# The Effect of Colestipol on Glycemic Control in Patients With Type 2 Diabetes

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Using an electronic chart review, the authors investigated the effect of colestipol, a bile acid sequestrant, on glycemic control in patients with type 2 diabetes.

Diabetes mellitus is a complex disease, characterized by hyperglycemia, and can be associated with abnormalities in fat, carbohydrates, and protein metabolism that result from defects in insulin secretion, insulin action, or both. Type 2 diabetes is the most common form of diabetes in the United States, accounting for as many as 90% to 95% of all cases.[1] As of 2011, 25.8 million patients were diagnosed with diabetes, or 8.3% of the U.S. population.[2] Type 2 diabetes is more common in African Americans, Mexican Americans, Native Americans, Asian Americans, Native Hawaiians, and other Pacific Islanders, as well as the elderly population.[1,3] Type 2 diabetes is characterized by insulin resistance and a relative lack of insulin secretion. Insulin is necessary for the breakdown of sugars and carbohydrates in the body and plays a vital role in the uptake of glucose into cells for energy.[1]

Uncontrolled diabetes is associated with numerous complications, including blindness, kidney damage, heart disease, and lower-limb amputations. In patients with diabetes, optimal control of glucose and low-density lipoprotein cholesterol (LDL-C) has been shown to delay or even prevent the development of complications. In general, every percentage point drop in glycosylated hemoglobin (A1C) can reduce the risk of microvascular complications (ie, eye, kidney, and nerve diseases) by 40%.[2] Improved control of LDL-C can reduce cardiovascular complications by 20% to 50%.[2] Current American Diabetes Association (ADA) guidelines recommend an A1C of < 7% and an LDL-C < 100 mg/dL in patients with diabetes.[4] However, to achieve these goals, patients with diabetes often need to use multiple medications.[1,2]

As a result, recent attention has shifted to the use of single agents with both glucose and lipid-lowering effects. One such class of agents is the bile acid sequestrants. To date, both colesevelam hydrochloride and cholestyramine have demonstrated A1C and glucose-lowering effects in clinical trials.

The Glucose Lowering Effect of Welchol Study (GLOWS) evaluated the A1C lowering effect of colesevelam hydrochloride in subjects with type 2 diabetes who were inadequately controlled by oral antihyperglycemic agents alone. Participants were on a stable dose of metformin or a sulfonylurea for ≥ 90 days before the initiation of colesevelam. Sixty-five study participants who had an A1C of 7% to 10% were randomized to receive either colesevelam 3.75 g/d or placebo for 12 weeks. After 12 weeks, results demonstrated a difference in mean change in A1C between the colesevelam group and the placebo group of − 0.5% ($P$ = .007). Additionally, in participants with a baseline A1C ≥ 8%, the difference in mean change in A1C was − 1.0% ($P$ = .002). Treatment with colesevelam was also associated with a reduction in postprandial glucose (− 31.5 mg/dL, $P$ = .026) and LDL-C (− 11.7%, $P$ = .007). The study authors concluded that colesevelam may improve both glycemic and lipid control in patients with type 2 diabetes.[5] Following the publication of this trial, colesevelam received an FDA indication as an adjunctive treatment in patients with type 2 diabetes, in addition to its prior indication for hypercholesterolemia.

Another similar trial evaluated the use of cholestyramine for dyslipidemia in patients with type 2 diabetes. The study researchers also examined the effect of cholestyramine on glucose levels as a secondary endpoint. This study was a randomized, double-blind, crossover study of 21 participants receiving cholestyramine 8 g bid vs a placebo for 6 weeks each. Study participants had type 2 diabetes that was well controlled for at least 1 month prior to the initiation of cholestyramine, using either insulin or glyburide therapy, and an LDL-C of > 130 mg/dL. Additionally, patients were on a stable dose of insulin or glyburide throughout the duration of the study. After 12 weeks, results demonstrated that treatment with cholestyramine reduced total

