Abstracts of the Alumi Association Memorial Lectures of the 74th Annual Meeting of the Medical Association of Nippon Medical School

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Abstracts of the Alumni Association Medical Research Fund Prize Memorial Lecture (1)

The Effects of Colestimide on Blood Glucose-lowering Activity and Body Weight in Patients with Type 2 Diabetes and Hypercholesterolemia

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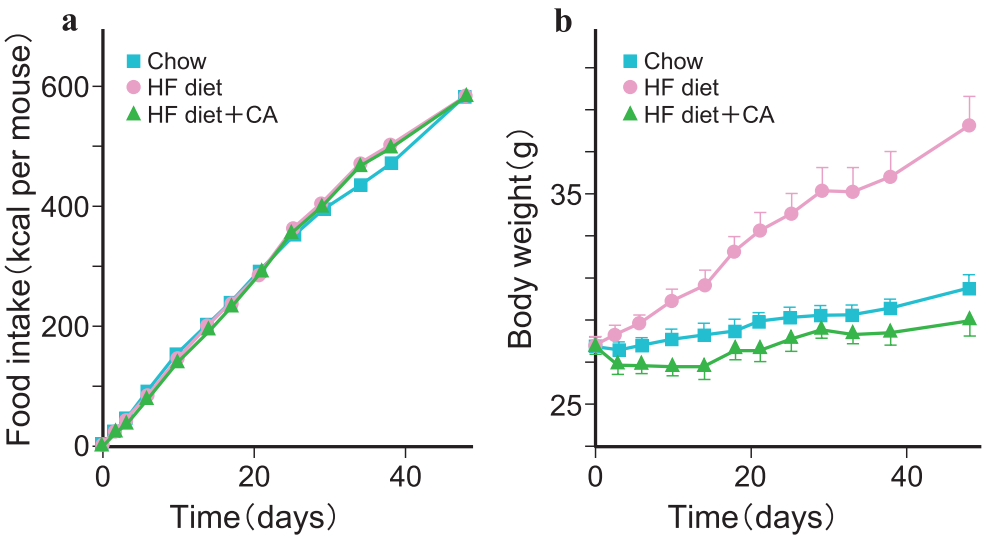
Recently, the prevalence of obesity has increased in Japan. Many factors, such as a westernized diet and lack of exercise, are considered as the reasons for this phenomenon. It is reported that insulin resistance induced by increase in visceral fat, which results in diseases due to metabolic disorders, including diabetes, hyperlipidemia, and hypertension, is observed in obese patients. As these diseases due to metabolic disorders are risk factors for coronary artery diseases, decreasing the visceral fat is clinically significant to control these diseases. Abnormal findings induced by the metabolic disorders due to obesity are closely related to the amount of visceral fat, and the change in secretion of a certain cytokine from fat cells due to obesity is reported to evoke insulin resistance. Colestimide, a new type of anion exchange resin developed in Japan, lowers plasma cholesterol concentrations by absorbing bile acids in the intestinal tract. The blood glucose-lowering activity of cholestyramine, another anion exchange resin, has previously been reported in patients with type 2 diabetes and hypercholesterolemia. To date, however, the relationship between glycemic control and the blood glucose-lowering activity of colestimide in patients with type 2 diabetes has not been reported. In addition, the mechanism by which cholestyramine decreases blood glucose levels remains unclear. A recent report has described that bile acids decrease body weight and lower blood glucose levels in metabolic syndrome model mice because the bile acids accelerate energy consumption via thyroid hormones **(Fig. 1, 2)**. Therefore, the involvement of an anion exchange resin in this mechanism is also conceivable.

In our recent study, the lowering effects of colestimide on plasma glucose and lipids were observed when a 2-week treatment with colestimide was performed in patients with hypercholesterolemia and diabetes **(Fig. 3, 4)**. We examine, in comparison with an α-glucosidase inhibitor, the usefulness of colestimide in lowering blood glucose levels in patients with type 2 diabetes and hypercholesterolemia. Thirty-three patients with type 2



a, **b**, Change in cumulative food intake (**a**) and body weight (**b**) of C57BL/6J mice over 47 days. Squares, chow (Ch); circles, HF diet (F); triangles, HF diet plus CA (FA).

