Colesevelam hydrochloride: a bile acid sequestrant for glycemic control and treatment of dyslipidemia in Type 2 diabetes mellitus

The complications of Type 2 diabetes mellitus (T2DM) include increased risk of macrovascular diseases such as coronary artery disease, stroke or peripheral vascular disease, and microvascular diseases such as retinopathy, neuropathy and nephropathy. The risk of macrovascular and microvascular diseases increases with the presence of dyslipidemia and hyperglycemia, respectively. Hence, treatment of T2DM must be aimed at treating hyperglycemia to prevent microvascular disease and dyslipidemia to prevent macrovascular complications. Recent clinical studies indicate that colesevelam hydrochloride, a bile acid sequestrant, appears to be promising as an add-on therapy for T2DM patients in reducing the hyperglycemia and dyslipidemia. The objective of the paper is to review the efficacy and safety of colesevelam hydrochloride in reducing both low-density lipid cholesterol and glycosylated hemoglobin A1c levels in T2DM patients when combined with metformin, sulfonylurea or insulin.

KEYWORDS: bile acid sequestrants ▪ colesevelam HCl ▪ farnesoid X receptor ▪ glycemic control ▪ low-density lipoprotein cholesterol ▪ Type 2 diabetes mellitus

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Type 2 diabetes mellitus (T2DM) affects approximately 3% of the world's population (estimate by WHO). The prevalence of T2DM in the USA appears to be increasing due to multiple factors, including changes in diet, decrease in activity levels and obesity [1]. The National Institutes of Health and Centers for Disease Control estimate that over 30% of individuals with T2DM may be undiagnosed. The major complications of T2DM include both microvascular diseases and macrovascular changes [2,3]. Examples of microvascular complications include retinopathy, neuropathy, nephropathy and macular changes. Patients with T2DM have an increased risk of macrovascular diseases such as coronary artery disease, stroke or peripheral vascular disease [2,3]. The incidence of cardiovascular diseases in T2DM patients is relatively higher than in patients without diabetes [4]. In 2007, the estimated cost of treating diabetics in the USA was nearly equivalent to one in ten of the dollars spent on healthcare [5]. Hence, T2DM is a major health and economic concern in the USA and worldwide.

There is a well-established direct relationship that exists between the degree of glycemic control and the risk of microvascular complications [2,6,7]. The primary goal of antidiabetes therapy is to maintain plasma glucose levels as close to normal as possible to minimize microvascular complications, without unacceptable side effects – particularly hypoglycemia. The American Diabetes Association recommends a glycated hemoglobin A1c (HbA1c) goal of less than 7.0%, the level at which clinical trials have demonstrated that the incidence of long-term microvascular complications is reduced [8]. However, a significant number of patients have not achieved this goal [1,9].

In addition to hyperglycemia, patients with T2DM may have associated lipid abnormalities. Lipid abnormalities may include elevated low-density lipoprotein cholesterol (LDL-C) levels, elevated triglyceride (TG) levels and decreased high-density lipoprotein cholesterol (HDL-C) levels. An elevated level of LDL-C is currently considered to be a major risk factor for macrovascular diseases [3]. Although low HDL-C and high TG levels are considered to be hallmarks of diabetic dyslipidemia, the American Diabetes Association recommends a primary LDL-C goal of less than 100 mg/dl for individuals without overt cardiovascular disease and T2DM, and an LDL-C goal of less than 70 mg/dl for those with overt cardiovascular disease and T2DM [8]. However, Kennedy *et al.* demonstrated in a community-based setting that only 49.4% had LDL-C concentrations less than 100 mg/dl, and only 15.7% achieved the more demanding LDL-C goal of less than 70 mg/dl, with 25% of patients requiring more than two lipid-lowering drugs at maximal doses to attain this goal [10].

Treatment of T2DM must be aimed at treating hyperglycemia to prevent microvascular complications (retinopathy, neuropathy and

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nephropathy), and treating dyslipidemia and hypertension to prevent macrovascular complications. Recent preclinical studies indicate that lipid and glucose homeostasis appear to be interrelated via bile acid-activated nuclear hormone receptor signaling pathways [11–13]. Drugs that affect these pathways could simultaneously treat hyperglycemia and dyslipidemia in patients with T2DM.

Several bile acid sequestrants (BASs) such as cholestyramine (cholestyramine), colesevelam hydrochloride (HCl), colestilan (colestimide) and colestipol, were investigated to examine their efficacy in reducing LDL-C and HbA1C [14–21]. Recently, colesevelam received more attention as an add-on therapy in T2DM. Colesevelam was reported to have a higher affinity for bile acids than the other BASs, including cholestyramine and colestipol [20,21]. Zieve *et al.* conducted a small pilot study of 65 patients with T2DM and demonstrated that add-on therapy of colesevelam HCl, along with oral antidiabetes drug therapy, significantly reduced both the lipid and glucose levels [21]. A more robust Phase III development program was undertaken to determine the safety and effectiveness of colesevelam in patients with T2DM. Colesevelam significantly reduced both LDL-C levels and HbA1c in patients with T2DM treated with a variety of glucose-lowering agents [22–24].

Colesevelam was recently approved by the US FDA to improve glycemic control (measured as HbA1c) in T2DM adults who are presently on metformin, sulfonylureas or insulin, either alone or in combination with other antidiabetic agents. The objective of this paper is to review the efficacy, safety and adverse effects of colesevelam, a bile acid-binding resin, in reducing the LDL-C levels and HbA1c levels in T2DM patients who are under treatment with metformin, sulfonylurea or insulin.

Colesevelam hydrochloride: a bile acid sequestrant

The BASs are a synthetic class of antihyperlipidemic drugs introduced into clinical practice over 25 years ago. BASs decrease the amount of bile reabsorbed to re-enter the enterohepatic circulation. This reduction in endogenous bile acid pool stimulates the liver to increase bile acid synthesis from cholesterol, and therefore increases uptake of plasma cholesterol and LDL-C by hepatic tissues. This reduction in bile acids leads to increased re-uptake of cholesterol and LDL-C to form new bile acids. The efficacy of BAS in lowering cholesterol and LDL-C was demonstrated in clinical trials conducted during the 1980s. The Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT) observed a decrease in cardiovascular events [25]. The reduction in plasma LDL-C levels can be 15–28% at maximal doses of BASs. Patients on BASs who participated in angiographic studies displayed a decrease in progression of coronary artery lesions [26–31]. Despite their benefits, BASs were not widely used because of the inconveniences associated with administration of large doses, as well as their side-effect profiles, which led to increased noncompliance with this class of drugs.

