Colesevelam Improves Oral but Not Intravenous Glucose Tolerance by a Mechanism Independent of Insulin Sensitivity and β-Cell Function

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OBJECTIVE—To determine the mechanism by which the bile acid sequestrant colesevelam improves glycemic control.

RESEARCH DESIGN AND METHODS—We performed a frequently sampled intravenous glucose tolerance test (FSIGT) with minimal model analysis and a meal tolerance test (MTT) in 20 subjects with impaired fasting glucose (11 men, 9 women; mean age 60.7 ± 1.9 years, BMI 29.4 ± 0.9 kg/m^2) in a single-blind study after 2 weeks of placebo treatment and 8 weeks of colesevelam 3.75 g daily. From these tests, insulin sensitivity, β-cell function, and glucose tolerance were determined, along with gastrointestinal peptide levels during the MTT.

RESULTS—Fasting plasma glucose and HbA_{1c} decreased with colesevelam (from 5.9 ± 0.1 to 5.7 ± 0.1 mmol/L, $P < 0.05$, and from 5.86 ± 0.06 to 5.76 ± 0.06%, $P = 0.01$, respectively), but fasting insulin did not change. Colesevelam had no effect on any FSIGT measures. In contrast, the MTT incremental area under the curve (iAUC) for both glucose (from 249.3 ± 28.5 to 198.8 ± 23.6 mmol/L · min, $P < 0.01$) and insulin (from 20,130 [13,542–35,292] to 13,086 [9,804–21,138] pmol/L · min, $P < 0.05$) decreased with colesevelam. However, the ratio of iAUC insulin to iAUC glucose was not changed. iAUC for cholecystokinin (CCK) increased (from 43.2 [0–130.1] to 127.1 [47.2–295.2] pmol/L · min, $P < 0.01$), while iAUC for fibroblast growth factor 19 decreased (from 11,185 [1,346–17,661] to 2,093 [673–6,707] pg/mL · min, $P < 0.01$) with colesevelam. However, iAUC for glucagon, glucose-dependent insulinotropic peptide, and glucagon-like peptide 1 did not change.

CONCLUSIONS—Colesevelam improves oral but not intravenous glucose tolerance without changing insulin sensitivity, β-cell function, or incretins. This effect may be at least partially explained by the colesevelam-induced increase in CCK.

Diabetes Care 35:1119–1125, 2012

Colesevelam is a bile acid sequestrant that is used for the treatment of hypercholesterolemia. More recent, it has been approved for use in patients with type 2 diabetes because it improves glycemic control, with decreases in HbA_{1c} of ~0.5% compared with placebo when used in combination with metformin, sulfonylurea, or insulin (1–4). However, the mechanism(s) by which colesevelam improves glucose tolerance is unknown.

It has been suggested that the glucose-lowering effect of colesevelam and other bile acid sequestrants is mediated by the nuclear receptors farnesoid X receptor (FXR) and liver X receptor (LXR) (3). Activation of FXR by bile acids leads to a negative feedback inhibition of bile acid biosynthesis and secretion, in part via increased expression of fibroblast growth factor (FGF)-19 by enterocytes resulting in diminished CYP7A1 expression in the liver (5,6). Binding of bile acids by bile acid sequestrants reverses these effects. FXR appears to directly affect glucose metabolism, but its specific role is currently under investigation with studies reporting conflicting results (6). There is a complex interaction between FXR and LXR, which often have counterbalancing effects (7). LXR has been described as a glucose sensor (8), capable of improving glucose tolerance by promoting glucose utilization and triglyceride synthesis and inhibiting gluconeogenesis (9,10). We hypothesized that independent of the precise mechanism of the effects of bile acid sequestrants on glucose, if the FXR-LXR hypothesis is correct, treatment of humans with colesevelam would result in improvement in insulin sensitivity. While animal studies show improvement in insulin sensitivity during treatment with bile acid sequestrants (11,12), such an effect has not been clearly demonstrated in humans (13).

The ability of bile acid sequestrants to lower blood glucose also has been linked to their possible effect on intestinal glucagon-like peptide 1 (GLP-1) secretion and, in some studies, peptide Tyr-Tyr (PYY) release (11,12,14). It has been suggested that sequestration of bile acids may interfere with free fatty acid absorption in the proximal small intestine, resulting in increased free fatty acid delivery to the ileum and, consequently, enhanced GLP-1 secretion by the ileal L-cells (11). Furthermore, the increased levels of bile acids in the intestinal lumen during treatment with bile acid sequestrants could also stimulate GLP-1 release via the G-protein–coupled receptor TGR5 (15). We hypothesized that if the glucose-lowering effect of colesevelam was related to increased incretin release, such an increase would be associated with an improvement in islet (β- and/or α-cell) function with meals.

