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.1 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.2 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.

In the past few years, this general concept has been challenged with the recognition that membrane cholesterol levels regulate insulin exocytosis from beta cells. In particular, the absence of the main cellular cholesterol transporter, ABCA1, drastically reduces insulin output.3,4 Because ABCA1 controls the first step in the extracellular process known as reverse cholesterol transport, mediated by the circulating HDL particle, this suggests that natural or drug-induced changes in HDL metabolism or composition may influence the ability of beta cells to respond to physiological stimuli, including glucose. Hence, it is possible that in some instances diabetes mellitus development may be accelerated or induced by low or non-functional HDL.5

At a therapeutic level, medications that control diabetes by and large are expected to improve the lipid profile, an effect which is seen as a consequence of improved glucose homeostasis and not as a direct effect of diabetes medications on lipid metabolism. In particular, thiazolidinediones and metformin cause significant reductions in the plasma levels of triglycerides and total cholesterol.6,7 Interestingly though, the HDL effects on glucose regulation and homeostasis are much more subtle, or nonexistent. Interventions that modulate plasma lipid levels are also known to interfere with glucose homeostasis, with effects ranging from negative, such as induction of diabetes in subjects without the disease, to beneficial, such as improved HbA1c levels in patients with diabetes. In particular, large meta-analyses have convincingly shown that chronic statin therapy is associated with a small but significant excess risk of new-onset diabetes, in the range of 2% per year more than that predicted by common risk factors.8,9 The mechanism of action of the statins on glucose metabolism has not been identified but may be related to modulation of insulin secretion by the beta cell.10 Another widely used lipid-lowering agent, niacin, has long been recognized to exert a negative influence on glucose and uric acid metabolism. However, this effect has recently returned prominently to the attention of clinicians with the presentation of data from a large randomized clinical trial, HPS2-THRIVE, which tested the effectiveness of extended-release niacin plus an antiflush agent (lanopristin) in addition to simvastatin (+/− ezetimibe) in the prevention of cardiovascular events in subjects with stable coronary artery disease (CAD). Although no vascular benefits of extended-release niacin were evident, the adverse event profile showed a very significant negative effect on new-onset diabetes (an increase of ≈25%, from 7.1% incidence in the control group to 9.3% among those taking niacin).11 Again, the mechanisms responsible for this effect on glucose metabolism are not established, given the multiple actions of niacin, but may be related to the increase in HDL levels or to changes in membrane cholesterol levels in the pancreatic beta cell.12 The fibrates, commonly used for management of hypertriglyceridemia, may also have beneficial effects on the incidence of diabetes mellitus. In particular, bezafibrate use has been found associated with significantly reduced rates of new-onset diabetes mellitus in comparison with other fibrates or no medication use in a large retrospective study (34% risk reduction).13 In addition, prospectively designed use of bezafibrate for 24 weeks
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.\textsuperscript{14} Finally, infusion of reconstituted HDL has been shown to increase insulin secretion and improve glucose metabolism in subjects with diabetes mellitus.\textsuperscript{15} However, no guidelines to date have endorsed the use, or suggested avoidance, of antilipemic 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.\textsuperscript{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, cholesterol 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\%.\textsuperscript{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.\textsuperscript{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, dalcevetrapib, was recently withdrawn from the pipeline after the demonstration of no clinical effects in a large clinical trial when used in addition to atorvastatin.\textsuperscript{19} Work in this area continues with 2 additional CETP inhibitors currently under evaluation in large clinical trials.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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 al\textsuperscript{23} 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.\textsuperscript{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,\textsuperscript{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.\textsuperscript{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.

Disclosures
The authors were partially supported by the National Institutes of Health (NIH) grants HL106645 and HL79886 (to S. Fazio), and NIH grants HL105375 and HL111945 (to M.F. Linton).

References

Key Words: Editorials • beta cell • CETP inhibitors • HDL • insulin
Killing Two Birds With One Stone, Maybe: CETP Inhibition Increases Both High-Density Lipoprotein Levels and Insulin Secretion

Sergio Fazio and MacRae F. Linton

_Circ Res._ 2013;113:94-96
doi: 10.1161/CIRCRESAHA.113.301832

_Circulation Research_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2013 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/113/2/94

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation Research_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation Research_ is online at:
http://circres.ahajournals.org//subscriptions/