Colesevelam (WelChol®, Daiichi Sankyo, Tokyo, Japan), the latest BAS, has a high affinity for bile acids and acts in the intestine to sequester these. Colesevelam HCl, when compared with cholestyramine and colestipol, was noted to have an enhanced ability to bind bile acids [32]. The sequestration of bile acids impedes their reabsorption and leads to subsequent loss of bile acids through the excretion of colesevelam–bile acid combinations through the feces [33]. Colesevelam reduces total cholesterol and LDL-C by 15–18% when used as monotherapy to treat dyslipidemia. When colesevelam was used as part of combination therapy with HMG-CoA reductase inhibitors (statins), an increased reduction in LDL-C was noted depending on the dose of the statin [34–36].

Colesevelam is the first BAS to be evaluated for reductions in glycemic parameters in double-blind placebo trials. An early 1990s study, by Garg and Grundy, which included patients with dyslipidemia and noninsulin-dependent T2DM, demonstrated improved glycemic control with a reduction in HbA1c of approximately 0.5% and plasma glucose concentrations of 13% in patients on cholestyramine, when compared with those on placebo [14]. However, conflicting results were reported afterwards on the use of cholestyramine or colestipol BASs in controlling glycemic parameters [15–17]. Subsequent investigations confirmed the LDL-C and glucose-lowering efficacy of colestimide [18,19]. These clinical trials warranted that BASs may also be a potential therapy for T2DM. Colesevelam received approval from the US FDA for the treatment of T2DM in 2008.

Chemistry of colesevelam HCl

Colesevelam is a nonabsorbable polymer whose empirical molecular formula is $C_{31}H_{67}Cl_3N_4O$. It has a molecular weight of 618.248 g/mol. The International Union of Pure and Applied Chemistry name of colesevelam is allylamine polymer with 1-chloro-2,3-epoxypropane,

[6-(allylamino)-hexyl]trimethylammonium chloride and N-allyldecylamine, hydrochloride. It has other synonyms, including CholestaGel®, WelChol, GT 31-104, GT 31-104HB and GT31-104. It is a poly-allylamine that has been cross-linked with epichlorohydrin and alkylated with 1-bromodecane and bromohexyltrimethylammonium bromide.

Colesevelam contains both hydrophobic and cationic sites. The cationic sites allow colesevelam to bind to negatively charged bile acids. Colesevelam has a structure that has more similarities to sevelamer than older bile acid resins [37]. The structure of colesevelam is responsible for its water-retaining traits that help create a soft, gelatinous-like material [38]. This gelatinous consistency, unlike the sandy consistency of cholestyramine and colestipol, appears to help minimize the potential for gastrointestinal (GI) irritation. The cross-linked epichlorohydrin structure is partially responsible for decreased interactions between the GI lining and polymer structure [39]. It has a backbone that maximizes hydrophobic interactions and has increased ionic binding with amines, which enables colesevelam to bind a larger number of bile acids per dose [37]. The chemical and structural features of this compound also play an important role in preventing colesevelam from being systemically absorbed [40,101].

Colesevelam binds to bile acids forming nonabsorbable complexes in the GI tract [101]. This interrupts enterohepatic recirculation of bile acids and increases bile acid elimination, mainly through feces [101]. Colesevelam can bind to both dihydroxy and trihydroxy bile acids: taurine-based dihydroxy bile acids and conjugates (e.g., taurodeoxycholic acid and taurochenodeoxycholic acid), glycine-based dihydroxy bile acids and conjugates (e.g., glycochenodeoxycholic acid and glycodeoxycholic acid) and trihydroxy bile acids (e.g., taurocholic acid, glycocholic acid) [32,37].

Pharmacodynamics

Bile acids play an important role in helping to absorb lipid molecules such as cholesterol from digestive chyme. A reduction in the number of available bile acids decreases the amount of lipid molecules absorbed from the digestive tract into the plasma. Colesevelam binds to both dihydroxy and trihydroxy bile acids, like other BASs, and subsequently reduces the bile acid pool [37]. Similar to other BASs, the binding affinity to bile acids in order of greatest to lowest is as follows: taurine-based dihydroxy bile acids and conjugates > glycine based dihydroxy bile acids and conjugates > trihydroxy bile acids [32,37]. Colesevelam has an increased binding affinity to and a decreased disassociation rate for trihydroxy bile acids [41]. The effects of colesevelam on bile acid kinetics are being studied further.

Colesevelam has a linear dose–response profile in lowering LDL-C. This is unlike traditional BASs that have a nonlinear dose–response profile. Colesevelam appears to have a maximal effect on lowering LDL-C at maximum doses (4.375 g/day). The patients, however, appeared to have an improved side-effect profile with lipid-lowering effects at 3.75 g/day [32,101]. In addition to lowering LDL-C and total cholesterol, colesevelam may affect TG concentrations, and may lead to an elevation of TG in some patients.

Pharmacokinetics & metabolism

Colesevelam is a water-insoluble polymer that is not hydrolyzed by digestive enzymes. The lack of absorption of colesevelam limits its distribution to the GI tract [42–44]. Colesevelam is not metabolized systemically and is mainly excreted in the feces [41,42]. It is not hydrolyzed by digestive enzymes and therefore does not undergo intestinal absorption (**Box 1**).

The peak therapeutic response of the lipid-lowering effects of colesevelam is achieved after approximately 2 weeks [40]. This peak response was maintained during long-term therapy. In clinical studies, colesevelam had a therapeutic response of LDL-C reduction by 6 weeks, with maximal effects by 24 weeks [34,40,101]. Studies demonstrated a reduction in hemoglobin A1C, initially by 4–6 weeks of treatment, and reached near-maximal effects after 12–18 weeks of treatment. There appears to be no adjustment required for weight and in the presence of renal or hepatic impairment [32,101]. Colesevelam effects on pregnancy and lactation are not yet well understood.