Thus, the primary objective of this study was to determine whether the glucose-lowering properties of colesevelam are the result of improvements in insulin sensitivity and/or β- and α-cell function. Furthermore, we wished to determine whether any improvements could be attributed to changes in the release of incretins or other gastrointestinal

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Received 20 October 2011 and accepted 4 February 2012.
DOI: 10.2337/dc11-2050. Clinical trial reg. no. NCT00990184, clinicaltrials.gov.

peptides. We chose to study subjects with impaired fasting glucose (IFG) because they are at high risk of developing type 2 diabetes and because with their mild impairment in glucose metabolism, it is possible to use a number of sensitive methods to quantify changes in several important parameters that regulate glucose without excess concern of the deleterious effects of glucose per se. Thus, we performed insulin-modified frequently sampled intravenous glucose tolerance tests (FSIGTs) to quantify insulin sensitivity and β-cell function (16) and standardized meal tolerance tests (MTTs) to evaluate postprandial glucose, insulin, glucagon, and incretin responses, all before and after treatment with colesevelam. Levels of gastrointestinal peptides were also measured immediately before and during the standardized meal, when they were expected to produce their physiological effects.

RESEARCH DESIGN AND METHODS

The study used a single-blind, single-treatment design with a 2-week placebo run-in phase followed by 8 weeks of treatment with unbranded active colesevelam hydrochloride (3.75 g daily) with the evening meal. Subjects were blinded to treatment throughout the study, having been told that any time during the study they may receive active medication or placebo. An insulin-modified FSIGT and an MTT were performed on days 14 and 70, before and at the end of treatment with colesevelam, respectively.

The study was registered at ClinicalTrials.gov as NCT00990184. The VA Puget Sound Health System Institutional Review Board approved the protocol, and written informed consent was obtained from all subjects prior to their participation in the study. An independent data safety monitoring committee oversaw the performance of the study.

Eligible subjects were males and females (postmenopausal, surgically sterile, or using double-barrier method of contraception), aged 18–75 years, with a fasting plasma glucose of 5.6–6.4 mmol/L (100–115 mg/dL) at screening (average of two measurements during screening) and an HbA_{1c} <6.5%. They also had to be otherwise in good health as determined by medical history, physical examination, electrocardiogram, and laboratory tests at screening.

Subjects were excluded if they had a history of diabetes or treatment with glucose-lowering agents, except for insulin during pregnancy; use of chronic oral or parenteral corticosteroids or bile acid sequestrants within 3 months; or use of HIV protease inhibitors, warfarin, phenytoin, or any investigational drug within 30 days. Other exclusion criteria were triglycerides >5.6 mmol/L, uncontrolled hypothyroidism, clinical hepatic disease or liver function tests greater than two times the upper limit of normal, and history of major gastrointestinal surgery (gastrectomy, gastroenterostomy, and bowel resection), dysphagia, swallowing disorders, intestinal motility disorder, or pancreatitis.

Study procedures

Interventions. Subjects were provided with blinded active medication (colesevelam) or matching placebo. Medication was taken with the evening meal, with placebo being consumed for 2 weeks prior to the performance of the first set of outcome assessments. Thereafter, subjects started taking 3.75 g colesevelam once daily with the evening meal and did so for the next 8 weeks, at the end of which they underwent a second series of outcome assessments. Medication compliance was assessed by counting the number of unused tablets returned on days 14, 42, and 70. No subjects were excluded based on the protocol requirement that subjects take >80% of the prescribed medication during the placebo period (first 14 days). Subjects were asked to maintain prior exercise and dietary habits throughout the study.

FSIGT. An FSIGT was performed on days 14 and 70 after a 10-h fast. After three basal blood samples were drawn, an intravenous glucose bolus (50% dextrose at 11.4 g/m^2 body surface area) was administered during a 60-s period at time 0. Eleven blood samples were collected during the next 19 min, followed at 20 min by the commencement of an insulin infusion (0.03 units/kg) administered during a 5-min period. Subsequently, 21 blood samples were collected up until 240 min after the start of glucose administration.