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| Table 1. Data collected using the electronic chart | |
|---|---|
| **Demographic information** | Age<br>Gender<br>Race |
| **Baseline information (within the 6 months prior to initiation of colestipol)** | A1C<br>Lipids (LDL-C, TGs, HDL-C)<br>LFTs (within normal limits [WNL] vs elevated) |
| **After initiation of colestipol** | A1C (at least 3 months after starting colestipol)<br>Lipids (LDL-C, TGs, HDL-C) (at least 4 weeks after starting colestipol)<br>LFTs (WNL vs elevated)<br>Any subsequent values for the above parameters following dose titration of colestipol for up to 6 months |
| **Adverse effects** | Medication intolerance as documented in the progress notes |
| **Medication information** | Colestipol<br>• Initial dose<br>• Maximum tolerated dose<br>• Date of initiation<br>• Date of discontinuation (if applicable)<br>Concomitant oral antihyperglycemic medications (including sulfonylureas, biguanides, insulin, thiazolidinediones, α-glucosidase inhibitors, meglitinides, dipeptidyl peptidase-4 inhibitors, glucagon-like peptide-1 agonists, and dopamine agonists)<br>• Dose when colestipol was started<br>• Dosage changes since colestipol was started<br>• Date of initiation<br>• Date of discontinuation (if applicable)<br>Concomitant lipid-lowering medications (including HMG-CoA reductase inhibitors, nicotinic acid, intestinal absorption inhibitors, fish oil, and fibric acid derivatives)<br>• Dose when colestipol was started<br>• Dosage changes since colestipol was started<br>• Date of initiation<br>• Date of discontinuation (if applicable) |
| **Medication compliance** | Determined by the refill history in the electronic medical record and documentation of nonadherence in the progress notes |
| **Patient education** | Counseling regarding the proper administration of colestipol in relation to other medications to minimize any possible interference with absorption (take other medications at least 1 hour before or 4 hours after colestipol) as documented in the progress notes or stated on the medication label |

cholesterol by 18% and LDL-C by 28%, when compared with placebo. In addition, cholestyramine therapy improved glycemic control. Mean plasma glucose levels decreased by 13%; a mean reduction in urinary glucose excretion of 0.22 g/d was noted, as well as a decrease in A1C values of 0.5%. The study authors concluded that cholestyramine therapy effectively reduced LDL-C and may also improve glycemic control in patients with diabetes.[6]

It is important to note that there is 1 additional agent in this class of medications: Colestilan. However, this agent is not approved in the United States and has been evaluated only as monotherapy, which does not comply with the current clinical approach in the United States of using bile acid sequestrants as adjunctive therapy in patients with diabetes. In other countries, colestilan has been proven effective in reducing both A1C and fasting plasma glucose in patients with type 2 diabetes.[7]

