Bile Acids and Metabolic Regulation
Mechanisms and clinical responses to bile acid sequestration

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Bile acids have long been known to facilitate digestion and absorption of lipids in the small intestine as well as regulate cholesterol homeostasis (1,2). Over the last decade, however, it has become clear that bile acids are not simply digestive detergents and the primary route governing cholesterol catabolism. Bile acids are now recognized as hormones involved in the regulation of various metabolic processes (3). Through activation of various signaling pathways, bile acids regulate not only their own synthesis and enterohepatic circulation, but also triglyceride, cholesterol, glucose, and energy homeostasis (2).

Manipulation of bile acid enterohepatic circulation by bile acid sequestrants (BASs) have been used for over 40 years in the treatment of dyslipidemia (1), more recently data have emerged that have expanded their role in the treatment of dysglycemia in type 2 diabetes (4–9). The initial data suggesting such an effect were derived from post hoc analysis of a clinical trial for dyslipidemia that determined that BASs lowered glucose, particularly when compared with other lipid-lowering drugs (4). This concept was subsequently proven in several studies showing that BASs, such as colesevelam, lower glucose (5–8).

This review examines recent data exploring possible mechanisms involved in regulation of glucose metabolism by bile acids and the potential impact of disruption of their enterohepatic circulation on diabetes. We will also summarize the available clinical trial data that supported the regulatory approval of colesevelam for the treatment of hyperglycemia in type 2 diabetes.

TRADITIONAL ROLE OF BILE ACIDS: DIGESTION, EXCRETION, AND AUTOREGULATION — Bile acids are potent “digestive surfactants” that promote absorption of lipids (including fatsoluble vitamins), acting as emulsifiers (1,2).

Bile acids represent the primary pathway for cholesterol catabolism and account for ~50% of the daily turnover of cholesterol (1). The synthesis of bile acids occurs exclusively in the liver in a series of enzymatic reactions in the hepatocyte that convert hydrophobic cholesterol into more water-soluble amphipathic compounds (2). The production of bile acids is localized primarily in the perivenous hepatocytes, that is, the cells surrounding the central hepatic vein (10).

The immediate products of the bile acid synthetic pathways are referred to as primary bile acids. Cholic acid and chenodeoxycholic acid are the primary bile acids formed in humans. The action of intestinal bacterial flora on primary bile acids results in the formation of secondary bile acid species: deoxycholic and lithocholic acids, derived from cholic acid and chenodeoxycholic acid, respectively (2).

The steps leading to formation of primary bile acids include hydroxylation of cholesterol, catalyzed by the cytochrome P450 enzyme cholesterol 7α-hydroxylase (CYP7A1), the first and rate-limiting step of the so-called classic or neutral pathway of bile acid biosynthesis (1,2,11,12). The activity of CYP7A1 is subject to complex modes of control. The conversion of cholesterol to bile acids is primarily determined by this pathway (2).

Bile acid synthesis can also occur by an “alternative” or “acidic” pathway, which is governed by the enzyme CYP27A1 and converts oxysterols to bile acids (1,2). Unlike CYP7A1, CYP27A1 is not regulated by bile acids (2). It is estimated that only 6% of bile acid synthesis occurs via this pathway (13), but data also suggest that under certain conditions, such as fetal development (14) and chronic liver disease (13), this pathway may contribute more significantly to bile acid synthesis. The subsequent conversion of bile acid intermediates from either the classical or alternative pathways to cholic acid or chenodeoxycholic acid is governed by CYP8B1; interaction of these intermediates with this enzyme determines the amount of cholic acid versus chenodeoxycholic acid formed. Hydroxylation via CYP8B1 results in the formation of the more hydrophilic cholic acid molecule. Thus, the cholic acid/chenodeoxycholic acid ratio determines the overall hydrophobicity (and biological properties) of the bile acids pool (2).