Clinical efficacy

Colesevelam & treatment of hyperlipidemia

Colesevelam was studied as both monotherapy and as part of combination therapy for the treatment of hyperlipidemia [45,46]. In monotherapy trials, it produced reductions in LDL-C and total cholesterol when compared with placebo [34,39]. Davidson's study demonstrated that the reduction in LDL-C and total cholesterol was greatest at doses of 3.0 g/day and 3.8 g/day. Insull's study observed that the responses were greater at 3.8 and 4.5 g/day (**Table 1**). The side effects of

Box 1. Pharmacokinetics and metabolism of colesevelam hydrochloride.

Structure

- Colesevelam hydrochloride is a positively charged polymer that can bind to negatively charged bile acids forming ion association complexes/compounds. It is an insoluble polymer.

Mechanism of action

- The exact mechanism of glucose lowering in patients by colesevelam hydrochloride is not fully understood. It may lower glucose levels through alteration of bile acid compositions of molecules such as chenodeoxycholic acid, ursodeoxycholic acid and related bile acid molecules.

Pharmacodynamics

- Lowering of hemoglobin A1C levels was observed within 4–6 weeks of treatment and reached maximal or near-maximal effect after 12–18 weeks of treatment.

Pharmacokinetics

- Absorption:
  - Plasma: none;
  - GI tract: 100%.
- Distribution: GI tract
- Elimination
  - Feces: 99.5%;
  - Urine: 0.5%.
- Metabolic clearance: Not metabolized systemically; does not interfere with systemic drug-metabolizing enzymes such as cytochrome P-450.

From Welchol® Product Information 2007 [101].

colesevelam appeared to be better tolerated at 3.8 g/day. When colesevelam was used as monotherapy for hyperlipidemia, there were increases in HDL-C and TG levels [34,35,47].

Colesevelam was also evaluated as part of combination therapy to treat hyperlipidemia in trials with both statin and nonstatin lipid-lowering drugs. Colesevelam was studied in combination with lovastatin [36], simvastatin [41], atorvastatin [35], ezetimibe [48] and fenofibrate [49]. When colesevelam (at a dose of 3.8 g/day) was used in combination with a low-dose statin, there was a significant reduction in LDL-C when compared with baseline (Table 1). When colesevelam was

Table 1. Colesevelam hydrochloride and lipid parameters (% changes from baseline) in patients with hyperlipidemia.

Trial	Type of trial	Drug names	Dosage	Total cholesterol (% change from baseline)	LDL-C (% change from baseline)	Ref.
Davidson *et al.* (1999)	Monotherapy	Colesevelam	3.0 g/day	-5	-9	[40]
			3.8 g/day	-8	-19	
Insull *et al.* (2001)	Monotherapy	Colesevelam	3.0 g/day	-6	-12	[34]
			3.8 g/day	-7	-15	
			4.5 g/day	-10	-18	
Davidson *et al.* (2001) (lovastatin trial)	Combination	Lovastatin	10 mg	-15	-22	[36]
		Lovastatin + colesevelam	10 mg 2.3 g/day	-21	-34	
Knapp *et al.* (2001) (simvastatin trial)	Combination	Simvastatin	10 mg	-19	-26	[41]
		Simvastatin + colesevelam	10 mg 3.8 g/day	-28	-42	
Hunninghake *et al.* (2001) (atorvastatin trial)	Combination	Atorvastatin	10 mg	-27	-38	[35]
		Atorvastatin + colesevelam	10 mg 3.8 g/day	-31	-48	
Bays *et al.* (2006) (ezitemide trial)	Combination	Ezitemide		–	-21.4	[48]
		Ezitemide + colesevelam	3.8 g/day	–	-32.3	
McKenney *et al.* (2005) (fenofibrate trial)	Combination	Fenofibrate	160 g/day	–	+2.3	[49]
		Fenofibrate + colesevelam	160 g/day 3.8 g/day	–	-10.4	

LDL-C: Low-density lipoprotein cholesterol.

added to ezetimibe and fenofibrate, decreases in LDL-C were also observed (Table 1). The combination of colesevelam and ezetimibe may be helpful in patients who do not tolerate statin therapy. The combination of colesevelam and fenofibrate did not have a statistically significant effect on TG levels; however, this combination may be useful for patients with hypertriglyceridemia [49].

Trials with a head-to-head comparison with older BASs or ezetemide have yet to be reported. Colesevelam may have similar effects as older BASs on coronary artery lesions, but this is unclear. Angiographic studies using colesevelam have yet to be published. The effects of colesevelam have yet to be reported with regards to cardiovascular morbidity and mortality.

Colesevelam HCl & treatment of T2DM

Anecdotal evidence and clinical studies suggested that BASs could be useful in lowering glucose levels [14]. This prompted researchers to further assess colesevelam for glucose-lowering effects. Since 2004, several clinical studies were undertaken to investigate the clinical efficacy and safety of colesevelam in controlling the glycemic parameters (measured as hemoglobin A1C) in adults with T2DM. Zieve *et al.* conducted a pilot study on the glucose-lowering effect of WelChol (GLOWS). It was proposed that colesevelam could lower glycemic parameters, with a treatment difference in HbAlc between the colesevelam group and the placebo group of -0.5% (0.18) (p = 0.007; using the least squares [LS] mean) [21]. They found that change in HbAlc between the colesevelam group and the placebo group was greater in patients with a baseline HbAlc of more than 8.0%, with a difference in LS mean change in HbAlc of -1.0% (0.27) (p = 0.002). The results of the GLOWS study were tempered by the fact that it was a pilot study with a small number of subjects and short trial duration.

The GLOWS study was followed by three major Phase III studies [22–24] to further evaluate the glucose-lowering effects of colesevelam HCl. These studies were carried out in various locations within the USA and some limited centers outside the USA. In these studies, the use of colesevelam was investigated in combination with metformin, sulfonylureas or insulin, either alone or in combination with other antidiabetic agents. It was not investigated as a monotherapy. A summary of these clinical trials and their key findings are provided in Table 2. In T2DM patients treated with colesevelam and a variety of glucose-lowering agents, these trials demonstrated a significant reduction in HbA1c (Figure 1), fasting blood glucose (Figure 2) and LDL-C levels (Figure 3) [22–24]. The trials also observed an increase in TGs for T2DM patients treated with colesevelam and a variety of glucose-lowering agents. A brief description of Phase III clinical studies and their major findings is given below.

