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Atypical Mechanism of Glucose Modulation by Colesevelam in Patients with Type 2 Diabetes

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ABSTRACT: Colesevelam's glucose-lowering mechanism of action is not completely understood. Clinical trials of colesevelam suggest that its mechanism, and often adverse effects, differ from those of other oral antidiabetes drugs. Colesevelam does not affect insulin sensitivity (unlike thiazolidinediones), insulin secretion (unlike sulfonylureas and meglitinides), or early insulin response or glucagon (unlike dipeptidyl peptidase-4 inhibitors). Colesevelam may have some effect on glucose absorption, but likely via a different mechanism than α-glucosidase inhibitors. Colesevelam and metformin have similarities regarding hepatic glucose production, but divergent effects on gluconeogenesis versus glycogenolysis, suggesting differing mechanisms of drug action for improving glycemic control. Colesevelam is thought to be a portal glucagon-like peptide-1 (GLP-1) secretagogue with primarily hepatic effects. Bile acid binding by colesevelam leads to TGR5 activation, increased secretion of GLP-1 or other incretins, and inhibition of hepatic glycogenolysis. Colesevelam's mechanism of action appears to be atypical of other antidiabetes medications, making it a potentially suitable component of many combination regimens in the treatment of type 2 diabetes.

KEYWORDS: colesevelam, type 2 diabetes mellitus, pharmacology

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Introduction

In type 2 diabetes mellitus (T2DM), a prevalent disease characterized by chronic hyperglycemia, the function of β-cells responsible for insulin secretion declines progressively together with increasing insulin resistance in target cells. Treatment options for T2DM include oral antidiabetes drugs (eg, the biguanide metformin, sulfonylureas, meglitinides, thiazolidinediones, dipeptidyl peptidase-4 [DPP-4] inhibitors, α-glucosidase inhibitors, bromocriptine, and the bile acid sequestrant colesevelam), and noninsulin injectable agents (eg, glucagon-like peptide-1 [GLP-1] receptor agonists), as well as insulin replacement therapy for patients who do not achieve goals on noninsulin therapy or who experience symptomatic hyperglycemia.[1,2]

The mechanisms of action vary among the different classes of antidiabetes drugs, allowing for use of agents with different and complementary mechanisms of action in patients with T2DM who require combination therapy.[1,2] Colesevelam is a polymeric bile acid sequestrant initially used as a lipid-lowering therapy. It is comprised of a polymer backbone with numerous hydrophobic side chains that were specifically added to enhance the binding of bile acids. These side chains make colesevelam differ structurally from conventional bile acid sequestrants and result in a high-affinity, high-specificity, and high-capacity for binding bile acids.[3] Colesevelam is not absorbed systemically and is excreted unchanged entirely through the gastrointestinal system.[4] Colesevelam was later found to have beneficial effects on glycemic control in T2DM, leading to its approval by the US Food and Drug Administration for this indication. However, its mechanism of action for glucose lowering is not completely understood. A number of studies in animal

models have contributed to the current hypotheses regarding the mechanism. Colesevelam increased portal levels of the incretin hormone GLP-1 in mice and rats with diet-induced obesity (DIO).[5,6] In mice, this effect was shown to be mediated by activation of TGR5 in the colon by bile acids bound to colesevelam. GLP-1 signaling led to suppression of hepatic glycogenolysis and improved hepatic glucose metabolism in DIO mice.[5] The glycemic effects of colesevelam may also be attributable in part to increased glucose clearance via reduced activity of the farnesoid X receptor (FXR), as observed in obese diabetic mice.[7] In a murine model of genetic obesity, colesevelam improved glucose homeostasis, but this effect was not observed in mice with FXR deficiency.[8]

In addition to these nonclinical studies, a number of clinical studies have also contributed to the current understanding of the glucose-lowering mechanism of colesevelam.[9] The purpose of this article is to review the relevant findings of these clinical studies in more detail and consider the putative mechanism of glycemic effects of colesevelam in light of the mechanism of action of other antidiabetes drugs.

Insulin Sensitivity

Insulin resistance is a key component of the pathophysiology of T2DM;[10] therefore, one approach to treating T2DM is to increase insulin sensitivity. Thiazolidinediones improve insulin resistance by increasing insulin-stimulated glucose disposal in skeletal muscle.[11]

A number of clinical trials involving colesevelam included assessments that provide insight into whether an effect on insulin sensitivity is relevant to colesevelam. A 16-week study comparing the effects of adding colesevelam, sitagliptin, or rosiglitazone to existing metformin therapy in subjects with T2DM showed a significant reduction from baseline in index of insulin resistance estimated by homeostatic model assessment (HOMA-IR) with rosiglitazone (–1.305; $P = 0.0085$), but not colesevelam or sitagliptin.[12] Colesevelam also had no effect on HOMA-IR in placebo-controlled studies in subjects with T2DM in which study medication was added to metformin-, sulfonylurea-, or insulin-based therapy (unpublished data).[13,14] In additional placebo-controlled studies that measured insulin sensitivity in subjects with T2DM using the insulin clamp method, colesevelam had no effect on peripheral or hepatic insulin sensitivity.[15,16] Similarly, colesevelam had no effect on insulin sensitivity measured by an extended glucose tolerance test in a study involving men with the metabolic syndrome.[17]

