

It is known that there are a lot of food components of which chronic deficiency harms human health conditions. In Japan, the intake of some of these food components has unconsciously been decreased as a result of the westernization of dietary habits. Dietary fiber is one example of food components of which intake is decreased by such westernization.

Decreased dietary fiber intake, along with the increased dietary fat intake which is also a feature of the westernization of dietary habits, is thought to cause the rapidly increasing incidence of diseases more commonly found in western countries, such as obesity, diabetes mellitus, arteriosclerosis, cholelithiasis, breast cancer and colon cancer. A daily intake of 20 to 25 grams of dietary fiber is recommended in order to prevent these diseases, but the fact is that an enough amount of dietary fiber is not always taken.

Indigestible oligosaccharides are an alternative to dietary fiber and are believed to exert diverse actions that can help maintain good health conditions, including delayed digestion and absorption, inhibited absorption of cholesterol, and improved intestinal flora. Therefore, the widespread application of such indigestible oligosaccharides can be expected in areas such as the prevention of diabetes mellitus and cardiac diseases, the inhibition of colon cancer, and the treatment of inflammatory bowel disease.

However, it is not always easy to consume an enough amount of oligosaccharide in the form of a supplement in order to maintain good health conditions. We are therefore researching ways in which the intake of a small amount of oligosaccharide-producing enzymes as supplements, which can produce oligosaccharides from food components, may be substituted for the intake of the oligosaccharides themselves.

The latest research results are shown below.

The use of oligosaccharide-producing enzymes to produce oligosaccharides from ingested foods

Transglucosidase, an oligosaccharide-producing enzyme, produces indigestible oligosaccharides (e.g., isomaltose, isomaltotriose, panose) from digestible starch. Levansucrase, another oligosaccharide-producing enzyme, produces indigestible oligosaccharides (lactosucrose, levan) from lactose and sucrose.

Since these enzymes can maintain their enzymatic activity in an acid environment in the stomach, they are able to produce oligosaccharides from foods that are ingested orally. In fact, the in vivo production of oligosaccharides from ingested foods in rats has already been demonstrated experimentally.

In addition, animal studies have confirmed that administration of oligosaccharide-producing enzymes with feed is effective in preventing weight gain and improving intestinal flora. These findings are described in "Enzyme Wave Vol. 1."

Development of a dietary supplement enzyme for the prevention of diabetes mellitus -verification of effects in animal studies-

The development of dietary supplement enzymes is being advanced as part of a collaborative initiative involving Nagoya City University and Nippon Veterinary and Life Science University.

Professor Toshinori Sako, at Nippon Veterinary and Life Science University, investigated the effect of transglucosidase intake on blood glucose, insulin secretion and blood triglyceride in a study using diabetes model dogs and normal dogs.

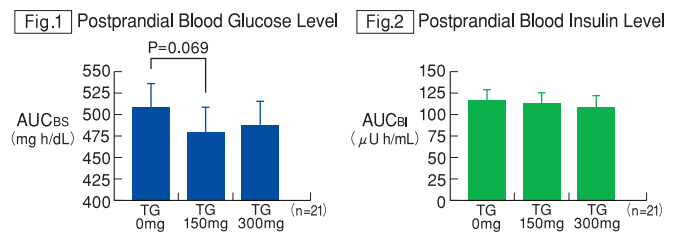
In normal dogs to which transglucosidase was administered, even though postprandial glucose levels did not change, insulin secretion and the absorption of triglycerides were inhibited. The inhibition of insulin secretion observed in normal dogs is thought to have resulted from transglucosidase inhibiting the absorption of orally ingested carbohydrates. Moreover, the inhibited absorption of triglyceride is also thought to reflect the effect of oligosaccharide production.

In a single-dose study of transglucosidase in diabetes model dogs, inhibition of increase in postprandial glucose levels was observed. Moreover, in a two-week repeated-dose study, transglucosidase intake was shown to improve blood glucose control by decreasing blood fructosamine levels, an index of diabetes mellitus.

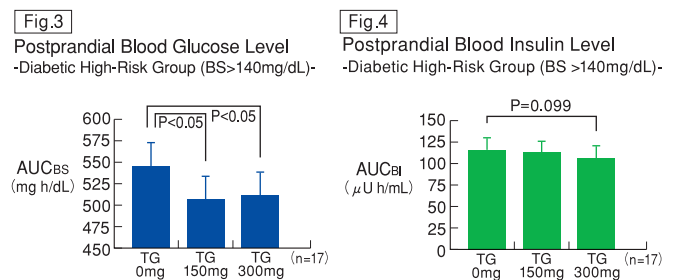
Development of a dietary supplement enzyme for the prevention of diabetes mellitus -Inhibition of postprandial glucose levels and insulin secretion in humans-

A clinical study of transglucosidase in healthy volunteers was conducted by Professor Takashi Joh and Doctor Makoto Sasaki of the Nagoya City University Graduate School of Medical Sciences. This was a randomized, placebo-controlled, three-way crossover trial involving 21 volunteers (17 males and 4 females, with a mean age of 48.3 years) in compliance with the WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI Ethical Principles. The mean body mass index (BMI) of the volunteers was slightly high at 24.7 ± 3.1 , suggesting a tendency towards obesity. However, the hemoglobin A1c was $5.4 \pm 0.5\%$ (4.6 to 6.4) and the fasting blood glucose was 95.3 ± 10.8 mg/dL (77 to 112), indicating that diabetic individuals had not been included as test subjects in this study.

After the volunteers were fed test meals with a total energy content of 522 kilocalories (protein, 14.4 g; fat, 2.1 g; carbohydrate, 111 g) and given transglucosidase (0 mg, 150 mg, or 300 mg) orally, their blood glucose and insulin levels were measured over time (at 0, 30, 60, 90, 120, 150, and 180 minutes postdose) and the effect of transglucosidase on postprandial glucose levels was evaluated. It was found that a postprandial increase in glucose levels tended to be inhibited in the enzyme-treated group (transglucosidase 150 mg or 300 mg) compared with the control group (transglucosidase 0 mg), although no effect on insulin secretion was observed (Figures 1 and 2).



However, in a sub-analysis of the group of subjects who were suspected of having impaired glucose tolerance because of a postprandial glucose level of 140 mg/dL or more when transglucosidase was not administered (N = 17), a postprandial increase in glucose levels was significantly inhibited in the transglucosidase-treated group compared with the control group and insulin secretion also tended to be inhibited (Figures 3 and 4). These results suggest that transglucosidase may be useful for preventing the development of diabetes mellitus.



Development of a dietary supplement enzyme for the prevention of inflammatory bowel disease

In animal studies, the oral administration of transglucosidase was shown to provide a prebiotic effect, improving the intestinal flora. The ability of transglucosidase to reduce the symptoms of inflammatory bowel disease (IBD) by application of this prebiotic effect is being investigated by Professor Takashi Joh and Doctor Makoto Sasaki of the Nagoya City University Graduate School of Medical Sciences. Many cases of IBD have been reported in European countries and the U.S; the number of patients with this disease in Japan has also been growing rapidly in recent years, along with the westernization of dietary habits.