Table 2. Phase III clinical trials investigating the effects of colesevelam hydrochloride.

Trial	Background antidiabetic therapy	Intervention	Duration	Demographics	Treatment difference in HbA1c at study end (%)	Treatment difference in LDL-C at study end (%)	Ref.
Bays *et al.* (2008) (metformin Phase III clinical trial)	Metformin alone or metformin in combination with other oral agents	Colesevelam HCl 3.8 g/day or placebo	26 weeks	316 subjects; metformin alone (n = 159) or metformin in combination with other oral agents (n = 157)	-0.54	-15.9	[22]
Fonseca *et al.* (2008) (sulfonylurea Phase III clinical trial)	Sulfonylurea alone or sulfonylurea in combination with other oral agents	Colesevelam HCl 3.8 g/day or placebo	26 weeks	460 subjects; sulfonylurea alone (n = 156) or sulfonylurea in combination with other oral agents (n = 304)	-0.54	-18.70	[23]
Goldberg *et al.* (2008) (insulin Phase III clinical trial)	Insulin alone or insulin in combination with other oral agents	Colesevelam HCl 3.8 g/day or placebo	16 weeks	287 subjects; insulin alone (n = 116) insulin in combination with oral agents (n = 171)	-0.5	-12.80	[24]

HCl: Hydrochloride; LDL-C: Low-density lipoprotein cholesterol.

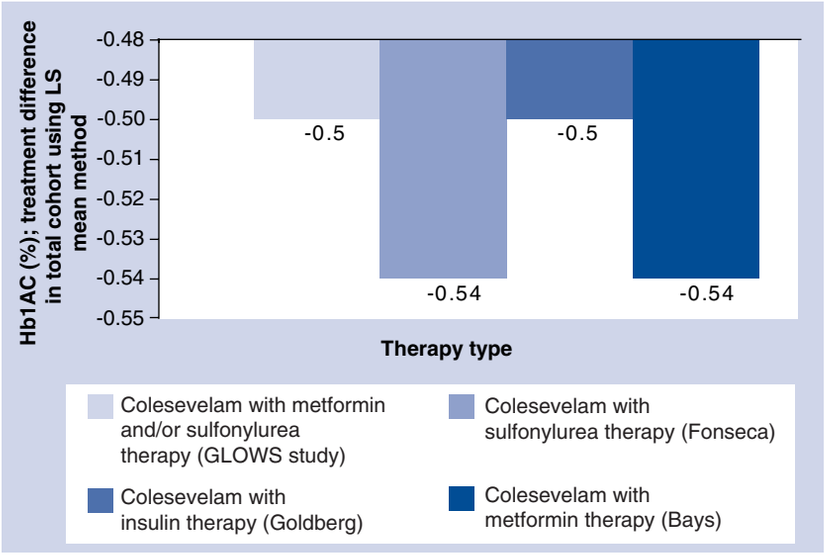

Figure 1. Mean placebo-adjusted change in HbA1C when colesevelam was added to antidiabetic agents in patients with Type 2 diabetes mellitus.
Data taken from [21–24].

Colesevelam & metformin

Bays *et al.* carried out a multicenter, randomized, double-blind, placebo-controlled, parallel-group Phase III study to investigate the effects of colesevelam when used in conjunction with metformin [22]. In this study, 316 subjects with T2DM (HbA1c between 7.5 and 9.5%) were randomized into a 26-week trial based on their history of being on metformin monotherapy or metformin in combination with other oral antidiabetic therapy. Of the 159 patients receiving metformin monotherapy (prior to randomization), 83 subjects were in the colesevelam arm and 76 subjects in the placebo arm. The primary end point of the study was mean change in A1C from baseline to week 26 for the total cohort. The subjects continued their metformin and other antidiabetic medication at the same dose and time throughout the study.

Treatment differences were observed when patients were placed on colesevelam in conjuction with metformin. The treatment difference of colesevelam HCl, using the LS mean method, demonstrated a 0.54% reduction in HbA1c levels (colesevelam relative to placebo) in the total cohort. There was a 0.62% reduction in the metformin plus other antidiabetic agents cohort. In the metformin monotherapy subset, there was a 0.47% ($p < 0.05$) reduction in HbA1c levels (colesevelam relative to placebo), a 17.8 µmol/l ($p < 0.05$) reduction in fructosamine levels and a 13.9% reduction in fasting plasma glucose relative to placebo. There was a 16% reduction in mean percentage serum LDL-C levels, and significant reductions in apolipoprotein B levels and C-reactive protein was observed with patients on colesevelam compared with placebo. In this study, there was no statistically significant effect of colesevelam on TGs compared with the placebo (median percent change = 11.8 vs 6.6%; $p = 0.221$).

Colesevelam & sulfonylurea

Fonseca *et al.* carried out a randomized double-blinded Phase III study [23] to investigate the effect of colesevelam when used in conjunction with sulfonylureas on glycemic control. The study focused on colesevelam as a potentially novel treatment for improving glycemic control in patients with T2DM who were inadequately controlled with sulfonylurea-based therapy. The effects of colesevelam on LDL-C in patients receiving sulfonylurea-based therapy were also studied. This was a 26-week randomized, double-blind, placebo-controlled, parallel-group, multicenter study trial where subjects with T2DM were randomized based on their history of being on sulfonylurea monotherapy or sulfonylurea in combination with other oral antidiabetic therapy and having HbA1C between 7.5 and 9.5%. In the study, 156 subjects were given sulfonylurea monotherapy prior to randomization into the study: 75 subjects were in the colesevelam arm, and 81 subjects were in the placebo arm. The primary end point of the study was the mean change in A1C from a baseline to week 26 for the total cohort (primary end point). The subjects continued their sulfonylurea and other antidiabetic medication at the same dose and time throughout the study. Treatment differences were witnessed when patients were placed on colesevelam in conjuction with sulfonylurea compared with those on placebo. The effect of treatment with colesevelam was calculated using the LS mean method. A treatment difference (colesevelam group relative to placebo) of 0.54% ($p < 0.001$) was noted in the total cohort. The treatment difference for HbA1c is -0.42 ($p < 0.001$) in sulfonylurea combination therapy and -0.79 ($p < 0.001$) in the sulfonylurea monotherapy cohort. Patients with HbA1c greater than 8.0% at baseline had an increased treatment effect in HbA1c levels, with a reduction of 0.58 ($p < 0.0001$). There were reductions in the colesevelam arm relative to the placebo in the fructosamine levels (-21.4 µmol/l; $p < 0.001$) and in fasting plasma glucose relative to the placebo (-13.5, $p < 0.009$). There was no difference in the C-peptide levels. The study also noted significant reductions in LDL-C from baseline (-16.1% in the colesevelam group and +0.6% in the placebo group).