In addition to these measurements of insulin resistance/sensitivity, assessments in the placebo-controlled studies of colesevelam when added to metformin-, sulfonylurea-, or insulin-based therapy included parameters with relevance to insulin resistance. In these studies, colesevelam had no effect on fasting insulin level (unpublished data),[13,18] which may be used as a marker for insulin resistance,[19] levels of adiponectin (unpublished data),[13] which decreases insulin resistance,[20] or fasting levels of free fatty acids (unpublished data), which induce insulin resistance.[21]

Colesevelam is not associated with weight gain and edema, adverse effects that are known to occur with thiazolidinediones.[22,23] Together with the findings regarding the lack of effect on insulin sensitivity, these observations suggest that the mechanism(s) of glucose lowering by colesevelam is not similar to those of thiazolidinediones.

Insulin Secretion

Another key component of the pathophysiology of T2DM is impaired function of beta cells and reduced secretion of insulin.[10] Insulin secretagogues such as sulfonylureas and meglitinides treat T2DM by enhancing insulin release by the pancreas.[2]

A number of clinical trials included assessments that provide insight into whether colesevelam effects insulin secretion. In two studies in subjects with T2DM receiving colesevelam or placebo for 8 or 12 weeks, there were no significant differences between treatments in change from baseline in area under the curve for insulin following a meal tolerance test.[15,16] Administration of colesevelam for 12 weeks also had no effect on insulin secretion, as estimated using the oral minimal model, in subjects with T2DM.[24]

Furthermore, as noted above, colesevelam had no effect on fasting (unpublished data)[13,18] or postprandial[18] insulin levels in placebo-controlled studies in subjects with T2DM in which study medication was added to metformin-, sulfonylurea-, or insulin-based therapy.

Colesevelam is not associated with weight gain or an increased incidence of hypoglycemia, adverse effects that are known to occur with insulin secretagogues.[25] Together with the findings regarding the lack of an effect on insulin secretion, these observations suggest that the mechanism(s) of glucose lowering by colesevelam is not similar to sulfonylureas and meglitinides.

Glucose Absorption

Another approach to the treatment of hyperglycemia in T2DM is to inhibit the absorption of glucose from dietary sources. α-Glucosidase inhibitors are intestinal absorption inhibitors that delay the digestion and absorption of carbohydrates by competitively binding to α-glucosidase enzymes.[2,26]

A number of clinical trials involving colesevelam included assessments that provide insight into whether an effect on glucose absorption is relevant to colesevelam. Long-term administration of colesevelam, compared with placebo, did not affect glucose absorption (as indicated by area under the glucose curve [AUC_g]) following an oral glucose or meal tolerance test in studies in subjects with T2DM.[15,16] In addition, a study assessing glucose absorption based on appearance rate in subjects with T2DM showed that colesevelam had no effect on the appearance of meal-derived glucose compared with placebo.[14]

However, other studies indicate possible effects upon glucose absorption, likely via a mechanism that differs from that of α-glucosidase inhibitors. In subjects with impaired fasting glucose, post–meal tolerance test incremental AUC_g was reduced with colesevelam (from 249.3–198.8 mmol/L × min; $P < 0.01$). No gastrointestinal-derived peptides were altered except for cholecystokinin, which showed an increase in incremental AUC (from 43.2–127.1 pM × min; $P < 0.01$).[27] Marina et al suggested that the increase in cholecystokinin may have been associated with slowed gastric emptying. Gastric emptying was not assessed in their study,[27] but a previous study showed that colesevelam moderately delayed gastric emptying versus placebo in subjects with diarrhea-predominant irritable bowel syndrome, although the difference was not significant.[28] Smushkin et al[24] suggested decreased intestinal absorption or increased hepatic uptake of glucose as the explanation for the reduction in the integrated rate of meal appearance they observed with colesevelam compared with placebo in subjects with T2DM (5191 vs 5817 mmol/kg/6 h; $P = 0.04$). In patients with long-standing T2DM, diabetic gastroparesis may also affect the postprandial glucose profile.[29]

While α-glucosidase inhibitors are associated with diarrhea as an adverse effect,[2] colesevelam is instead associated with constipation. Together with the studies assessing the effects of colesevelam on glucose absorption, these observations suggest that while colesevelam may have some effect on glucose absorption, its effects are otherwise not similar to those of α-glucosidase inhibitors.