Before their secretion into the bile canalicular lumen for storage in the gallbladder as mixed micelles with phospholipids and cholesterol, primary bile acids are conjugated with taurine or glycine, further enhancing their hydrophilicity (2). Upon ingestion of a meal, gallbladder contraction releases micellar bile acids into the intestinal lumen to aid digestion. Enterohepatic circulation enables 95% of bile acids to be reabsorbed from the distal ileum and transported back to the liver via the portal circulation. Interestingly, the perivenous hepatocytes, which account for the production of bile acids, are not involved in the reuptake of bile acids; bile acids are taken up and transported primarily by pericentral hepatocytes that surround the portal triads, where portal blood enters the liver acinus (13). The zonation differences accounting for where bile acids are produced and reenter the liver are relatively unexplored; thus, the
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(physiological) relevance of these observations is unknown at this time (2). Only ~5% of bile acids are not reabsorbed and are eliminated in the feces. This small amount of loss is replenished via de novo synthesis of bile acids in the liver (1,2).

The size of the bile acid pool is tightly regulated within the liver and intestine to prevent cytotoxic accumulation of bile acids (2). As the bile acid pool size increases, a feedback mechanism, governed by the interplay of several nuclear receptors, is activated to inhibit de novo bile acid synthesis. In the liver, the nuclear receptor living receptor homolog (LRH)–1 activates gene transcription of the CYP7A1 gene (2). In 1999, bile acids were identified as the natural ligands for the farnesoid X receptor (FXR). By binding to the nuclear receptor FXR, bile acids mediate control of their own synthesis (16,17). FXR is thus a “bile acid sensor.” FXR can be activated by both primary and secondary conjugated bile acids, but chenodeoxycholic acid appears to be the most potent natural bile acid ligand (16,17). FXR functions as a biological regulator of bile acid synthesis through its transcriptional induction of the inhibitory nuclear receptor SHP (2). In the liver, small heterodimer partner (SHP) exerts its inhibitory effect by interacting with LRH–1 and subsequently repressing CYP7A1 transcription activation by LRH–1 (2). Bile acids can also inhibit transcription of CYP7A1 by repressing another nuclear receptor, hepatocyte nuclear factor (HNF)-4α (2). Intestinal FXR activation due to transintestinal bile acid flux after a meal also induces the expression of fibroblast growth factor (FGF)-19, which is released by small intestine epithelial cells (2). Meal also induces the expression of fibroblast growth factor (FGF)-19, which is released by small intestine epithelial cells (2). Due to transintestinal bile acid flux after a meal also induces the expression of fibroblast growth factor (FGF)-19, which is released by small intestine epithelial cells (2). Due to transintestinal bile acid flux after a meal also induces the expression of fibroblast growth factor (FGF)-19, which is released by small intestine epithelial cells (2). Due to transintestinal bile acid flux after a meal also induces the expression of fibroblast growth factor (FGF)-19, which is released by small intestine epithelial cells (2).

**FXR: BEYOND BILE ACID METABOLISM/HOMEOSTASIS**

**Lipid metabolism**

Whereas manipulation of bile acid metabolism by bile acid sequestration has been recognized as a means to control systemic lipid concentrations since the 1960s, the underlying molecular mechanisms linking bile acids and lipid metabolism have only begun to be unraveled over the last decade. BASs, as well as ileal resection, which both interrupt the enterohepatic circulation of bile acids, decrease plasma total and LDL cholesterol while increasing levels of HDL cholesterol, apolipoprotein (apo)-AI, and triglycerides (18–21).

As a direct consequence of interrupting the return of bile acids to the liver, CYP7A1 expression becomes repressed, and conversion of cholesterol into bile acids is stimulated. The depletion of hepatic cholesterol due to increased diversion to bile acid synthesis leads to increased hepatic LDL receptor expression to harvest cholesterol from the systemic circulation (18). It is this indirect effect on LDL receptor expression that accounts for the decline in total and LDL cholesterol produced by BASs or ileal resection. However, the increase in HDL cholesterol and triglyceride levels observed with interruption of the enterohepatic circulation of bile acids cannot be explained by changes in LDL receptor expression. Animal data have revealed an independent regulatory role for FXR in both HDL cholesterol and triglyceride metabolism. With regard to HDL cholesterol, FXR represses apoAI expression (22) and plays a role in HDL particle remodeling through induction of phospholipid transfer protein (23). FXR activation increases clearance of triglycerides by influencing lipoprotein lipase (LPL) activity through induction of apoC-II expression (24) and repression of apoC-III (25) and by inducing peroxisome proliferator–activated receptor–α expression (2) (Fig. 1).