Colesevelam & insulin

Goldberg *et al.* carried out a randomized double-blind study [24] that investigated the glucose-lowering effects of colesevelam when used in conjunction with insulin. The study focused on colesevelam as adjunctive therapy for improving glycemic control in T2DM patients inadequately controlled (HbA1c between 7.5 and 9.5%) on insulin therapy. The study also observed the effects of colesevelam on LDL-C in patients on insulin therapy. In this trial, 287 subjects with T2DM were randomized in a 16-week multicenter study based on their history of insulin monotherapy, or on insulin in combination with other oral antidiabetic therapy. The primary end point of the study was the mean change in A1c from baseline to week 16 for the total cohort (primary end point).

Treatment differences were observed when patients were placed on colesevelam in conjuction with insulin. This was calculated using the LS mean method. In the total cohort, a treatment difference of 0.5% ($p < 0.001$) was found in patients who were on colesevelam relative to placebo. There was a treatment difference of -0.59% ($p < 0.001$) in the insulin monotherapy cohort. In the cohort of insulin combination therapy with colesevelam HCl, the treatment difference for HbA1c was -0.44 ($p < 0.001$). Similar to findings in other trials [21–23], in patients with HbA1C greater than 8.0% at baseline, the treatment effect was increased, with HbA1C levels displaying a reduction of 0.57% ($p < 0.0001$). There were reductions in the colesevelam arm relative to placebo in the fructosamine levels (-21.7 µmol/l; $p < 0.001$). Although there was a reduction in fasting plasma glucose relative to placebo (-14.6 mg/dl; $p < 0.08$), there was no difference in the mean change in C-peptide levels. The study also noted significant reductions in LDL-C with a treatment difference of -12.8%. This study also demonstrated a reduction in fasting plasma glucose and fructosamine levels, HbA1c and lipid control measures in patients treated with colesevelam and insulin.

Cumulative findings of the Phase III clinical studies

Colesevelam was evaluated in large-scale placebo-controlled trials for antidiabetic effects. Colesevelam appears to be safe when used concomitantly with existing antidiabetes monotherapy of insulin, metformin and sulfonylureas. The clinical studies demonstrated decreases in various glycemic parameters, such as fasting blood glucose, fructosamine and a reduction in HbA1C (0.5–0.54%) in the total cohort (Table 3) [22–24]. Patients in both subgroups, colesevelam with antidiabetic monotherapy and colesevelam with antidiabetic combination therapy, displayed significant decreases in HbA1c (Table 3). This was observed across subgroups of gender, race and body mass index in patients who received colesevelam in combination with metformin, sulfonylurea or insulin. In the colesevelam and sulfonylurea, and colesevelam and insulin trials, the percentage of subjects with an HbA1c reduction of greater than 0.7% compared with a placebo was greater. These clinical studies also demonstrated a significant reduction of critical lipid parameters (Table 4). Some of the other major findings were: reduction of LDL (12–16%) observed in patients that were on colesevelam with metformin, sulfonylureas or insulin; and a significant increase in TG levels in patients on insulin and patients on a sulfonylurea, but not with patients on metformin.

Colesevelam is a drug that can improve both glycemic control and help achieve lipid lowering in patients with T2DM; however, it has not yet been investigated as a monotherapy for treatment of diabetes. Currently, there is no published evidence regarding its efficacy and safety with other oral antidiabetic medication classes such as dipeptidyl peptidase IV inhibitors or thiazolidinediones. The use of colesevelam offers a clinical benefit among antidiabetic agents by reducing LDL-C levels [50]. When colesevelam is used as an adjunctive treatment, it can help reduce the number of prescriptions needed by individuals

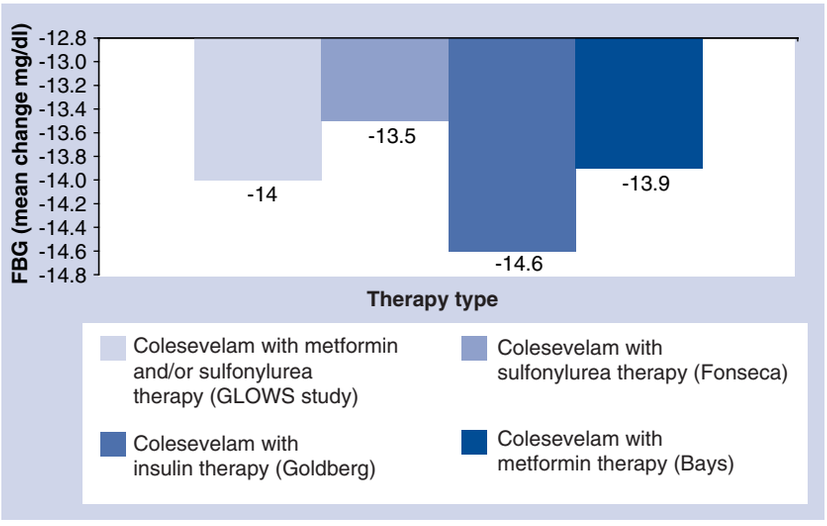

Figure 2. Change in fasting blood glucose relative to placebo. Mean placebo-adjusted change in fasting plasma glucose when colesevelam was added to antidiabetic agents in patients with Type 2 diabetes mellitus.
FBG: Fasting blood glucose.
Data taken from [21–24].