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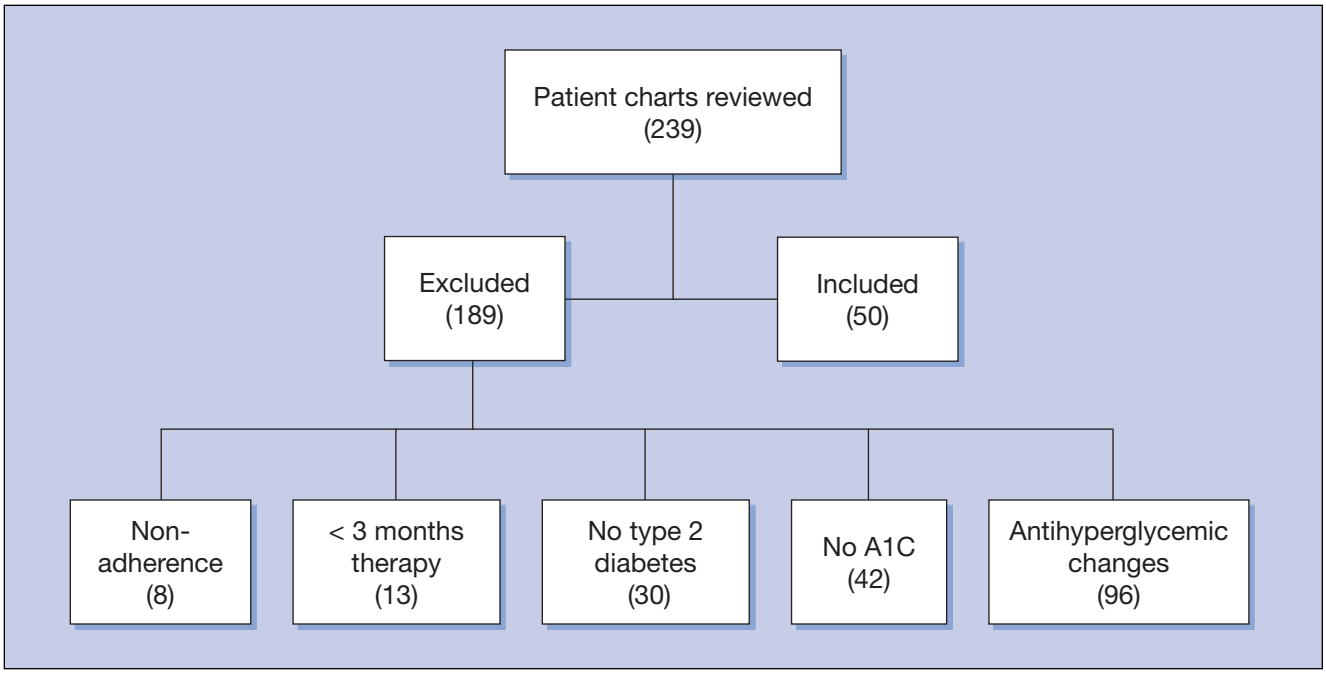


Figure 1. Study design.

In general, bile acid sequestrants act by binding bile acids, forming a complex that is then excreted in the feces, thus preventing reabsorption in the intestines. This action also results in partial removal of bile acids from the enterohepatic circulation, which prevents its reabsorption. This leads to the depletion of serum bile acids, which activates cholesterol 7 alpha-hydroxylase to convert cholesterol into bile acids. Consequently, a demand for cholesterol in the liver is increased, resulting in increased 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase transcription and activity, and an increased number of LDL-C receptors. HMG-CoA reductase is the rate-controlling enzyme in the metabolic pathway that produces cholesterol. This compensatory action increases LDL-C clearance from the blood, resulting in lowered LDL-C levels.[8,9]

The mechanism by which bile acid sequestrants exert their glycemic effects is not fully understood. One proposed mechanism is that bile acid sequestrants cause a reduction in glucose absorption or a change in the time course of glucose absorption in the gastrointestinal tract. Another theory is that by interrupting the enterohepatic pathway of bile metabolism, bile acid sequestrants deactivate the farnesoid X receptor. This receptor is a bile acid-activated nuclear receptor that plays a significant role in the metabolism of bile acids, cholesterol, and glucose.[8,9]

While previous trials with both colesevelam and cholestyramine have demonstrated beneficial effects on both LDL-C and A1C in patients with type 2 diabetes, the specific effect of colestipol on glycemic control has yet to be evaluated. Currently, colestipol is FDA approved for the treatment of primary hypercholesterolemia, and it is the bile acid sequestrant that is currently on the formulary at Jesse Brown VAMC.