MTT. At 30 min after completion of the FSIGT, subjects were given a standardized liquid meal consisting of a can of Resource 2.0 (237 mL; 480 kcal; 20 g protein, 52 g carbohydrate, 21 g fat, with added minerals and vitamins). A dose of placebo or colesevelam was taken at the beginning of the standardized meal. Blood samples were obtained at 5 and 1 min before the meal and every 30 min for 120 min after starting the meal.

Safety assessments. A medical history, vital signs, and physical examination were performed prior to randomization and at the end of the study. Reported adverse events were recorded, and laboratory safety assessments (complete blood count, electrolytes, plasma creatinine, liver function tests, lactate dehydrogenase, creatine phosphokinase, lipid panel, and urinalysis) were performed on days 14, 42, and 70. A standard 12-lead electrocardiogram was recorded on days 14 and 70.

Assays

Plasma glucose was measured using the hexokinase method (Roche Diagnostics, Indianapolis, IN), lipids were measured by enzymatic methods (Roche Diagnostics), and dextran sulfate precipitation for HDL cholesterol. Insulin and C-peptide levels were measured using two-site immunoenzymatic assays (Tosoh Bioscience, San Francisco, CA). Radioimmunoassays were used to measure plasma levels of proinsulin (Millipore, St. Charles, MO; HPI-15K, minimum detection limit 2 pmol/L, intra-assay coefficient of variation [CV] 1.5–6.9%, interassay CV 1.5–10.1%), glucagon (Millipore; GL-32K, minimum detection limit 20 ng/L, intra-assay CV 4–6.8%, interassay CV 7.3–13.5%), total PYY (Millipore; PYYT-66HK, minimum detection limit 10 pg/mL, intra-assay CV 2.9–9.4%, interassay CV 5.5–8.5%), and sulfated cholecystokinin (CCK) (ALPCO, Salem, NH; 13-CCK-HU-R100, minimum detection limit 0.3 pmol/L, intra-assay CV 2–5.5%, interassay CV 4.1–13.7%). Enzyme-linked immunosorbent assays were used to measure total glucose-dependent insulinotropic peptide (GIP) (Millipore; EZHGIP-54K, minimum detection limit 1.65 pmol/L, intra-assay CV 3–8.8%, interassay CV 1.8–6.1%), total GLP-1 (ALPCO; 43-GPTHU-E-01, minimum detection limit 0.6 pmol/L, intra-assay CV 3.7–4.7%, interassay CV 6.2–9.5%), FGF-19 (R&D Systems, Minneapolis, MN; DF1900, minimum detection limit 0.53–3.35 pg/mL, intra-assay CV 3.6–6.4%, interassay CV 4.5–5.5%), and FGF-21 (R&D Systems; minimum detection limit 1.61–8.69 pg/mL, intra-assay CV 2.9–3.9%, interassay CV 5.2–10.9%). When the result was below the minimum detection limit for the assay, the minimal detectable concentration was used for the analyses.

Calculations

A number of measures were calculated from the FSIGT. The insulin sensitivity index (S_I) was determined from the glucose and insulin data using Bergman's minimal model (16). The acute insulin, acute C-peptide, and acute proinsulin responses

to glucose (AIRg, ACRg, and APIRg, respectively) were calculated as the mean incremental responses above basal from time 0 to 10 min and the glucose disappearance constant (K_g) as the slope of the regression line relating the natural log of the glucose concentration from 10 to 19 min. The disposition index was computed as the product of S_I and AIRg and provides a measure of β-cell function (17).

From the MTT, incremental areas under the curves (iAUCs) for glucose, insulin, C-peptide, and glucagon were calculated using the trapezoidal method. In a similar manner, iAUCs were calculated for the gastrointestinal peptides GLP-1, GIP, PYY, and CCK, as well as for FGF-19 and FGF-21.

Statistical analysis

Sample size was determined for AIRg based on a one-sample, two-sided *t* test at a significance level of 5% for comparison between the value at the end of the placebo run-in period and the value after 8 weeks of colesevelam treatment. The use of 20 subjects was calculated to provide 85% power to detect a clinically relevant 30% change from baseline in AIRg, assuming an intrasubject CV of 0.3 (18).

