The Effect of Colestimide on Visceral Fat Mass and Cytokine Levels in Patients with Metabolic Syndrome

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Bile acid–binding resins (BABRs) improve hyperglycemia in patients with type 2 diabetes, and the BABR colesevelam has been approved by the U.S. Food and Drug Administration for use as an antihyperglycemic agent. Colestimide (colestilan) is a new type of anion resin that increases the number of hepatic low-density lipoprotein receptors and decreases serum cholesterol levels by promoting the excretion of bile acids and inhibiting the absorption of cholesterol in the intestine; with these changes, the serum level of low-density lipoprotein cholesterol decreases [1]. In our previous study, we observed that colestimide decreased levels of plasma glucose and lipids after 2 weeks of treatment in patients with hypercholesterolemia and diabetes [2]. In addition, we recently reported that colestimide decreases fasting glucose levels, but also reduces body weight (BW), body-mass index (BMI), and visceral fat mass [3]. Furthermore, colestimide could be useful for the management of impaired glucose tolerance in patients with metabolic syndrome, because it decreases not only cholesterol levels but also BW and insulin resistance in mice [4].

To the best of our knowledge, however, no previous study has examined whether colestimide decreases plasma glucose and visceral fat area in patients with metabolic syndrome.

Hence, we performed the present study to examine whether colestimide decreases plasma glucose and visceral fat area and whether it changes levels of cytokines associated with obesity in Japanese patients with hypercholesterolemia with metabolic syndrome when used as a long-term treatment.

Ten outpatients with hypercholesterolemia and metabolic syndrome were enrolled in the present study. The Japanese version of metabolic syndrome diagnostic criteria [5] was used as the diagnostic criteria for metabolic syndrome. Before the start of the study, informed consent was obtained from all subjects after they were provided with a sufficient explanation. The subjects were being treated at our hospital with both statin preparations and diet therapy. Colestimide at a dosage of 1500 mg twice daily (before breakfast and supper) was administered for 24 weeks to each patient by their attending physician. To calculate BMI, subject’s BWs were measured before and after 24 weeks of treatment with colestimide. Visceral fat area was measured with computed tomography at the umbilical level. The BMI was calculated as weight (kg)/height (m²).

Blood samples were obtained in the early morning after an overnight fast both before and after 24 weeks of treatment with colestimide. In addition, the serum concentration of HbA1c was measured with high-performance liquid chromatography, and serum immunoreactive insulin (IRI) was measured with a radioimmunoassay. The HbA1c (%) is given as NGSP equivalent values (%), which were calculated with the following formula [6]: HbA1c (%) = HbA1c (Japan Diabetes Society; %) + 0.4%. The fasting plasma glucose (FPG), HbA1c, and IRI were measured, and homeostasis model assessment insulin resistance (HOMA-IR) was calculated. Serum lipids, plasma adiponectin, plasma plasminogen activator inhibitor type 1 (PAI-1), plasma tumor necrosis factor (TNF)-α, and plasma resistin were also measured.

The diet therapy that had been performed before the study was continued during the study period to maintain dietary control and kinesitherapy without modifying the procedures. During the study period, the type and dosage of administered drugs, including concomitant drugs, were not changed, and other new drugs were withheld.

Differences between mean values before and after treatment with colestimide were analyzed with paired Student’s t-tests. The data are presented as means ± standard deviations. P values of less than 0.05 were considered to indicate statistical significance.

The subjects were 8 women and 2 men. Their mean age was 64.9 ± 10.2 years, mean BMI was 30.8 ± 3.5 kg/m², and the mean total cholesterol value was 234.6 ± 30.8 mg/dL. Eight of the 10 subjects had diabetes, and 7 of the 10 had hypertension. One patient was being treated with glibenclamide and thiothiazone, and another was being treated with gliclazide.

Diachronic changes observed in each variable between before and after treatment with colestimide are shown in table 1. Significant decreases were observed in BMI (from 30.8 ± 3.5 kg/m² to 29.7 ± 3.4 kg/m²; p = 0.017) and visceral fat area (from 184.0 ± 55.6 cm² to 139.0 ± 41.8 cm²; p = 0.001). Significant decreases were also observed in FPG (from 142.3 ± 27.0 mg/dL to 94.1 ± 17.9 mg/dL; p = 0.001) and HbA1c (from 7.9% ± 1.7% to 6.1% ± 0.8%; p = 0.007). However, in the present study, the mean total cholesterol value was 234.6 ± 30.8 mg/dL. Eight of the 10 subjects had diabetes, and 7 of the 10 had hypertension. One patient was being treated with gliclazide and thioglibesterin, and another was being treated with gliclazide.