## METHODS

The purpose of this study was to evaluate the effect of colestipol on glycemic control in patients with type 2 diabetes in a veteran population. This study was an Institutional Review Board and VA Research and Development Committee approved, retrospective, electronic chart review of patients with an ICD-9 di-

**Table 2. Demographic information**

| Gender n (%) | | Age (y) | Race n (%) | | | |
|---|---|---|---|---|---|---|
| Male | Female | Mean ± SD | African American | White | Pacific Islander | Unknown |
| 50 (100) | 0 (0) | 70.9 ± 8.1 | 26 (52) | 15 (30) | 2 (4) | 7 (14) |

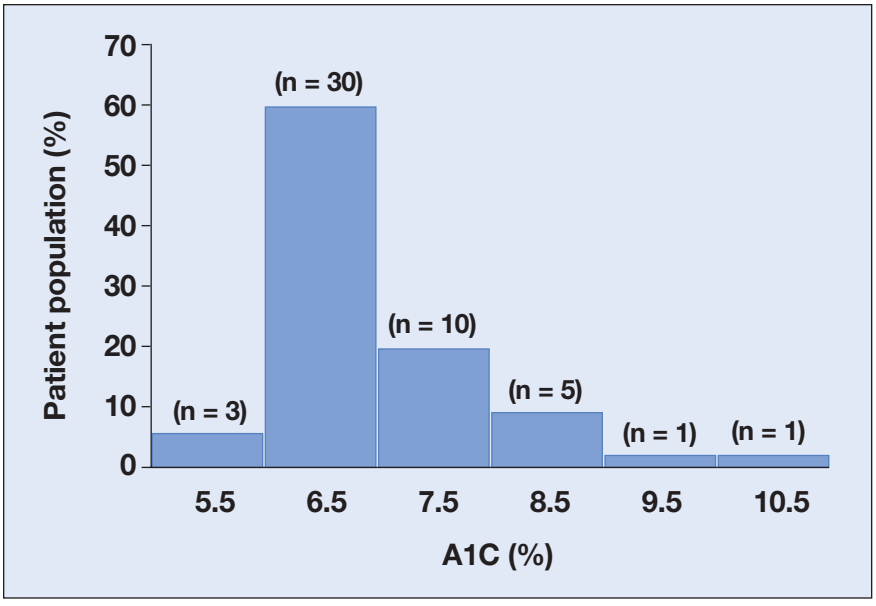


Figure 2. Baseline A1C.

agnosis of type 2 diabetes and with an active prescription for colestipol anytime between January 1, 2005 and June 15, 2010. Patients aged ≥ 18 years with a diagnosis of type 2 diabetes and with a prescription for colestipol were included in the study. Study participants who were not receiving treatment with colestipol for a minimum of 12 weeks were excluded from the study. Additionally, patients with any changes in their antihyperglycemic medications during the 3-month period before or after the initiation of colestipol and patients that lacked an A1C within the 6 months prior to or following the initiation of colestipol were excluded. Patients were followed throughout the study period, and each subject served as his or her own control.

The primary efficacy endpoint was a change in A1C from baseline to follow-up after the initiation of colestipol. Secondary endpoints included the percent change in lipid parameters and percentage of patients experiencing an increase in liver function tests (LFTs) from baseline to follow-up after initiation of colestipol. Additional secondary endpoints included the documentation of appropriate counseling regarding the proper administration of the medication, as well as the occurrence of adverse events related to the study medication.

The data collected, using the electronic chart, are shown in Table 1. Statistical analysis of the collected data was performed using both a paired *t* test and Wilcoxon signed rank test, depending on the data distribution. Data analyzed included change in A1C (Wilcoxon), lipid parameters (*t* test), LFTs (none), the occurrence of counseling and adverse effects (none), and dose-dependent changes in A1C (Wilcoxon).

## RESULTS

Based on the aforementioned criteria, a total of 239 patient charts were reviewed, and 50 patients were ultimately included in the study (Figure 1). Overall, 100% of the patients were male, with a mean age of 70.9 years. Additionally, the majority of the patients were African American (52%), followed by white (30%) (Table 2).

