Bile Acid Sequestrants and Diabetes: Introduction and Overview to the Supplement

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Abstract

Diabetes is a global epidemic. The recommended goals for glycated hemoglobin (HbA1c), low-density lipoprotein cholesterol (LDL-C), and blood pressure are achieved only in a very small minority of patients. In this supplement to *Metabolic Syndrome and Related Disorders*, we review the data showing that the bile acid sequestrant colesevelam lowers both HbA1c and LDL-C in patients with diabetes. These data make colesevelam an attractive therapy to get more patients to achieve their LDL-C and HbA1c goals.

Introduction

DIABETES IS A MAJOR health-care problem globally, and in the United States alone at least 24 million people have diabetes. Furthermore, the prevalence is increasing in both men and women of all ages.¹ Diabetes, especially type 2 diabetes, confers a 2-4 risk of cardiovascular death and stroke. In fact, cardiovascular disease is the leading cause of mortality in diabetic patients.

The American Diabetes Association (ADA) recommendations for glycemia for all diabetes include fasting plasma glucose in the range of 70–130 mg/dL, a postprandial glucose of less than 180 mg/dL, and a glycated hemoglobin (HbA1c) level below 7%. However, the evidence base with regard to diabetes would support a multipronged approach targeting glycemia, lipids, and blood pressure.² Table 1 shows the author's targets for treatment.³

Although the ADA goals also include a triglyceride level of <150 mg/dL and an high-density lipoprotein cholesterol (HDL-C) level >40 in males and >50 mg/dL in females, this author does not believe there is a sufficient evidence base to target triglycerides except under certain scenarios.⁴ Also whereas it is desirable to optimize HDL-C levels, the evidence base to support this endeavor with pharmacotherapy remains to be established in diabetes.

The recent publication by Holman,⁵ which was a follow up of the United Kingdom Prospective Diabetes Study (UKPDS) at 10 years, revealed a benefit of intensive glucose lowering, including a 15% reduction in myocardial infarction ($P=0.014$) and a 13% reduction of death from any cause ($P=0.0007$), arguing for a legacy effect.

It is startling that given the advances that we have seen with regard to the evidence base for targeting blood pressure, low-density lipoprotein cholesterol (LDL-C), and HbA1c that only 12.2% of people with diabetes meet all three goals (HbA1c <7%, blood pressure <130/80, and LDL-C <100 mg/dL).⁶

The divide between the clinical trial data and clinical practice and the emerging role of the bile acid sequestrants (BAS) in diabetes have prompted this supplement to *Metabolic Syndrome and Related Disorders*.

Papers in This Supplement

Dr. Staels reviews potential glucose-lowering mechanisms for BAS in patients with diabetes. He focuses largely on the nuclear receptor farnesoid X receptor (FXR) and on the G-protein-coupled membrane receptor TGR5 activated by bile acids. He points to the beneficial effect of the BAS colesevelam in increasing the incretin, glucagon-like peptide-1 (GLP1), as a potential mechanism for lowering glucose levels.

Dr. Levy reviews the literature with regard to the three placebo control studies that show clearly colesevelam therapy compared to placebo results in the reduction of HbA1c and LDL-C in diabetic patients on insulin, metformin, and sulfonylurea-based therapies. This was also confirmed in the pooled analysis.⁷

Dr. Ganda's review article provides an excellent assessment of the recent advances in the management of type 2 diabetes focusing largely on the LDL-C and HbA1c goals. He points to the benefit of additional therapy with colesevelam.

TABLE 1. TARGETS FOR FORESTALLING VASCULAR COMPLICATIONS IN DIABETES

Glycated hemoglobin (HbA1c)	<7%
Blood pressure	<130/80 mmHg
Low-density lipoprotein cholesterol (LDL-C)	<100 mg/dL ^a
Non-high-density lipoprotein cholesterol (HDL-C)	<130 mg/dL ^a

^aThe LDL-C and non-HDL goals for diabetics with cardiovascular disease should be <70 mg/dL and <100 mg/dL, respectively.

Finally, Dr. Handelsman provides a summary and a view of future directions with respect to the use of colesevelam in the treatment of diabetes.

Conclusion

This supplement provides a state-of-the-art update of the underappreciated use of BAS in diabetes treatment, given their benefit with regard to two of the major goals that we target in our diabetic patients—HbA1c <7% and LDL-C cholesterol <100 mg/dL. Furthermore, it should be pointed out⁷ that, in addition to reducing HbA1c and LDL-C, BAS such as colesevelam have also been shown to reduce non-HDL-C, apolipoprotein B levels, and high-sensitivity C-reactive protein (hsCRP) levels. Given the recent interest in the role of CRP after the Jupiter Study showed the benefit of the concomitant reduction LDL-C and hsCRP, this might emerge as an additional advantage for colesevelam therapy.⁸

We hope that this supplement will provide a useful guide to health-care providers for understanding the rationale for using BAS such as colesevelam in the treatment of diabetes, particularly because it has the attraction of reducing both LDL-C and HbA1c.

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Author Disclosure Statement

Dr. Jialal is on the Advisory Board and Speaker for Merck-Schering Plough and also serves on the Advisory Board for Daiichi Sankyo, Inc.

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