Paired-sample *t* tests were used to compare the means of normally distributed variables before and at the end of treatment with colesevelam. Relationships between variables were examined using linear regression. Those variables that were not normally distributed were log-transformed to achieve normal distribution or analyzed using the Wilcoxon signed rank test. Unless otherwise specified, all data are mean ± SEM for normally distributed variables and median (interquartile range) for nonnormally distributed data. Statistical analyses were performed with SPSS, version 13.0, with $P < 0.05$ considered significant.

RESULTS

Subject characteristics and disposition

A total of 21 subjects met eligibility criteria and were enrolled in the study. Of these, 20 (11 men, 9 women) completed the study. A male subject was withdrawn during the placebo run-in phase because of an acute cerebrovascular accident.

At randomization, subjects were 60.7 ± 8.7 years (mean ± SD; range 40–75) and had a BMI of 29.4 ± 4.2 kg/m^2 (range 23.5–36), consistent with the subjects on average being overweight. Their fasting plasma glucose was 6.0 ± 0.2 mmol/L (range 5.6–6.4). All subjects were compliant with medication usage, taking >80% of both placebo and colesevelam study medication. In general, colesevelam was well tolerated, with 35% of subjects reporting constipation while on the medication. One subject had an acute episode of cholelithiasis while taking colesevelam but was not excluded from the study. There were no other serious adverse events.

Effect of colesevelam on body anthropometry and lipids

As listed in Table 1, after 8 weeks of treatment with colesevelam, weight did not change. While subjects were not required to have lipid abnormalities for entry into the study, the changes in plasma lipid levels with colesevelam treatment were consistent with the known effect of the medication to decrease total and LDL cholesterol, further supporting that subjects were compliant with the use of colesevelam.

Effect of colesevelam on glucose tolerance, insulin sensitivity, and islet function

Treatment with colesevelam improved glucose levels, which were quantified as significant decreases in fasting plasma glucose and HbA_{1c} (Table 1). Fasting plasma insulin, proinsulin, and C-peptide concentrations did not change with colesevelam administration (Table 1).

As illustrated in Fig. 1, glucose and insulin concentrations during the FSIGT did not differ at the end of the placebo run-in and colesevelam treatment periods. Thus, as listed in Table 1, S_I, AIRg, ACRg, and APIRg did not change with treatment. Furthermore, the disposition index also was not altered with colesevelam treatment, and intravenous glucose tolerance, determined as K_g, did not change.

In contrast to what was observed with the FSIGT, changes in glucose, insulin, and C-peptide profiles were observed during the MTT (Fig. 2). Glucose tolerance during the MTT, calculated as the iAUC for glucose, improved with colesevelam treatment (from 249.3 ± 28.5 to 198.8 ± 23.6 mmol/L · min, $P < 0.01$). Furthermore, colesevelam administration was associated with decreases in the iAUC for both insulin (from 20,130 [13,542–35,292] to 13,086 [9,804–21,138] pmol/L · min, $P < 0.05$) and C-peptide (from 122.8 [91.9–194.3] to 95.4 [75.3–140.2] nmol/L · min, $P < 0.05$). The result of the parallel changes in glucose and the two β-cell peptides meant that the ratios of each peptide to glucose were not different for insulin (ratio of iAUC insulin to iAUC glucose: 125.4 ± 16.2 to 109.2 ± 16.2 [pmol/L]/[mmol/L], $P = 0.08$) or C-peptide (ratio of iAUC C-peptide to iAUC glucose: 0.66 ± 0.06 to 0.60 ± 0.06 [nmol/L]/[mmol/L], $P = 0.18$), indicating that β-cell function had not changed.

Table 1—*Weight, fasting plasma lipids, and measures of β-cell function, insulin sensitivity, and glucose tolerance before and at the end of treatment with colesevelam*

