Killing Two Birds With One Stone, Maybe
CETP Inhibition Increases Both High-Density Lipoprotein Levels and Insulin Secretion

Sergio Fazio, MacRae F. Linton

Connections between glucose and lipid metabolism have long been recognized. It is well known that impaired glucose metabolism, particularly in diabetes mellitus, influences plasma levels of both apoB- and apoAI-containing lipoproteins and induces an abnormal lipid phenotype known as atherogenic dyslipidemia. This is characterized by high triglycerides, low high-density lipoprotein (HDL), and elevated low-density lipoprotein (LDL) particle concentration attributable to a preponderance of smaller-sized LDL. These effects are seen as secondary to the insulin-resistant state and caused by its interference with the lipid homeostatic mechanisms, including increased secretion of apoB-containing lipoproteins and reduced lipolysis of triglyceride-rich particles. However, a direct influence of primary abnormalities in lipid metabolism on glucose homeostatic mechanisms is not commonly recognized, with the exception of subjects with extreme hypertriglyceridemia caused by lipoprotein lipase deficiency, where diabetes mellitus may develop during periods of uncontrolled dyslipidemia, and control of glucose levels is achieved by adjustment of triglycerides. Although lipotoxicity is known to harm many tissues and cells, the presence of common dyslipidemia is not considered as a risk factor for changes in insulin sensitivity by liver, muscle, or adipose tissue, or in insulin production by the pancreatic beta cell.

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significantly decreased HbA1c levels irrespective of type and dose of antidiabetic agent used, more effectively in patients with a recent diagnosis of diabetes, and proportionally to the rate of reduction in triglyceride levels.14 Finally, infusion of reconstituted HDL has been shown to increase insulin secretion and improve glucose metabolism in subjects with diabetes mellitus.15 However, no guidelines to date have endorsed the use, or suggested avoidance, of antilipidemic medications as tools for diabetes mellitus prevention. The strongest evidence for a positive link between glucose and lipid metabolism at the therapeutic level is the recent demonstration that 1 of the bile acid–binding resins, colesevelam, is capable of inducing an HbA1c level drop of half a point, while reducing LDL by 15% during a 6-month period in subjects with type 2 diabetes on sulfonylurea therapy.16 This led to the Food and Drug Administration approval of this agent indicated for the control of both plasma cholesterol levels in hypercholesterolemia and glucose levels in diabetes mellitus.

Therefore, it is important to monitor carefully the appearance and evolution of adverse or beneficial effects on glucose metabolism when developing new categories of lipid medications, some of which have recently come to market or are undergoing phase 3 clinical testing. In this context, cholesteryl ester transfer protein (CETP) inhibitors are agents that can cause extreme changes in lipid metabolism, increasing HDL cholesterol levels by as much as 140% and reducing LDL levels by as much as 40%.17 By inhibiting CETP in plasma, these agents prevent the natural exchange of lipids between HDL and the apoB-containing lipoproteins, therefore, disallowing the discharge of cholesterol cargo from the HDL. However, the CETP inhibitors have had a troubled history so far, as the first 2 molecules failed to make it into the market, by a long shot. The first one, torcetrapib, was tested in a series of trials, the most important of which was a clinical outcome study (Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events [ILLUMINATE]) interrupted before the end of the first year for excess of cardiovascular events attributed to the medication.18 Because of the several off-target effects of torcetrapib, the general consensus was that a different CETP inhibitor molecule with a cleaner safety profile might have a better chance of demonstrating vascular benefits. However, a second drug, dalcetrapib, was recently withdrawn from the pipeline after the demonstration of no clinical effects in a large clinical trial when used in addition to atorvastatin.19 Work in this area continues with 2 additional CETP inhibitors currently under evaluation in large clinical trials.20

The silver lining on the CETP clinical program thus far has been the recognition of a possible beneficial effect on diabetes. Indeed, the ILLUMINATE study provided proof that among patients with diabetes, subjects taking torcetrapib had significant lower HbA1c and glucose levels than patients taking atorvastatin only.21 However, no significant differences were seen in new-onset diabetes among those without the disease at baseline. However, no effects on fasting glucose or HbA1c levels were found in the DAL-outcomes study, a larger study and of longer duration than ILLUMINATE, and where new-onset diabetes rates were similar between those who were taking CETP inhibitors and those who were only taking the statin.16,22 Therefore, it still remains unclear whether CETP inhibition may be a promising intervention for modulation of glucose homeostasis, either for full therapeutic use in patients with diabetes or as an additional benefit should this drug category manage to get FDA approval for dyslipidemia.

The article of Siebel et al23 published in the current issue of Circulation Research adds to the information on this subject using a different CETP inhibitor and different conditions from those of large randomized clinical trials. The authors gave 1 dose a day of an oral CETP inhibitor to a group of healthy volunteers for a period of just 14 days. The CETP inhibitor, as expected, increased HDL cholesterol levels by 46% and also reduced LDL significantly (by 32%). They found that postprandial insulin levels were significantly increased among subjects taking the CETP inhibitor. This was supported by an upward trend in C-peptide levels and occurred in the absence of changes in postprandial glucose and incretin levels. In addition, plasma from subjects exposed to the CETP inhibitor for 14 days showed increased ability to extract insulin and cholesterol from mouse pancreatic beta cells (MIN6N8) that were pretreated with oxidized LDL, but the effect was seen only after glucose stimulation, and not under basal conditions. This effect was not attributable to the CETP inhibitor, per se, but rather the consequence of the increased HDL levels in plasma of treated subjects. This is in agreement with the long-held knowledge that CETP activity does not correlate with parameters of insulin sensitivity.24 Overall, the study supports the notion that a short-term exposure to a CETP inhibitor, enough to produce the expected large changes in HDL and LDL levels, is capable of influencing glucose metabolism in ways that may be either beneficial or negative for metabolic and vascular health. Although it is tempting to consider higher insulin secretion rates from beta cells as measure of improved glucose regulatory ability, it must be kept in mind that increased insulin levels have been related to cardiovascular risk,25,26 and that overproduction of insulin from beta cells in the absence of changes in incretin levels may be indicative of accelerated beta cell metabolism and may be a predictor of future loss of beta cell mass and diminished insulin–producing capacity after prolonged periods of therapy.27 This issue is particularly important considering that the in vitro studies were done using an insulinoma cell line, which already produces large amounts of insulin at baseline when no effects from the CETP inhibitor treatment were seen. The increase in insulin production after glucose stimulation from cells that make excessive amounts of insulin at baseline again may indicate a dysregulated, unhealthy overproduction of insulin that may harm both metabolism and the vasculature over time. Thus, we may be learning how to use 1 stone to kill 2 birds, raising HDL and coaxing insulin secretion, but we are unsure whether either of these birds should instead be left alone.

A final observation is about the nature of the study: a very short-term investigation of a small group of normal individuals, using low-tech approaches and simple in vivo and in vitro determinations. This is a reminder that even in the era of mega-trials, insightful contribution to drug development and biological discovery can be achieved with a small data set and only few weeks of work. However, the small N and the large variability in some of the assays represent critical limitations to the strength of the conclusions. Therefore, these findings
are hypothesis generating at best, though worthy of further exploration in prospective trials.

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