The majority of patients had a baseline A1C between 6% and 7% (Figure 2 ), which explains the lack of changes in concomitant antihyperglycemic medications during the study period. On average, patients receiving colestipol experienced a statistically significant reduction in A1C of 0.24% ($P < .0001$). When dividing patients into different categories based on their A1C level at baseline (< 7%, 7%-8%, or > 8%), there was a trend toward a greater reduction in A1C in those patients with a higher initial A1C (0.16%, $P = .001$; 0.34%, $P = .01$; and 0.56%, $P = .31$, respectively). However, due to the small patient population in the > 8% baseline category (n = 7), there may not have been enough power to determine statistical significance. Additionally, there was not a statistically signifi-

**Table 3. A1C reduction**

| Parameter | Baseline (%) | Final (%) | Change (%) | *P* value |
|---|---|---|---|---|
| Average overall A1C (%) | 6.9 | 6.7 | – 0.24 | < .0001 |
| < 7 | 6.5 | 6.3 | – 0.16 | = .001 |
| 7-8 | 7.4 | 7.1 | – 0.34 | = .01 |
| > 8 | 9.0 | 8.5 | – 0.56 | = .31 |

cant difference in the change in A1C between the 3 baseline categories ($P = .38$) (Table 3).

The average maximum tolerated dose of colestipol was 4.5 g/d. When comparing the average A1C reduction with the maximum tolerated dose of colestipol (1 g bid, 2 g bid, 3 g bid, and 4 g bid), there was a trend toward a greater reduction in A1C with a higher colestipol dose (0.2%, $P = .15$; 0.2%, $P = .01$; 0.3%, $P = .25$; and 0.3%, $P = .06$, respectively). However, similar to the previous discussion, there may not have been enough patients in the various dosage groups to determine statistical significance. Additionally, there was not a statistically significant difference in the change in A1C levels between the 4 dosage categories ($P = .60$) (Table 4).

All the study patients failed to achieve therapeutic lipid goals with optimal doses of statins or had documented intolerance(s) to other available agents, and were, therefore, initiated on colestipol for additional LDL-C lowering. Patients receiving colestipol experienced a statistically significant reduction in LDL-C of 13.4% ($P < .0001$). Following initiation of colestipol, patients experienced an increase in triglycerides (TGs) of 18.9% ($P = .26$) and overall, high-density lipoprotein cholesterol (HDL-C) remained relatively unchanged, increasing slightly by 0.6% ($P = .89$) (Table 5). Of note, 4 of the 50 patients (8%) had concomitant changes to their other lipid-lowering medications during colestipol therapy (medication initiation [n = 2], medication conversion [n = 1], and medication discontinuation [n = 1]).

In terms of the additional secondary endpoints, LFTs remained stable following initiation of colestipol and throughout the study period. Eight of 50 patients (16%) had persistently elevated LFTs due to either alcohol use or hepatitis (Table 6). Education regarding the proper administration of colestipol, in relation to other medications, was documented in 13 of 50 patients (26%). Finally, gastrointestinal-related adverse events, which are commonly associated with the administration of colestipol, were reported by 2 of 50 patients (4%) following dose titration of colestipol. In both instances, the patients experienced constipation, the dose of colestipol was reduced to the previously tolerated dose, and the patients were able to continue therapy.

**Table 4. Maximum dose**

| Colestipol dose | Average change in A1C (%) | Patients (n) | *P* value |
|---|---|---|---|
| 1 g bid | – 0.2 | 7 | = .15 |
| 2 g bid | – 0.2 | 32 | = .01 |
| 3 g bid | – 0.3 | 5 | = .25 |
| 4 g bid | – 0.3 | 6 | = .06 |

**Table 5. Lipid parameters**

| Parameter | Baseline | Final | Change (%) | *P* value |
|---|---|---|---|---|
| LDL-C (mg/dL) | 130.8 | 112.3 | – 13.4 | < .0001 |
| HDL-C (mg/dL) | 40.5 | 40.4 | 0.6 | = .89 |
| TGs (mg/dL) | 153.8 | 170.4 | 18.9 | = .26 |

**Table 6. LFT (AST/ALT) changes**

| Classification | Baseline (n) | Final (n) | Change (%) |
|---|---|---|---|
| WNL | 42 | 42 | 0 |
| Elevated | 8 | 8 | 0 |

AST/ALT: aspartate aminotransferase/alanine aminotransferase.