	Day 14 (before treatment)	Day 70 (end of treatment)	*P* value
Weight (kg)	86.3 ± 2.9	86.8 ± 3.0	0.53
Total cholesterol (mmol/L)	4.59 ± 0.19	4.06 ± 0.19	<0.001
LDL cholesterol (mmol/L)	2.79 ± 0.18	2.25 ± 0.16	<0.001
HDL cholesterol (mmol/L)	1.02 (0.87–1.30)	0.97 (0.90–1.32)	0.89
VLDL cholesterol (mmol/L)	0.57 (0.45–0.91)	0.65 (0.48–0.82)	0.46
Triglycerides (mmol/L)	1.23 (0.97–1.96)	1.40 (1.03–1.78)	0.46
Fasting plasma glucose (mmol/L)	5.9 ± 0.1	5.7 ± 0.1	0.01
HbA_{1c} (%)	5.86 ± 0.06	5.76 ± 0.06	0.01
Fasting insulin (pmol/L)	56 (26–92)	43 (25–83)	0.28
Fasting proinsulin (pmol/L)	11.6 (9.4–16.4)	11.5 (8.2–16.5)	0.68
Fasting C-peptide (nmol/L)	0.8 (0.5–1.2)	0.7 (0.5–1.2)	0.42
S_I ($\times 10^{-5}$ min^{-1} · [pmol/L]$^{-1}$)	4.8 ± 0.5	4.6 ± 0.6	0.76
AIRg (pmol/L · min)	1,752 (564–3,306)	1,866 (678–2,670)	0.12
ACRg (nmol/L · min)	5.8 (2.5–9.3)	6.7 (3.1–9.1)	0.16
APIRg (pmol/L · min)	45.2 (24.1–92.6)	44.6 (15.0–84.4)	0.15
Disposition index ($\times 10^{-4}$)	569 (290–1,235)	639 (325–1,012)	0.69
K_g (% · min^{-1})	1.26 ± 0.08	1.32 ± 0.10	0.55

Data are mean ± SEM or median (interquartile range).

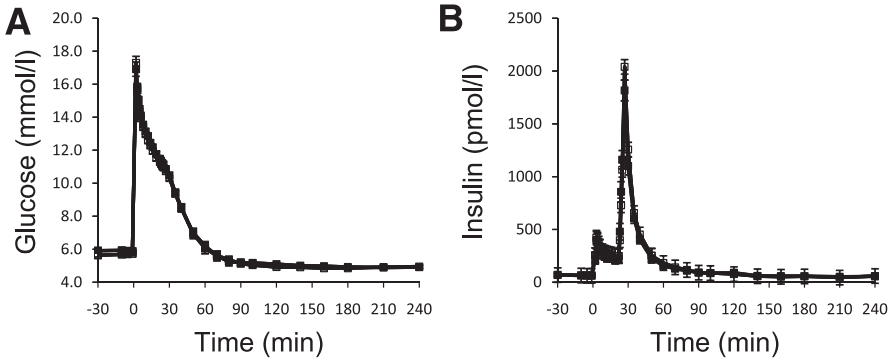

Figure 1—*Plasma glucose* (A) *and insulin* (B) *levels during the FSIGT.* ■ *and solid line, before treatment with colesevelam (day 14);* □ *and dashed line, end of treatment with colesevelam (day 70).*

On the basis of the glucagon profile, colesevelam treatment also had no effect on α-cell function. The iAUC for glucagon was similar before and at the end of therapy (617 ± 133 vs. 434 ± 118 ng/L · min, $P = 0.23$) (Fig. 2).

Effect of colesevelam on the release of gastrointestinal tract–related proteins

The effect of colesevelam on various gastrointestinal peptides is illustrated in Fig. 3.

Colesevelam was associated with differences in the MTT profile of FGF-19 but not FGF-21. The iAUC for FGF-19 was significantly lower with colesevelam treatment (from 11,185 [1,346–17,661] to 2,093 [673–6,707] pg/mL · min, $P < 0.01$), while that for FGF-21 did not change (from −1,157 ± 948 to 175 ± 980 pg/mL · min, $P = 0.30$).

Treatment with colesevelam was associated with increases in CCK during the MTT at 60, 90, and 120 min, the result being a significant increase in iAUC (from 27.5 [2.4–109.2] to 200.3 [40.3–300] pmol/L · min, $P = 0.001$). Basal MTT CCK concentrations did not differ before and after treatment. During the MTT, iAUC for incretin peptides GLP-1 and GIP was not affected by colesevelam therapy (from 133 [38–172] to 98 [26–166] pmol/L · min, $P = 0.25$, and from 4,610 ± 404 to 4,209 ± 451 pmol/L · min, $P = 0.33$, respectively). In a similar manner, there was no effect of colesevelam on the basal or postprandial levels of PYY (from 2,816 [1,108–4,323] to 2,271 [1,079–4,373] pg/mL · min, $P = 0.46$).

The changes in CCK during the MTT were not correlated with the changes in glucose or the islet peptides insulin, C-peptide, or glucagon.