**Glucose metabolism**

The first clinical indication that manipulation of the bile acid pool plays a role in glucose homeostasis resulted from observations made in a small study conducted by Garg and Grundy (4). In this study, the efficacy of 8 g b.i.d. of cholestyramine or placebo was evaluated in a crossover fashion over 12 weeks in 21 patients with type 2 diabetes stabilized on insulin or glyburide, with a baseline LDL cholesterol >3 mmol/l (>120 mg/dl) and triglycerides <8 mmol/l (<300 mg/dl). Unexpectedly, cholestyramine was associated with a modest improvement in glycemic control, with mean plasma glucose values lowered by 13% and a median reduction in urinary glucose excretion of 0.22 g/day (P < 0.001) and a trend toward lower glycated hemoglobin concentrations. These changes occurred without a dosage adjustment for insulin or glyburide. These results were later corroborated with colesevelam and colestipol (5–9). Similar data on the glucose-lowering effects of BASs and ileal biliary diversion have been observed in animal studies as well (26).

Mechanistic data on the influence of bile acids on glucose metabolism have been mounting. Effects on bile acid pool composition, FXR-mediated alterations in hepatic glucose production and intestinal glucose absorption, influences on peripheral insulin sensitivity, incretin effects, and energy use may all contribute to glucose regulation.

There is evidence that the bile acid pool size and composition are altered in animal models of either type 1 or type 2 diabetes (27–29) as well as in humans with type 1 or 2 diabetes (30,31). The mechanisms underlying these observations are unclear, but preliminary evidence suggests a role for insulin (32) and glucose (33) in modulation of bile acid synthesis. In the most extensive evaluation of bile acid kinetics to date in age- and BMI-matched subjects with type 2 diabetes (31), a higher rate of total bile acids synthesis, driven by an elevated rate of cholic acid synthesis and subsequent conversion to deoxycholic acid, was noted. Whether this alteration in bile acid pool composition could play a role in abnormal metabolism in diabetes remains speculative, but it is an intriguing possibility.

The type 1 diabetes rat model induced by streptozotocin is associated with an increased bile acid pool size due to enhanced synthesis. Hepatic FXR expression in this model is decreased. As FXR negatively regulates CYP7A1 activity, a molecular link between decreased expression of FXR and increased bile acid pool size in this model is suggested, since CYP7A1 mRNA levels are increased. It is also noteworthy that insulin represses FXR gene expression, whereas glucose produces the opposite effect (33). To-
Table 1—Bile acid sequestrant therapy: summary of cardiovascular outcome and plaque regression clinical trials