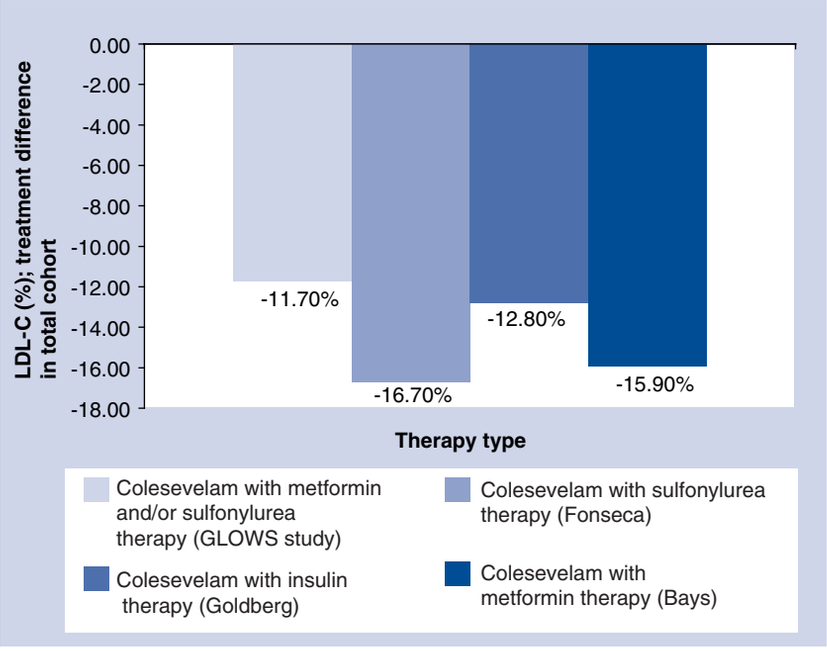

Figure 3. Mean placebo-adjusted change in LDL-C (%). Least squares mean change from baseline when colesevelam was added to antidiabetic agents in patients with Type 2 diabetes mellitus.
LDL-C: Low-density lipoprotein cholesterol.
Data taken from [21–24].

to improve control of T2DM and dyslipidemia. However, it does add to the patient's pill burden, because colesevelam requires an additional six tablets per day.

Colesevelam hydrochloride mechanism of action

Bile acid sequestrants bind bile acids in the intestine, and this leads to increased bile acid excretion via the feces. This leads to a decrease in bile acids that return through enterohepatic circulation and subsequent upregulation of key enzymes (e.g., cholesterol-7-α-hydroxylase – CYP7A1) that are important for bile acid synthesis from cholesterol [51]. The increased hepatic need for plasma cholesterol is accompanied by an increase in hepatic LDL receptor activity, and this helps clear LDL-C from the circulation and subsequently reduce plasma LDL-C levels [39].

Bile acids have an ability to act as hormones and activate signaling pathways, and the molecular mechanisms involved are still being elucidated [52]. It may involve various nuclear receptors such as the farnesoid X receptor-α (FXR-α) and the G-protein coupled receptor TGR5 [52–54]. Bile acids are important ligands for FXR and the activation of FXR plays a role in exerting negative feedback on bile acid synthesis [52–54]. FXR appears to play an important role in bile acid metabolism by helping to increase bile acid efflux from the liver, decreasing hepatic bile acid synthesis by affecting CYP7A1 activity and increasing bile acid enterohepatic circulation [52,53,55].

An interplay between bile acid metabolism and glucose metabolism may exist through both FXR-dependent and FXR-independent mechanisms [52,53,55]. The mechanisms for FXR-dependent and -independent interactions are still being elucidated and explored in detail [52,53]. In one animal model, glucose levels were reported to affect the FXR receptor levels in the liver [56]. FXR-α-related effects on glucose homeostasis may occur at specific time points during fasting and feeding [52]. One evolving model of the FXR-dependent pathway (based on animal studies) includes FXR activation leading to modifications in levels of small heterodimer protein (SHP), and the ability of SHP to bind to molecules such as hepatocyte nuclear factor 4-α (HNF-4α) [52,53]. The binding of SHP with HNF-4 can affect the expression of various genes involved in gluconeogenesis, glucose transport and glycolysis [53]. There may be a reduction in gluconeogenesis partly through the reduction in the levels of glucose-6-phosphatase and phosphoenolpyruvate carboxykinase [52,55]. FXR-dependent pathways may also be involved in glycogenesis [52]. Some FXR-independent pathways may also be important in increasing glycogen synthesis. They may involve molecules and pathways such as the epidermal growth factor receptor, the phosphoinositide 3-kinase (PI3K)–AKT pathway, and PI3K–AKT–glycogen synthase kinase 3β (GSK3β) [52].

There is limited data to clearly indicate the ways in which BASs may alter glucose and insulin metabolism. A reduction in the hepatic bile acid pool may alter intrahepatic pathways related to gluconeogenesis and other pathways of glucose homeostasis, and affect glucose diffusion from the intestinal lumen to the intestinal wall [55,57,58]. There are conflicting reports on the effects of BASs on HNF-4α concentrations *in vivo* [53,55]. There may exist alterations to the release of gut-derived glucose homeostatic hormones [56,59]. The exact mechanism(s) through which colesevelam has glucose-lowering effects remains unclear. Further research is needed to determine the mechanism underlying the glucose-lowering effect of colesevelam HCl.

Safety & tolerability

In the three previously mentioned Phase III studies, colesevelam was found to be generally safe and well-tolerated in subjects with T2DM. The treatment-related adverse events in the colesevelam

Table 3. Effects of colesevelam hydrochloride on glycemic parameters of Type 2 diabetes mellitus patients who were receiving metformin, sulfonylurea or insulin therapy.