Watanabe.M; Nature.439(7075)484-489.2006

Fig. 1 Change in cumulative food intake and body weight

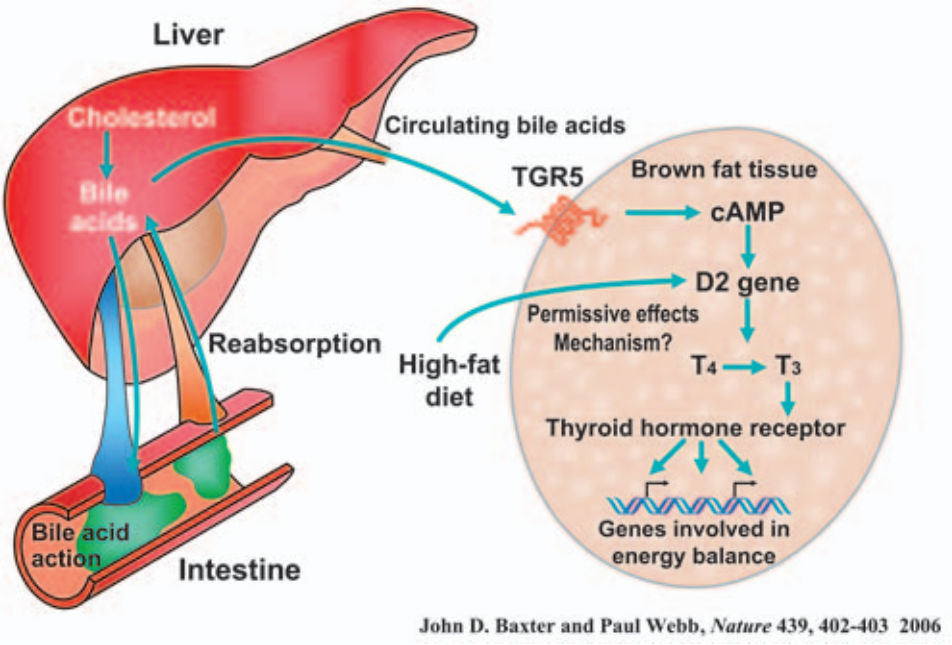


Fig. 2 Bile acids in energy homeostasis

diabetes and hypercholesterolemia were more or less randomly assigned to receive either colestimide (17 patients) or acarbose (16 patients). At 10 time points before and after administration, plasma glucose levels and serum lipid concentrations were measured in all subjects, and the J-index and M-value were calculated. Patients receiving colestimide showed significant decreases in glucose levels 2 hours after breakfast (from 216.9 ± 37.2 mg/d*l* before treatment to 191.1 ± 40.9 mg/d*l* after treatment; $p=0.008$), in the J-index (from 42.6 ± 14.5 to 32.6 ± 9.8; $p<0.001$), and in the M-value (from 23.1 ± 12.1 to 14.6 ± 7.1; $p<0.001$). In patients with type 2 diabetes and hyperlipidemia, colestimide was suggested to have blood glucose-lowering activity as does acarbose.

In another study of ours, as the further investigation of the efficacy of colestimide in patients with the