| Study | Agents | Study duration (years) | LDL cholesterol reduction (%) | Patients with cardiovascular events (%) | Patients with coronary artery disease regression (%)* | Patients with coronary artery disease progression (%)* |
|-------|--------|------------------------|-------------------------------|----------------------------------------|---------------------------------|---------------------------------|
| BAS monotherapy | Dorr et al. (47) | Colestipol | 1,149 48 2† | −12† | 4§|| ND | ND |
| Placebo | 1,129 48 | −2† | 9|| ND | ND |
| Lipid Research Clinics Coronary Primary Prevention Trial (46,48) | Cholestyramine | 1,906 100 7.4† | −20§ | 8§¶ | ND | ND |
| Placebo | 1,900 100 | −8 | 10¶ | ND | ND |
| National Heart, Lung, and Blood Institute Type II Coronary Intervention Study (20,21) | Cholestyramine | 59 81 5 | −26§ | ND | 32§# | 7 |
| Placebo | 57 81 | −5 | ND | 49# | 7 |
| St Thomas' Atherosclerosis Regression Study (49) | Cholestyramine + diet | 24 100 3.3† | −36***†† | 4§ | 12§ | ND |
| Diet | 26 100 | −16***** | 11† | 15 | ND |
| Usual care | 24 100 | 0 | 36 | 46 | ND |
| BAS combination therapy | Cholesterol Lowering Atherosclerosis Study (50) | Colestipol + niacin | 94 100 2 | −438** | 25 | 10§‡‡ | ND |
| Placebo | 94 100 | −5** | 25 | 22‡‡ | ND |
| Familial Atherosclerosis Treatment Study (51) | Colestipol + niacin | 36 100 2.5 | −32****†† | 4§ | 25§# | 39§# |
| Colestipol + lovastatin | 38 100 | −46***** | 7§ | 21§# | 32§# |
| Usual care | 46 100 | −7** | 19 | 46# | 11# |
| Kane et al. (52) | Colestipol + niacin + lovastatin | 40 45 2.2 | −38§ | ND | 20§§ | 33 |
| Control (plus low-dose colestipol [14/32 patients]) | 32 41 | −11 | ND | 41§§ | 13 |
| Harvard Atherosclerosis Reversibility Project (53) | Stepwise: pravastatin + niacin + cholestyramine + gemfibrozil | 40 90 2.5 | −38§ | 14 | 33# | 13# |
| Placebo | 30 87 | +3 | 21 | 38# | 15# |
| Probucol Quantitative Regression Swedish Trial (54) | Cholestyramine + probucol | 138 57 3 | −3§ | 28 | ND | 0.6, 3|| |
| Cholestyramine + placebo | 136 58 | +8 | 21 | ND | 4**, 4|| |
| Armed Forces Regression Study (55) | Cholestyramine + niacin + gemfibrozil | 71 90 2.5 | −22§ | 13§ | 30¶¶ | 52 |
| Placebo | 72 94 | +5 | 26 | 50¶¶ | 42 |
| Partial ileal bypass Program on the Surgical Control of the Hyperlipidemias (19) | Partial ileal bypass | 421 91 10 | −39‡‡ | 19§### | 55$$‡‡ | 6‡‡ |
| Control | 417 91 | −6‡‡ | 30 | 85 | 4‡‡ |