Early Insulin Response/Glucagon

In T2DM, loss of the first phase insulin response to glucose is among the first detectable effects of beta-cell dysfunction,[30] while hypersecretion of glucagon contributes to glucose dysregulation.[31] DPP-4 inhibitors increase insulin secretion and decrease glucagon secretion (both glucose-dependent).[2]

A number of clinical trials involving colesevelam included assessments that provide insight into whether an effect on early insulin response or glucagon is relevant to colesevelam. In a placebo-controlled study in subjects with T2DM, colesevelam did not restore first-phase insulin response or disposition index, a measure of β-cell function; in addition, plasma glucagon levels were unaffected.[24] In another study in subjects with impaired fasting glucose, results from a frequently sampled intravenous glucose tolerance test followed by a meal tolerance test showed no effect of colesevelam on insulin sensitivity index (ISI), acute insulin (AIRg), C-peptide, proinsulin responses to glucose, or disposition index (the product of AIRg and ISI). In addition, plasma glucagon levels were unaffected.[27] Thus, these findings suggest that the mechanism(s) of glucose lowering by colesevelam is not like that of DPP-4 inhibitors.

Hepatic Glucose Production

Excessive hepatic glucose production contributes to fasting hyperglycemia in T2DM.[32] Biguanides, including the widely used metformin, decrease hepatic glucose production.[2]

A number of clinical trials involving colesevelam included assessments that provide insight into whether an effect on hepatic glucose production is relevant to colesevelam. In subjects with T2DM, administration of colesevelam versus placebo resulted in a reduction of fasting glucose levels (7.0 vs 6.6 mmol/L; $P = 0.004$) and a corresponding reduction of postprandial glucose levels (3145 vs 2896 mmol/6 h; $P = 0.01$).[24] The shape of the postprandial glucose curve did not change, but was shifted down after colesevelam treatment, suggesting an effect on hepatic glucose production. Another study in subjects with T2DM showed that colesevelam had no effect on hepatic gluconeogenesis, and glycogenolysis in the fasting state increased significantly in the placebo group ($P = 0.05$ vs baseline), but not in the colesevelam group, although the treatment difference was not significant.[14]

These observations suggest that while there may be certain similar aspects to the mechanisms of colesevelam and metformin with both having hepatic effects, the divergent effects on gluconeogenesis versus glycogenolysis still suggest that the glucose-lowering mechanism(s) of colesevelam differs from that of metformin.

Effects on Incretins

The effects of colesevelam described above could potentially be related to an effect on incretins. Studies indicate that administration of GLP-1 or a GLP-1 receptor agonist, or increasing GLP-1 levels via DPP-4 inhibition, results in reduced fasting endogenous glucose production, due to a reduction in glycogenolysis, and increased hepatic glucose disposal.[33–35]

A number of studies have explored the effects of colesevelam on incretins. In a study in T2DM, colesevelam versus placebo showed an increase in fasting total GLP-1 (least-squares mean treatment difference 1.0 pM; $P < 0.05$) (unpublished data). Another study showed a significant increase from baseline in fasting total GLP-1 with colesevelam (from 18.3–21.9 pM; $P = 0.006$), although the increase was not significant compared with placebo.[24] In a third placebo-controlled study in T2DM, colesevelam increased fasting total GLP-1 (treatment difference 10 pM; $P < 0.05$), postprandial total GLP-1 AUC (8 pM × min; $P < 0.01$), and total glucose-dependent insulinotropic polypeptide AUC (13 pM × min; $P < 0.001$). The increase in GLP-1 may have caused the effect on hepatic glycogenolysis observed with colesevelam in this study.[14] Although the liver lacks GLP-1 receptors, hepatic glycogen synthesis has been shown to be regulated via GLP-1 receptors in the brain.[36]

An increase from baseline in 2-hour postprandial GLP-1 levels (from 64 to 72 pM; $P = 0.015$), but not preprandial or

1-hour postprandial levels, has also been seen with administration of the bile acid sequestrant colestimide in subjects with T2DM.[37]

Putative Mechanism of Colesevelam

Based on the observations discussed, the mechanism of action of colesevelam appears to be unlike that of other antidiabetes medications. Since the pharmacological rationale for combination therapy is to use agents from different pharmacological classes and/or with complementary mechanisms, our observations suggest that colesevelam is potentially a good partner for many of the currently available oral antidiabetes drugs and injectable antidiabetes drugs (including insulin and GLP-1 agonists). Based on both nonclinical and clinical evidence, colesevelam is thought to be a portal GLP-1 secretagogue, with effects primarily on the liver. Current evidence suggests that bile acid binding by colesevelam results in activation of TGR5, a G protein-coupled receptor for bile acids, leading to the increased secretion of GLP-1 or other incretins and inhibition of hepatic glycogenolysis (unpublished data).[14,24,38]

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Contributed to the writing of the manuscript: OMN, MRJ. Agree with manuscript results and conclusions: OMN, MRJ. Jointly developed the structure and arguments for the paper: OMN, MRJ. Made critical revisions and approved final version: OMN, MRJ. Both authors reviewed and approved of the final manuscript.

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As a requirement of publication the authors have provided signed confirmation of their compliance with ethical and legal obligations including but not limited to compliance with ICMJE authorship and competing interests guidelines, that the article is neither under consideration for publication nor published elsewhere, of their compliance with legal and ethical guidelines concerning human and animal research participants (if applicable), and that permission has been obtained for reproduction of any copyrighted material. This article was subject to blind, independent, expert peer review. The reviewers reported no competing interests.

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