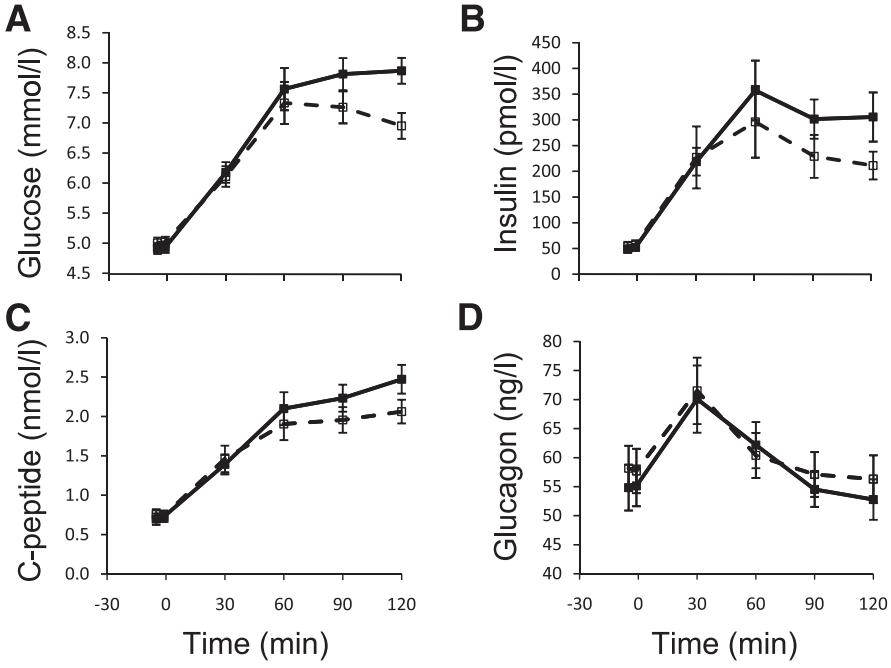

Figure 2—*Plasma glucose* (A)*, insulin* (B)*, C-peptide* (C)*, and glucagon* (D) *levels during the MTT.* ■ *and solid line, before treatment with colesevelam (day 14);* □ *and dashed line, end of treatment with colesevelam (day 70).*

CONCLUSIONS—We found that colesevelam significantly improved glucose metabolism in subjects with IFG as demonstrated by reductions in both the fasting plasma glucose and HbA_{1c}. These beneficial changes in glucose control did not appear to be the result of improvements in insulin sensitivity or β-cell function because we observed no change in S_I using the minimal model of glucose kinetics or AIRg, respectively. In keeping with the lack of changes in these two important determinants of intravenous glucose tolerance (17), we observed no change in this measure determined as K_g. Of great interest was the finding that in contrast to what we observed for intravenous glucose tolerance, oral glucose tolerance did improve with colesevelam administration. Again, on the basis of the fasting insulin concentrations and the insulin and C-peptide responses after meal ingestion, insulin sensitivity and β-cell function were not changed by colesevelam treatment. The lack of change in the incretins GLP-1 and GIP is compatible with our observation of a lack of change in β-cell function. Thus, it appears that the improvement in glucose metabolism is probably independent of an effect of insulin.

By what mechanism does colesevelam affect glucose tolerance independent of insulin sensitivity or β-cell function? Our observation that colesevelam treatment is associated with an elevation in CCK levels after the meal may provide an explanation. CCK is produced by the enterochromaffin I cells of the proximal small intestine and has numerous physiologic effects, including decreasing food intake, slowing gastric emptying, and stimulating pancreatic exocrine and endocrine secretion, bile release, and intestinal motility (19). Given that our subjects did not lose weight and we observed no improvement in β-cell function, one hypothesis is that colesevelam-induced increases in CCK could improve oral glucose tolerance in part by a delay in gastric emptying. This hypothesis is supported by studies showing that concomitant CCK