*Includes patients who may have also had regression/progression, except where indicated. †Mean follow-up time reported. ‡Total cholesterol levels reported because LDL cholesterol levels not available. §P < 0.05 compared with placebo, usual care, or control. ¶Percentage represents only the men enrolled in the study (n = 1,094). Differences were nonsignificant for women. ¶¶Only coronary artery disease deaths and nonfatal myocardial infarctions are included. Risk reduction was 19% relative to the incidence of cardiovascular events in the placebo-treated group. ¶¶Definite or probable progression with no regression or regression with no progression. **P < 0.05 compared with baseline. ††Statistical comparisons not conducted between treatment groups. †††Number represents percentage of patients with new lesions in native vessels. §§Although not statistically significant, there was a strong trend towards favoring active treatment over control. |||Numbers represent % increase in femoral artery lumen volume from baseline and % decrease in roughness of arterial edge. §§Statistical comparisons were only conducted for the percentage of patients who had "controlled" coronary artery disease (that is, patients who had regression or no change). That comparison (70 vs. 50% for drug therapy vs. placebo) was significant (P < 0.05). §§§Only coronary artery disease deaths and nonfatal myocardial infarctions are included. ***Represents a 35% risk reduction. †††Data on 10 years of follow-up reported; a significant difference was also observed after 3, 5, and 7 years of follow-up. ND, not determined (values were not determined or not reported). Used with permission from Insull (1).
| Reference          | Study design          | Treatment       | Duration | n   | Background antidiabetic therapy | Δ from Baseline | Treatment Difference | Δ from Baseline | Treatment Difference | Δ from Baseline | Treatment Difference |
|--------------------|-----------------------|-----------------|----------|-----|---------------------------------|----------------|----------------------|----------------|----------------------|----------------|---------------------|
| Garg and Grundy (4) | R, B, PC, and crossover | Placebo         | 6 weeks  | 21  | Added to insulin (n = 9) or glyburide (n = 12) | Week 6:        | −0.4*                | Week 6:         | NR                  | Week 6:        | −1.9                 |
|                    |                       | Cholestyramine 16 g/day |          | 19  |                                  | Week 6:        | −0.9*                | Week 6:         | −0.8†‡               | Week 6:        | −28.9               |
| Zieve et al. (5)   | R, DB, PC, and PG     | Placebo         | 12 weeks | 34  | Added to SU alone (n = 27), MET alone (n = 9), SU + MET (n = 29) | Week 12:       | +0.2                 | Week 12:        | −0.78               | Week 12:        | +2.1†               |
|                    |                       | Colesevelam 3.75 g/day |          | 31  |                                  | Week 12:       | −0.3                 | Week 12:        | −0.28               | Week 12:        | −9.6                |
| Goldberg et al. (8)| R, DB, PC, and PG     | Placebo         | 16 weeks | 147 | Added to insulin alone (n = 116) or in combination with OAD(s) (n = 171) | Week 16:       | +0.1                 | Week 16:        | −0.81               | Week 16:        | −12.8‡               |
|                    |                       | Colesevelam 3.75 g/day |          | 140 |                                  | Week 16:       | −0.4                 | Week 16:        | −0.22               | Week 16:        | −12.3‖               |
| Fonseca et al. (7) | R, DB, PC, and PG     | Placebo         | 26 weeks | 231 | Added to SU alone (n = 156) or in combination with other OAD(s) (n = 304) | Week 26:       | +0.2                 | Week 26:        | −0.75§               | Week 26:        | −16.7‡               |
|                    |                       | Colesevelam 3.75 g/day |          | 230 |                                  | Week 26:       | −0.3                 | Week 26:        | −0.31               | Week 26:        | −16.1‖               |
| Bays et al. (6)    | R, DB, PC, and PG     | Placebo         | 26 weeks | 157 | Added to MET alone (n = 159) or in combination with other OAD(s) (n = 157) | Week 26:       | +0.2                 | Week 26:        | −0.77§               | Week 26:        | −15.9‡               |
|                    |                       | Colesevelam 3.75 g/day |          | 159 |                                  | Week 26:       | −0.4                 | Week 26:        | −0.26               | Week 26:        | −12‖                |
FXR appears to play a role in modulating gluconeogenesis, since FXR-deficient mice displayed fasting hypoglycemia through maintenance of glucose-6-phosphatase in vitro (34). FXR appears to be involved in glucose metabolism in the liver, since FXR-deficient mice displayed fasting hypoglycemia through maintenance of glucose-6-phosphatase in vitro (34). FXR appears to be involved in glucose metabolism in the liver, since FXR-deficient mice displayed fasting hypoglycemia through maintenance of glucose-6-phosphatase in vitro (34). FXR appears to be involved in glucose metabolism in the liver, since FXR-deficient mice displayed fasting hypoglycemia through maintenance of glucose-6-phosphatase in vitro (34). FXR appears to be involved in glucose metabolism in the liver, since FXR-deficient mice displayed fasting hypoglycemia through maintenance of glucose-6-phosphatase in vitro (34). FXR appears to be involved in glucose metabolism in the liver, since FXR-deficient mice displayed fasting hypoglycemia through maintenance of glucose-6-phosphatase in vitro (34). FXR appears to be involved in glucose metabolism in the liver, since FXR-deficient mice displayed fasting hypoglycemia through maintenance of glucose-6-phosphatase in vitro (34). FXR appears to be involved in glucose metabolism in the liver, since FXR-deficient mice displayed fasting hypoglycemia through maintenance of glucose-6-phosphatase in vitro (34). FXR appears to be involved in glucose metabolism in the liver, since FXR-deficient mice displayed fasting hypoglycemia through maintenance of glucose-6-phosphatase in vitro (34). FXR appears to be involved in glucose metabolism in the liver, since FXR-deficient mice displayed fasting hypoglycemia through maintenance of glucose-6-phosphatase in vitro (34). FXR appears to be involved in glucose metabolism in the liver, since FXR-deficient mice displayed fasting hypoglycemia through maintenance of glucose-6-phosphatase in vitro (34). FXR appears to be involved in glucose metabolism in the liver, since FXR-deficient mice displayed fasting hypoglycemia through maintenance of glucose-6-phosphatase in vitro (34). FXR appears to be involved in glucose metabolism in the liver, since FXR-deficient mice displayed fasting hypoglycemia through maintenance of glucose-6-phosphatase in vitro (34).
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binding to a recently identified G-protein–coupled cell surface receptor known as TGR5 (41). This receptor is expressed in multiple tissues, including the gallbladder, liver, intestine, brown adipose tissue, central nervous system, and monocytes/macrophages (41). Lithocholic acid appears to be the most potent bile acid agonist for the receptor (41). TGR5 biology is incompletely understood, but it may play a role in immune modulation and hepatocyte protection from the cytotoxic effects of bile acids (41). Bile acid activation of TGR5 was also recently shown to induce intestinal glucagon-like peptide (GLP)-1 secretion (42). In type 2 diabetic patients, bile acid sequestration withcolesteamide may also increase GLP-1 release (43). This observation has lent support to the involvement of bile acids in mediating the enteroinsular response to feeding.