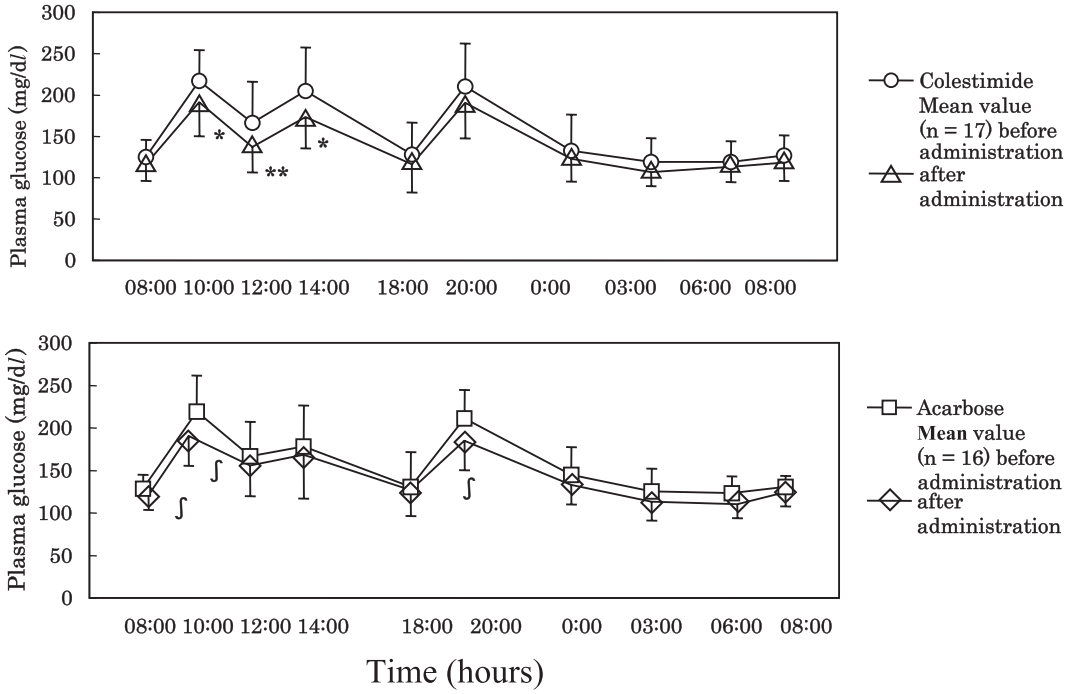


Fig. 3 Diurnal changes in plasma glucose levels before and after oral administration of colestimide (upper) and acarbose (lower) Values are expressed as mean ± SD.
*: p<0.05, **: p<0.01, before vs. after administration of colestimide (paired t-test)
∫: p<0.05, before vs. after administration of acarbose (paired t-test)
(Tatsuya Suzuki, Kenzo Oba, Shoko Futami, et al. J Nippon Med Sch 2006; 73(5): 281)

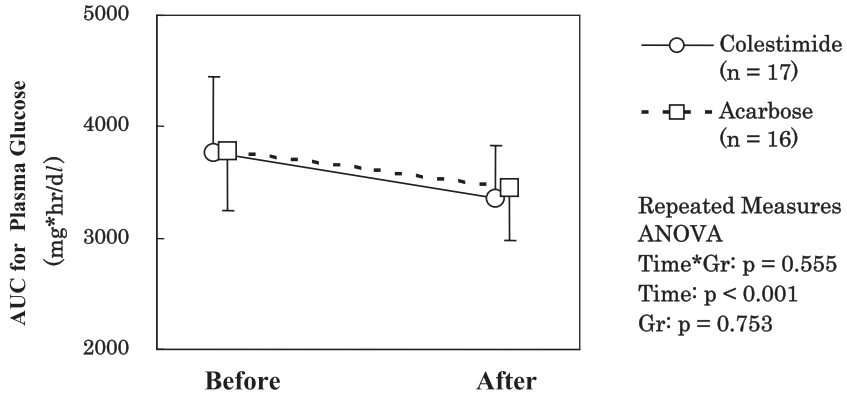


Fig. 4 Comparison of diurnal changes in AUC for plasma glucose levels before and after oral administration of colestimide and acarbose.
A significant difference (p<0.001) was noted in the time-course for AUCs of plasma glucose levels. No significant difference was found (p=0.753) between groups C and A. The interaction was not significant (p =0.555).
Values are expressed as mean ± SD.
(Tatsuya Suzuki, Kenzo Oba, Shoko Futami, et al. J Nippon Med Sch 2006; 73(5): 281)

diseases due to metabolic disorders, the effects of a long-term treatment with colestimide on visceral fat and cytokines associated with obesity were investigated in patients with hypercholesterolemia and obesity or the

tendency to obesity. In addition, the effects of colestimide on plasma glucose and HbA_{1c} were investigated in patients with hypercholesterolemia and diabetes. Changes in body mass index (BMI), visceral fat, plasma glucose, serum lipids and cytokines associated with obesity were investigated after a 24-week treatment with colestimide in patients with hypercholesterolemia and obesity or the tendency to obesity. The following variables were measured before and after treatment with colestimide and the changes were analyzed using a paired t-test: body weight, BMI, visceral fat, fasting plasma glucose, HbA_{1c}, immunoreactive insulin, homeostasis model assessment of insulin resistance, serum lipids, plasma adiponectin, plasma plasminogen activator inhibitor type 1, and plasma tumor necrosis factor-alpha. Significant decreases in body weight, BMI, and visceral fat were observed after the 24-week treatment with colestimide. Significant decrease in fasting plasma glucose, the tendency for decrease in total cholesterol and significant increase in high-density lipoprotein cholesterol were also observed. Furthermore, significant increase in adiponectin, significant decrease in PAI-1, and tendency to decrease in TNF-α were observed. It was indicated that colestimide improved obesity and accumulation of visceral fat in hypercholesterolemic patients with obesity and tendency to obesity by adjusting the levels of serum lipids and cytokines associated with obesity. Accordingly, colestimide may be expected to be effective against diseases due to metabolic disorders including obesity and diabetes.

Therefore, in future studies, we are plan to investigate the effects and mechanisms of colestimide on blood glucose-lowering activity and changes in body weight, visceral fat, and cytokines associated with obesity in patients with type 2 diabetes and hypercholesterolemia.