Trial and background antidiabetic therapy	Fasting plasma glucose	Fructosamine level change from baseline (µmol/l)	HbA1C			Ref.
			Colesevelam relative to placebo	*Colesevelam (patient with HbA1C < 8.0% at baseline) relative to placebo*	*Colesevelam (patient with HbA1C > 8.0% at baseline) relative to placebo*	
Bays *et al.* (2008) (metformin and colesevelam study)	-13.9 mg/dl	-23.20	-0.54% ($p < 0.05$)	-0.47% ($p = 0.002$)	-0.62% ($p < 0.001$)	[22]
Fonseca *et al.* (2008) (sulfonylurea and colesevelam study)	-13.5 mg/dl	-21.40	-0.54% ($p < 0.001$)	-0.48% ($p < 0.0002$)	-0.58% ($p < 0.0001$)	[23]
Goldberg *et al.* (2008) (insulin and colesevelam study)	-14.6 mg/dl (not statistically significant)	-21.70	-0.5% ($p < 0.001$)	-0.38% ($p < 0.0007$)	-0.57% ($p < 0.001$)	[24]

treatment groups were similar to that of the placebo group [22–24]. The most frequently reported adverse event was constipation. Significant weight gain, a common side effect of some oral antidiabetic agents, was not observed in the colesevelam group. Adverse reactions/side effects observed in the diabetes clinical trials are summarized in TABLE 5. Colesevelam is not approved for use in ketotic states and Type 1 diabetes mellitus.

Because colesevelam is not absorbed from the digestive tract, it may have improved GI tolerability compared with other BASs. Colesevelam was reported to have GI-related adverse effects such as constipation. In a meta-analysis that reviewed trials combining colesevelam with statins, the occurrence of constipation was reported to be less than 10% [51]. Currently, there is no direct comparison between colesevelam and other BASs. The manufacturer recommended that healthcare providers exercise judgment in giving colesevelam to patients with bowel obstruction, GI motility disorders and those who have undergone major GI-tract surgery, because of the constipating effects of colesevelam [101]. Similar to other BASs, colesevelam can increase levels of alkaline phosphatase, aspartate transaminase and alanine transaminase [32]. However, there is no current restriction for the use of colesevelam in patients with hepatic impairment [101].

Colesevelam was studied for treatment of dyslipidemia; however, it was not studied for the treatment of Fredrickson type I, III, IV and V dyslipidemias. It appears to not only be safe when used in conjunction with statins and ezetimide, but may also help lower lipid profiles when used concomitantly [59]. Like other BASs, which are known to potentiate hypertriglyceridemia, colesevelam appears to be associated with increased serum TG levels [34–36,60]. In the trials using sulfonylureas with colesevelam and insulin with colesevelam, an increase in TGs was observed. Healthcare providers need to be aware that

Table 4. Effects of colesevelam hydrochloride on lipid parameters of Type 2 diabetes mellitus patients who were receiving metformin, sulfonylurea or insulin therapy.

Trial and background antidiabetic therapy	Mean percentage change in TC	Mean percentage change in LDL-C levels	Mean percentage change in HDL-C levels	Median percentage change in triglycerides	Mean percentage change in ApoB	Ref.
Bays *et al.* (2008) (metformin)	-7.2	-15.90	0.9 (NS)	4.7 (NS)	-7.9% ($p < 0.001$)	[22]
Fonseca *et al.* (2008) (sulfonylurea)	-5.00	-16.70	0.1 (S)	17.7 (NS)	-6.7% ($p < 0.001$)	[23]
Goldberg *et al.* (2008) (insulin)	-3.70	-12.80	-0.9 (S)	21.5 (NS)	-5.4% ($p < 0.04$)	[24]

HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; NS: Not significant; S: Significant; TC: Total cholesterol.

Table 5. Adverse reactions of colesevelam hydrochloride add-on therapy with metformin, insulin and sulfonylurea.

Side effects	Number of patients (%)	
	Welchol® n = 566	*Placebo n = 562*
Constipation	49 (8.7)	11 (2.0)
Nasopharyngitis	23 (4.1)	20 (3.6)
Dyspepsia	22 (3.9)	8 (1.4)
Hypoglycemia	17 (3.0)	13 (2.3)
Nausea	17 (3.0)	8 (1.4)

From Welchol® Product Information 2007 [101].

colesevelam can increase serum TG concentrations and monitor TG levels. Currently, it is not recommended for use in patients with TG levels greater than 500 mg/dl or TG-induced pancreatitis [101]. The effects of colesevelam on cardiovascular morbidity and mortality have yet to be determined.

Colesevelam continues to be monitored for potential side effects in different groups. It was placed in pregnancy category B because no adequate and well-controlled studies were performed in pregnant women; however, animal studies did not demonstrate evidence of harm to the fetus [101]. As a class, BASs are approved for use in children with significant hypercholesterolemia, although the safety and efficacy of colesevelam has not specifically been established in pediatric patients [61]. The manufacturer does not recommend the use of colesevelam in children owing to pill size [101].

Colesevelam was generally well-tolerated at different doses [32,60]. It was tested and found to be relatively safe in doses up to 4.375 g/day [32]. It was not tested in doses in excess of 4.5 g/day. The drug manufacturer recommended that drugs with a narrow therapeutic index should either be monitored for drug levels or administered at least 4 h prior to colesevelam. Some have felt that colesevelam can be administered concurrently with other drugs [53]. The manufacturer stated that colesevelam can be given to patients with hepatic impairment without special considerations or dosage adjustments [101]. In addition, there appears to be no significant difference in safety or efficacy in patients with creatinine clearance (CrCl) less than 50 ml/min when compared with those with CrCl greater than 50 ml/min [101].

There are potential drug–drug interactions that were noted through *in vitro* binding, *in vivo* drug interaction studies and in postmarketing reports. The potential drug–drug interactions are given in Table 6. The manufacturer noted that phenytoin levels may be affected with the concomitant use of colesevelam, and recommended that it be administered 4 h prior to colesevelam [101]. While not observed *in vivo*, the postmarketing studies suggested that concomitant use of warfarin and colesevelam may cause drug–drug interactions [101]. Healthcare providers should exercise caution when treating patients with a susceptibility to vitamin K or fat-soluble vitamin deficiencies [60]. Colesevelam appears to affect the levels of drugs such as verapamil, glyburide, oral contraceptives containing ethinyl estradiol and norethindrone when there is concomitant administration [42,101].

