is a uremic toxin that stimulates the progression of chronic renal failure,7-10 and is synthesized from indole through indoxyl in the liver. Indole is produced from tryptophan in the
large intestine by tryptophanase in intestinal bacteria such as *Escherichia coli*. Indole is absorbed from the intestine into the blood, and is finally converted to indoxyl sulfate in the liver. Bifidobacteria do not have tryptophanase activity, and thus cannot produce indole. These facts raise the possibility that the oral administration of *Bifidobacterium* to HD patients may reduce the serum level of indoxyl sulfate by normalizing the intestinal microflora.

**Effect of Bifidobacteria on Serum Indoxyl Sulfate in Uremic Patients**

We showed that the oral administration of *Bifidobacterium longum* in a gastroresistant seamless capsule, but not *Bifidobacterium* in a powder formation, significantly decreased the serum level of indoxyl sulfate in HD patients. Intestinal microflora is deranged in HD patients as increased aerobic bacteria and decreased anaerobic bacteria. Accumulation of such putrefactive substances as indole in the intestine is because of excessive production by overgrowth of aerobic bacteria. Bifidobacteria produce acetic acid and lactic acid and acidify the intestinal milieu, thus preventing the growth of pathogenic aerobic bacteria such as *Escherichia coli* that produce harmful substances including indole.
the oral administration of *Bifidobacterium longum* in a gastroresistant seamless capsule may be effective in reducing serum levels of homocysteine in HD patients.

**Effect of Bifidobacteria on Serum Homocysteine in Uremic Patients**

*Bifidobacterium longum* in a gastroresistant seamless capsule (Bifina, Morishita Jintan, Osaka, Japan) was orally administered to 27 HD patients (age, 63.9 ± 9.8 years; 14 male and 13 female subjects; duration on HD, 9.2 ± 7.9 years; serum creatinine, 1.0 ± 0.2 nmol/L mean ± standard deviation; blood urea nitrogen: 25.6 ± 6.9 nmol/L; serum albumin, 3.7 ± 0.3 g/dL; 4-hour HD 3 times per week) for 12 weeks in total, at 3.0 × 10⁹ colony-forming units (CFU)/day of *Bifidobacterium longum* for 4 weeks (from 0 to 4th week), 6.0 × 10⁹ CFU/day for 4 weeks (from 4th to 8th week), and 12.0 × 10⁹ CFU/day for 4 weeks (from 8th to 12th week), respectively.

Oral administration of *Bifidobacterium longum* in a gastroresistant seamless capsule significantly decreased the serum levels of homocysteine in HD patients (Fig 4) (before, 39.2 ± 3.6 μmol/L; 4th week, 35.2 ± 2.4 μmol/L [P < .05 versus before by paired Student’s t-test]; 8th week, 34.0 ± 2.7 μmol/L [P < .01 versus before]; 12th week, 34.8 ± 2.8 μmol/L [P < .05 versus before]; mean ± standard error; n = 27). The most effective dose of *Bifidobacterium longum* for decreasing the serum levels of homocysteine (reduction rate, 13.3%) is 6.0 × 10⁹ CFU/day.

Further, oral administration of *Bifidobacterium longum* in a gastroresistant seamless capsule significantly increased the serum levels of folate in HD patients (before, 27.8 ± 2.1 nmol/L; 4th week, 29.0 ± 2.5 nmol/L; 8th week, 31.7 ± 3.0 nmol/L [P < .05 versus before]; 12th week, 28.3 ± 2.1 nmol/L; mean ± standard error; n = 27). The most effective dose of *Bifidobacterium longum* for increasing the serum levels of folate (rate of increase, 14.0%) is 6.0 × 10⁹ CFU/day. However, oral administration of *Bifidobacterium longum* in a gastroresistant seamless capsule did not increase the serum levels of vitamin B12. Although Bifidobacteria can produce many kinds of vitamins, the amounts of produced vitamins varied among their different species and strains. We found that *Bifidobacterium longum* shows a high ability to produce folate as compared with vitamin B12 and consequently decreases the serum levels of homocysteine.

Oral administration of *Bifidobacterium longum* in a gastroresistant seamless capsule also significantly decreased the serum levels of triglyceride (reduction rate, 16.0%) in HD patients (before, 124.5 ± 11.1 mg/dL; 4th week, 108.1 ± 9.1 mg/dL; 8th week, 106.6 ± 11.5 mg/dL [P < .05 versus before]; 12th week, 104.6 ± 8.5 mg/dL [P < .05 versus before]; mean ± standard error; n = 27). Because Bifidobacteria can produce nicotinic acid, a possible mechanism for the reduction in serum triglyceride levels may be the production of nicotinic acid by Bifidobacteria.

We also confirmed that oral administration of *Bifidobacterium longum* in a gastroresistant seamless capsule significantly decreased the serum levels of indoxyl sulfate compared with before administra-
tion in HD patients (before, 164.6 ± 15.0 μmol/L; 4th week, 145.4 ± 14.5 μmol/L (P < .01 versus before); 8th week, 148.7 ± 14.1 μmol/L (P < .05 versus before); 12th week, 149.6 ± 15.5 μmol/L (P < .05 versus before); mean ± standard error; n = 27).

In conclusion, the correction of deranged intestinal microflora is important for reducing the serum levels of uremic toxins such as homocysteine and indoxyl sulfate. *Bifidobacterium longum* in a gastroresistant seamless capsule is a promising tool for correcting the intestinal microflora in uremic patients.

**References**

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