Bile acids may also play a role in metabolic regulation through modulation of energy expenditure. This effect appears to be mediated through modulation of thermogenesis. For example, bile acids given to high-fat–fed mice increase energy expenditure in brown adipose tissue, preventing obesity and insulin resistance. This effect appears to be mediated by induction of the cAMP-dependent thyroid hormone–activating enzyme type 2 iodothyronine deiodinase (D2); bile acids increase D2 activity and oxygen consumption in brown adipose tissue, an effect believed to be mediated by TGR5, not FXR (44). Support for bile acids mediating energy expenditure has been provided by a study in FXR knockout mice. Intriguingly, when these mice were fasted, they exhibited accelerated entry into torpor; this appeared to be associated with an impaired ability to mobilize energy substrates (glucose and free fatty acids) (45). These results suggest that bile acids may also play a complementary role in thermogenesis throughFXR-mediated regulation of energy substrate mobilization and storage (45).

**Clinical Utility of Bile Acid Sequestration: Leveraging the Metabolic Effects of Bile Acids Through Manipulation of the Bile Acid Pool** — As discussed previously, manipulation of the bile acid pool through bile acid sequestration to alter bile acid metabolism has been used since the 1960s to treat dyslipidemia (1). BASs deplete the bile acid pool by ~40% and can increase bile acid synthesis over 15-fold (1). This increases diversion of hepatic cholesterol to bile acid formation, which indirectly lowers LDL cholesterol by enhancing hepatic LDL receptor expression. Lipid alterations produced through bile acid sequestration have been shown to reduce cardiovascular morbidity and mortality in high-risk males (46) and have also been shown to induce atherosclerotic plaque regression alone or in combination with other dyslipidemia treatments. A summary of these data are provided in Table 1 (1, used with permission).

The precise molecular mechanisms involved in BAS modulation of the bile acid pool and subsequent effects on glucose metabolism in diabetes are only beginning to be understood and are the subject of ongoing investigation. In a recently reported study of subjects with type 2 diabetes, colesevelam-associated reductions in A1C and fasting glucose did not appear to be related to an improvement in peripheral glucose disposal rate, but were associated with improvements in total-body insulin sensitivity, as determined by an improvement in the Matsuda index. Moreover, data from meal tolerance tests showed that colesevelam treatment resulted in reductions in fasting glucose and systemic glucose exposure (area under the curve for glucose [AUCgl]) without significant changes in insulin levels. These results suggest that colesevelam may have effects on both insulin sensitivity and insulin secretion (Schwartz SL et al. Effect of colesevelam on postprandial glucose levels in subjects with type 2 diabetes mellitus. Abstract. Sixth Annual World Congress on the Insulin Resistance Syndrome, Los Angeles, CA, 25–27 September 2008). In another preliminary study in db/db diabetic mice, colesevelam administration improved insulin secretion and insulin sensitivity in the presence of hyperglycemia. Moreover, microarray analysis of genes abnormally expressed in the ileum, liver, skeletal muscle, and adipose tissue of db/db diabetic mice showed a partial or complete normalization of expression in the db/db diabetic mice relative to controls, particularly in the ileum, after treatment with colesevelam (Forman BM et al. Colesevelam affects gene expression in metabolic tissues in db/db mice. Abstract. American Diabetes Association 68th Annual Scientific Sessions, San Francisco, CA, 6–10 June 2008). Whether the genes dysregulated and subsequently normalized in the db/db diabetic mice reflect disruption of FXR and TGR5 pathways (among other bile acid–influenced and non-bile acid–influenced pathways) requires further study.