Clinical use & treatment guidelines

Colesevelam is a BAS that has been shown to improve glycemic control and lipid parameters. The recommended dose of colesevelam HCl, whether used as monotherapy or as part of combination therapy, is six tablets once-daily or three tablets twice-daily (3.75 g/day). It can be titrated up to a maximal dose of 4.375 g/day. In the USA, colesevelam received an approval from the US FDA in 2000 for lowering lipid parameters, and in 2008 for

Table 6. Drugs tested for *in vitro* binding or *in vivo* drug interaction.

Nature of interaction	Drugs
Drugs with known interaction with colesevelam	Levothyroxine, oral contraceptives containing ethinyl estradiol and norethindrone, glyburide
From postmarketing reports: potential drug–drug interactions with concommitant use	Phenytoin, warfarin
No interactions based on *in vitro* or *in vivo* testing	Digoxin, quinidine, metoprolol, fenofibrate, lovastatin, metformin, pioglitazone, repaglinide, valproic acid, ciprofloxacin

From Welchol® Product Information 2007 [101].

improving glycemic control. It is marketed under the name Welchol by Daiichi-Sankyo. In Europe, the EMEA approved colesevelam in March 2004 for lowering lipid parameters. In Europe, it is currently marketed under the name Cholestagel by Genzyme (MA, USA). Genzyme also intends to pursue regulatory approvals for Cholestagel in Latin America, Canada and the Asia Pacific region.

Primary hyperlipidemia

Colesevelam can be used as adjunct therapy in patients unable to attain goal LDL-C levels with statins or other lipid-lowering agents. It can be used in patients who are not able to reach target LDL goals (LDL goals based on guidelines from the American Association of Clinical Endocrinologists) using statins when monotherapy is insufficient to achieve LDL-C goals. When patients are administered colesevelam concomitantly with statins, there are increased reductions in LDL-C [34–36]. In patients who have primary hypercholesterolemia requiring moderate LDL-C reduction (<20%) and who are unable to tolerate other lipid-lowering drugs, colesevelam may be used as a first-line agent. It may be of particular use in patients with dyslipidemia and T2DM because it can lower both LDL-C and HbA1c.

Type 2 diabetes mellitus

Colesevelam was approved by the US FDA for improving glycemic control in adults with T2DM in the USA. Colesevelam is the only bile acid sequestrant that has FDA approval for use in both dyslipidemia and T2DM. It has yet to receive approval for glycemic control from the EMEA.

Colesevelam HCl is the only US FDA-approved antilipidemic drug to have beneficial effects on glycemic parameters by concurrently reducing HbA1c. It may help patients with T2DM achieve both LDL-C and HbA1c goals. Colesevelam will be useful as adjunctive therapy for treatment of T2DM. Many patients will require more than one agent to help maintain glycemic control. It can be used in combination with insulin, sulfonylurea and insulin. On average, colesevelam appears to reduce HbA1c by 0.5% when used as part of an adjunctive therapy over a 16-week to 26-week time period. The recommended dose of colesevelam is six tablets once-daily or three tablets twice-daily, and it has not been studied in T2DM as a monotherapy. Colesevelam has not been approved for use in Type 1 diabetes or diabetic ketoacidosis. It has yet to be studied in combination with dipeptidyl peptidase-4 inhibitors or with thiazolidinediones.

Conclusion

Colesevelam is a nonabsorble polymer-based BAS that has a high affinity for both trihydroxy and dihydroxy bile acids. In the USA, it is approved for use as monotherapy or as part of combination therapy to improve glycemic control and lipid parameters. The use of colesevelam appears to be safe and efficacious when used in combination with metformin, sulfonylureas or insulin for improving glycemic control in patients with T2DM. This may lead to a greater percentage of patients meeting glycemic goals and achieving a further reduction in LDL-C concentrations. The capability of colesevelam to improve both glycemic control and lipid parameters gives healthcare providers a unique option in the treatment of T2DM.

Future perspective

The efficacy and safety of colesevelam for treating hyperglycemia in diabetes is now established. Future studies will need to focus on elucidation of the mechanism of action, expanding on the role of the GI tract in regulation of glucose metabolism. The role of colesevelam in prediabetes will also need to be evaluated. Finally, outcome studies are needed to assess the effect of combined glucose and LDL-C lowering in the prevention of cardiovascular events.

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Executive summary

- Type 2 diabetes mellitus (T2DM) affects approximately 100 million people worldwide (~3% of total population).
- The treatment of T2DM must be aimed at treating hyperglycemia, reducing microvascular disease (retinopathy, neuropathy and nephropathy) and addressing dyslipidemia to help minimize macrovascular complications.
- Drugs that can simultaneously treat hyperglycemia and dyslipidemia may help patients with T2DM reach recommendations for both glucose and lipid parameters.
- Recent studies indicate that there is crosstalk between lipid and glucose metabolism. It may be partly due to bile acid-activated nuclear hormone receptor signaling pathways.
- Colesevelam is a bile acid sequestrant that has been investigated to examine the efficacy in treating dyslipidemia. Colesevelam has higher affinity for bile acids and has been shown to lower lipids at 3.75 g/day and at 4.375 g/day.
- Colesevelam has been approved as monotherapy or as part of combination therapy to lower low-density lipoprotein cholesterol (LDL-C) and total cholesterol. The US FDA and EMEA have approved the use of colesevelam as an adjunct to diet and exercise to reduce elevated LDL-C in patients with primary hyperlipidemia.
- In the USA, colesevelam has received US FDA approval as an add-on therapy to lower glycemic parameters in patients with T2DM. Clinical studies have demonstrated that treatment with colesevelam seems to be safe and efficacious when used concomitantly with metformin, sulfonylureas or insulin.
- Colesevelam was shown to improve glycemic control and lipid management in patients with T2DM. This may lead to a greater percentage of patients meeting glycemic goals and achieving a further reduction in LDL-C concentrations – critical factors in the management of T2DM.
- The mechanism through which colesevelam lowers plasma glucose is still being elucidated.
- In clinical trials, colesevelam was generally well-tolerated. The side effects observed in the diabetes clinical trials are: constipation, nasopharyngitis, dyspepsia, hypoglycemia, nausea and hypertension.

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