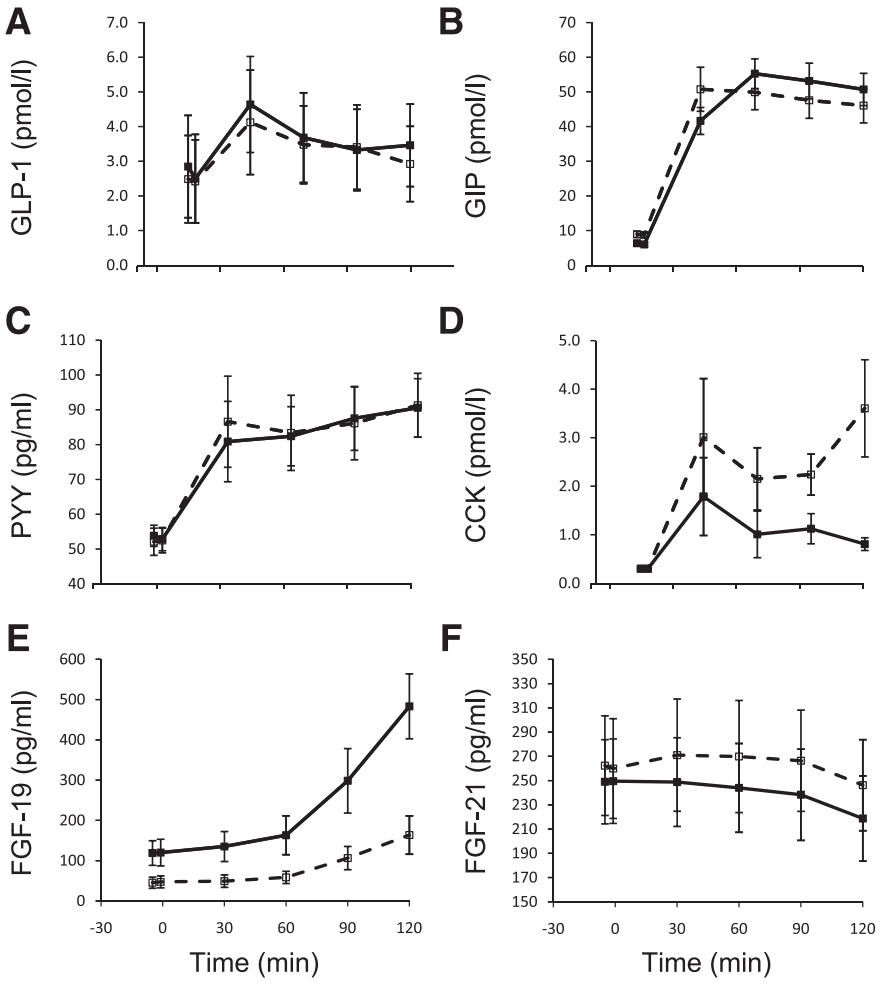

Figure 3—*Plasma total GLP-1* (A)*, total GIP* (B)*, PYY* (C)*, CCK* (D)*, FGF-19* (E)*, and FGF-21* (F) *levels during the MTT.* ■ *and solid line, before treatment with colesevelam (day 14);* □ *and dashed line, end of treatment with colesevelam (day 70).*

infusion, which achieved physiological postprandial plasma CCK concentrations, and oral glucose administration delayed gastric emptying and significantly reduced postprandial hyperglycemia and plasma insulin levels in healthy subjects (20). In the same study, this effect was not observed when glucose was administered intraduodenally, confirming that CCK lowers postprandial blood glucose by slowing gastric motility. However, the data supporting that colesevelam slows gastric emptying are limited. One study that examines this issue suggests trends toward a delay of gastric emptying with colesevelam (21). Because we did not measure gastric emptying or rate of appearance of glucose, we cannot say whether CCK had any of these effects in our study. Thus, a more definitive assessment of this issue deserves further study, and consideration should be given to comparing colesevelam's effects on solid and liquid meals.

Although a decrease in MTT glucose after treatment with colesevelam could be related to a CCK-induced delay of gastric emptying, this would not explain the decrease in the fasting glucose level. Thus, it is likely that some other mechanism is operative. Recent work in rats provides another possible explanation for a CCK effect applicable to our study. Intraduodenal administration of CCK in the basal state decreases hepatic glucose production by stimulating duodenal CCK-A receptors, with the signal transmitted to the nucleus of the solitary tract in the hindbrain and then to the liver; this occurs without any spillover so that circulating CCK levels did not change (22). It is possible that the increase in plasma CCK after meal ingestion was associated with increased duodenal CCK levels and a centrally mediated effect to enhance suppression of hepatic glucose output during the meal.

Bile acid sequestrants have been shown to mildly increase basal CCK levels during the first days of treatment. This effect subsequently wears off, which may be related to the adaptation of CCK receptors (23,24) and may explain why we did not see an increase in basal CCK levels with colesevelam. In keeping with our observation of increased CCK levels after meal ingestion with colesevelam treatment, the cholestyramine-induced increase in plasma CCK levels persisted after the effect on the basal levels could no longer be detected (24). This effect of bile acid sequestrants to alter CCK levels appears to be mediated by an effect of bile acids (25–28).