## DISCUSSION

On average, patients receiving therapy with colestipol for additional LDL-C lowering experienced an overall reduction in A1C of 0.24%. This value is slightly lower than the reductions observed with other agents of this class: 0.3% to 0.7% with colesevelam and 0.5% with cholestyramine. However, the doses of those agents used in the previously mentioned studies were higher in comparison with the average colestipol dose observed in this study. A trend toward a greater reduction in A1C with higher initial A1C levels at baseline was observed; however, due to the small patient population, these results did not achieve statistical significance. Additionally, a trend toward a greater reduction in A1C with higher colestipol doses was noted. Similarly, the sample size may have limited the ability to determine statistical significance. Of note, the maximum recommended dose of colestipol is 16 g/d in divided doses; the average maximum tolerated dose among patients in this study was 4.5 g/d.

Patients receiving therapy with colestipol experienced a reduction in LDL-C of 13.4%, an increase in TGs of 18.9%, and a slight increase in HDL-C of 0.6%. These results are fairly consistent with the documented therapeutic effects of colestipol showing

a decrease in LDL-C of 15% to 30%, an increase in HDL-C of 3% to 5%, and either no change or an overall increase in TGs. Overall, study patients tolerated therapy with colestipol fairly well. Two patients reported constipation following dose titration of colestipol; however, this was resolved with a reduction to the previously tolerated dose. Additionally, no patients experienced an increase in LFTs following initiation of colestipol. Eight patients had persistently elevated LFTs, due to alcohol use or hepatitis, which remained stable throughout therapy with colestipol. Education regarding the proper administration of colestipol, in relation to other medications, was documented in only 26% of patients. This is an important counseling point in order to minimize any potential interference with the absorption of other essential medications.

Studies have demonstrated that pharmacist involvement in patient care can lead to beneficial outcomes. One such study evaluated 40 men with hypercholesterolemia who were randomized to receive either pharmaceutical care (pharmacist-physician comanagement) or standard care by a physician alone. Patients in the pharmaceutical care group received education from a pharmacist regarding hypercholesterolemia, colestipol-dose titration, and adverse-effects management. After 52 weeks of colestipol therapy, the pharmaceutical care group achieved greater LDL-C reductions than the standard group (16% vs 9.4%), and more patients in the pharmaceutical care group achieved their LDL-C goal (29.4% vs 5.0%, $P < .5$).[10] Therefore, this may represent an opportunity for pharmacists to fill a vital role to ensure that the appropriate counseling is provided and documented.

There are several limitations to this study, including its retrospective design. Based on the study's inclusion and exclusion criteria, most notably, the occurrence of any change in antihyperglycemic medications during the 3-month period before or after the initiation of colestipol, a small number of patients were ultimately included in the study. This small study population may have limited the ability to decisively determine statistical significance for a number of the study endpoints. External validity of the study results is also limited, given the entirely male and elderly study population. Additionally, a lack of documentation regarding patient compliance, outside medications, and concurrent diet and exercise programs may influence the study outcomes. To minimize these limitations, larger prospective studies, with a longer observation period, are needed to fully evaluate the effect of colestipol on glycemic control.

## CONCLUSION

Overall, therapy with colestipol for additional LDL-C lowering in patients with type 2 diabetes resulted in an average overall A1C reduction of 0.24% ($P < .0001$). The results of this study contribute to the growing evidence supporting the use of bile acid sequestrants as adjunctive therapy in patients with type 2 diabetes. Although agents with more evidence of improved glycemic control should be used first, as recommended by the ADA, providers may consider the use of colestipol in patients with type 2 diabetes who need additional LDL-C lowering despite optimal doses of statins or intolerability of other agents.

### *Author disclosures*

*The authors report no actual or potential conflicts of interest with regard to this article.*

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