It is possible that alterations in bile acid pool composition produced by BASs may be involved in the effects observed with colesevelam on gene regulation and metabolism described above. The binding characteristics of a given BAS may have long-term effects on the bile acids pool by selectively depleting certain bile acid species through fecal elimination, resulting in an altered ratio of bile acid species in the pool (56). Preliminary animal data suggest that alteration of the bile acids pool can induce profound alterations in bile acid synthesis, which in turn may modulate multiple metabolic processes. In a study of CYP8B1 knockout mice, changing the composition of the bile acids pool by preventing the generation of cholic acid resulted in numerous alterations in bile acid metabolism that included a striking elevation in CYP7A1 expression and reduced SHP expression, but no alteration in expression of the bile salt export protein (57). Conventional BASs (cholestyramine and colestipol) have been shown to markedly alter the composition of bile. For example, cholestyramine preferentially binds the more hydrophobic bile acids chenodeoxycholic acid and deoxycholic acid over the more hydrophilic cholic acid and, therefore, over time causes a shift in the bile acids pool to one that is depleted in chenodeoxycholic acid and deoxycholic acid and enriched in cholic acid (56). The altered bile acid ratio also affects the relative degree of hydrophilicity of the bile acid pool; cholic acid enrichment results in a more hydrophilic bile acid pool. In addition to binding chenodeoxycholic acid and deoxycholic acid, colesevelam differs from cholestyramine and colestipol in that it binds cholic acid more effectively (58). Thus, the bile composition produced by colesevelam may differ from first-generation BASs, such as cholestyramine. The impact of bile acid sequestration on further modification (or normalization) of bile acid pool composition is currently under investigation (29).

Based on the preliminary observations of Garg and Grundy (4), BASs have also been discovered to have utility in the treatment of type 2 diabetes; colesevelam specifically received a labeled indication as adjunctive treatment of this condition in 2008. In
addition to its well-characterized effects on lipid metabolism, colesevelam also produced consistent modest incremental reductions in A1C of up to 0.8% in addition to LDL cholesterol reductions of up to 17% when given to type 2 diabetic subjects inadequately controlled on stable regimens of metformin, sulfonylureas, or insulin (6–8). Reductions in A1C resulting from the addition of colesevelam are similar to changes observed with other adjunctive antidiabetic therapies in subjects with comparable baseline A1C values of 8–9%, with the added advantage of a neutral effect on weight. Side effects across the pivotal trials were mild and included constipation, nausea, and dyspepsia. A detailed summary of these data are provided in Table 2. Another BAS, colestamide, has also demonstrated effects on glucose metabolism in an animal model of diet-induced obesity and insulin resistance, suggesting that BASs might also find clinical application in the treatment of metabolic syndrome or pre-diabetes (60). This represents a potentially attractive therapeutic role for these drugs, considering that they are not systemically absorbed and have a good safety record, which may be attractive for long-term preventive use.

CONCLUSIONS — Knowledge of bile acid physiology has dramatically evolved from the concept of digestive detergents to an elegant story of bile acid functioning as hormones involved in the modulation of a variety of metabolic processes. Manipulation of bile acids composition and pool size through bile acid sequestration takes advantage of this physiology and has found clinical application for dyslipidemia and, more recently, type 2 diabetes. Further research will continue to refine our knowledge of bile acid physiology and will contribute to potential additional therapeutic applications for these complex molecules.

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