We did not observe an effect of colesevelam to change postprandial glucagon levels, which is in keeping with the findings of others (14,29). Furthermore, we observed no increase in GLP-1, GIP, and PYY release. The lack of an increase in GLP-1 in the peripheral circulation is contrary to what has been reported by others (11,12,14). The reason we failed to replicate this finding is not readily apparent, but the lack of improvements in β- and α-cell function is consistent with our observation of unchanged GLP-1 levels. However, the effect of treatment to decrease FGF-19 levels is compatible with the occurrence of other enteric effects of colesevelam.

Some animal studies suggest that the beneficial effect of bile acid sequestrants on glucose metabolism is related to an improvement in insulin sensitivity (11,12). The data in humans is not extensive but would support our observations of no change in insulin sensitivity or fasting insulin after 8 weeks of treatment. A study using the euglycemic hyperinsulinemic clamp showed no improvement in peripheral insulin sensitivity, although hepatic insulin sensitivity was not evaluated (13). Furthermore, in this same study, coadministration of the first dose of colesevelam with a standard meal had no effect on postprandial glucose levels compared with baseline or placebo, suggesting that colesevelam does not impair glucose absorption. In our opinion, whether bile acid sequestrants affect hepatic insulin sensitivity in humans is unclear and also deserves further investigation.

The finding of a change in glucose tolerance after meal ingestion but not with intravenous glucose administration was quite unexpected. This observation does suggest that when an intervention known to alter glucose tolerance is also

known to have an effect via the gastrointestinal tract, it should not be assumed that changes in insulin sensitivity and β-cell function will be discernable, and especially on intravenous testing. In fact, if we had performed only intravenous studies, we would not have observed the dissociation of glucose tolerance that was critically dependent on the route of glucose administration. We believe this difference in glucose tolerance was due to the treatment and not related to the study design in which the MTT followed the FSIGT. This conclusion is based on the fact that glucose levels at the end of the FSIGT had reached a steady state and at this time point did not differ between placebo and active treatment. Lastly, whether the same outcome would apply in subjects who have normal glucose tolerance or type 2 diabetes studied under similar conditions with colesevelam is not known.

We elected to study subjects with mild IFG so as to reduce any possible effects of glucose toxicity on our outcome measures. Of interest, our observation of a lack of change in insulin sensitivity and β-cell function despite glucose lowering with colesevelam suggests that there was no glucotoxic effect. Whether the change in CCK was a consequence of the improvement in glucose tolerance or vice versa cannot be answered definitively, but we favor the change in CCK being the primary event. We also believe the lack of change in insulin sensitivity and β-cell function is not related to the study design because we made quantitative measures and have previously demonstrated a treatment effect on glucose metabolism using this approach (30).

In conclusion, colesevelam improves fasting glucose and oral but not intravenous glucose tolerance. Our data suggest that this effect of colesevelam is independent of changes in insulin sensitivity, β-cell function, and plasma incretins. Increased plasma CCK concentrations observed during treatment may be contributing to postprandial glucose control via a delay in gastric emptying. Furthermore, given the reduction in fasting glucose together with the decrease in the postprandial glucose excursion, the effect of colesevelam and other bile acid sequestrants may be occurring through changes in hepatic glucose production. Thus, further studies are needed to elucidate the mechanism(s) by which altering bile acid metabolism modulates glucose metabolism in humans.

Acknowledgments—This study was supported in part by the U.S. Department of Veterans Affairs, National Institutes of Health Grants DK-007247 and DK-017047.

The study was also supported by an investigator-initiated proposal sponsored by Daiichi Sankyo. No other potential conflicts of interest relevant to this article were reported.

A.L.M. researched data and wrote the manuscript. K.M.U., L.A.W., and S.E.K. researched data, contributed to the discussion, and reviewed and edited the manuscript. B.K.M. and S.M.M. reviewed and edited the manuscript. A.L.M. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Parts of this study were presented in abstract form at the 71st Scientific Sessions of the American Diabetes Association, San Diego, California, 24–28 June 2011.

The authors thank the study participants; Morgan Arnold and Alison Emery, VA Puget Sound Health Care System, for expert technical assistance; and John Brunzell, Alan Chait, and William Hazzard, University of Washington, and the late Robert Knopp for serving as members of the data safety monitoring committee.

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