Concerning the antiobesity effects of cholesterol, another anion exchanger, decreased weight has been reported in both rats [7] and in obese patients with hyperlipidemia [8]. In the present study, colestimide was found to decrease BW, BMI, and visceral fat area in patients with hypercholesterolemia and metabolic syndrome. Adiponectin has been reported to decrease insulin resistance, and higher serum adiponectin levels have protective effects against both...
diabetes and arteriosclerosis [9]. The accumulation of visceral fat increases PAI-1 gene expression and, subsequently, increases the serum concentration of PAI-1 [10]. Furthermore, TNF-α decreases the production and secretion of adiponectin and inhibits its genetic transcription system [11]. In the present study, colestimide was observed to improve glucose and lipid metabolism, to significantly increase the plasma adiponectin level, and to significantly decrease the plasma PAI-1 level. These results support the results of a previous study indicating a relationship between metabolic disorders and adipocytokines [9]. We have recently reported that colestimide reduces BW, BMI, and visceral fat mass via an increase in the cholic acid ratio in humans and in mice by enhancing energy metabolism through the so-called G- protein–coupled receptor 5-cAMP D2 pathway [3,4].

Colestimide has been reported to decrease plasma glucose levels in patients with hypercholesterolemia and type 2 diabetes [2,12]. The present study confirmed that the hypoglycemic effect of colestimide is maintained after 24 weeks of treatment. We have already reported that colestimide increases the secretion of glucose-like peptide 1 [13]. Furthermore, colestyramine is reported to increase cholecystokinin [14,15], a gastrointestinal hormone. Incretins, such as cholecystokinin, are also reported to have hypoglycemic effects [16]. Because colestimide is a drug that acts in the intestine, as does colestyramine, we can speculate that colestimide also affects gastrointestinal hormones, which produce its hypoglycemic effects. However, the mechanism by which colestimide decreases blood glucose levels remains unclear. To clarify colestimide’s mechanisms of action, further fundamental research is necessary.

In addition, previous clinical studies [3,17] and a preclinical study [4] also support our results. However, BABRs have reported to cause no change in BW [12,18,19]. On the other hand, preclinical studies in model mice have reported the BW-reducing effect of colestimide [4,20]. The reason why the results are different in humans remains unknown. In the present study, the subjects were 8 women and 2 men. We suspect there may be a difference in susceptibility to changes in the cholic acid ratio of the serum bile acid composition in humans due to the so-called TGR5-cAMP-D2 pathway because brown adipose tissue is detected more frequently in women [21].

Unfortunately, the present study was not a case-control study. However, we have performed another study in 11 patients who did not receive colestimide and had no change in administered drugs during the 24 weeks of the observation period. The subjects were 9 women and 2 men. Their mean age was 65.0 ± 13.7 years, mean BMI was 30.5 ± 3.3 kg/m², and the mean total cholesterol value was 215.1 ± 18.7 mg/dL. Eight of the 11 subjects had diabetes, 10 of the 11 subjects had dyslipidemia, and all subjects had hypertension. One patient was being treated with pioglitazone, and two patients were being treated with glimepiride. In these patients, no longitudinal changes were found in any variable, including fasting plasma glucose, IRI, total cholesterol, high-density lipoprotein cholesterol, triglycerides, and apolipoprotein (Apo) A-1, ApoB, and ApoE, except for BMI, BW and HbA1C (Table 2). Moreover, the present study was not a randomized, controlled trial. We believe that a case-control study with a greater number of patients will be required.

In summary, the present study has found that colestimide decreases plasma glucose levels and visceral fat area, likely by affecting cytokines, such as adiponectin and PAI-1, associated with obesity, in patients with hypercholesterolemia and metabolic syndrome. Consequently, we believe that colestimide will be useful for the primary and secondary prevention of arterial diseases by reducing its risk factors, including hypercholesterolemia, obesity, and type 2 diabetes mellitus.

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References

196 and bile acids or other biological substances - Comparison with cholestyramine. Jpn Pharmacol Ther 24: 127-132.


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