

Opinion on Improving Diabetes Outcomes: Beyond Glucentricity

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Opinion

One hundred years have passed since the discovery of insulin—an achievement that transformed diabetes from a fatal illness into a manageable chronic condition. The decades since that momentous achievement have brought ever more rapid innovation and advancement in diabetes research and clinical care. To celebrate the important work of the past century and help to chart a course for its continuation into the next, the Canadian Institutes of Health Research's Institute of Nutrition, Metabolism and Diabetes and the U.S. National Institutes of Health's National Institute of Diabetes and Digestive and Kidney Diseases recently held a joint international symposium, bringing together a cohort of researchers with diverse interests and backgrounds from both countries and beyond to discuss their collective quest to better understand the heterogeneity of diabetes and thus gain insights to inform new directions in diabetes treatment and prevention. This article summarizes the proceedings of that symposium, which spanned cutting-edge research into various aspects of islet biology, the heterogeneity of diabetic phenotypes, and the current state of and future prospects for precision medicine in diabetes.

Alteration in glucose homeostasis is the sine qua none of diabetes. Independent of the type of diabetes, all individuals with diabetes shares some perturbation in the ability to maintain glucose within a specified range. Not surprisingly, glucose regulation has been a key focus in understanding disease pathogenesis and progression as well as the target of diabetes interventional trials. Indeed, the seminal clinical trials in diabetes during the past 15 years (the Diabetes Control and Complications Trial, the U.K. Prospective Diabetes Study, and the Diabetes Prevention Program) have all given core attention to glucose regulation, either as treatment or prevention. All three trials have demonstrated the wisdom and benefit of an approach that addresses glucose control. Yet a focus on glucose alone is an incomplete approach to the care of individuals with diabetes. The profound impact of improving other disturbances in diabetes has become clear during the past 10-15 years; it is no longer adequate to address only glucose control.

In this issue of *Clinical Diabetes*, attention is given to an additional common attribute of diabetes: dyslipidemia [1]. The authors provide what may superficially appear to be differing views on cholesterol management that, in the end, are quite complementary and functionally similar in their call for increased statin use. Peters argues that attention should be given to non-HDL cholesterol (calculated as total cholesterol minus HDL cholesterol), whereas Nesto encourages attention to LDL cholesterol as the primary target while conceding the value of the approach that Peters champions [2].

As both Peters and Nesto point out, individuals with diabetes traditionally do not have LDL cholesterol levels that are much different from those without diabetes who are matched on appropriate variables (i.e., age, sex, and BMI).

Yet the LDL in those with diabetes appears to be characterized by a larger number of small, dense particles rendering the LDL more atherogenic. This key awareness should either encourage more aggressive cholesterol management in individuals with seemingly "normal" LDL or perhaps, as Peters advocates, more attention to both LDL and triglycerides as the combined non-HDL cholesterol index, which should be controlled to 30 mg/dl above the LDL goal, or 130 mg/dl. It is difficult to predict whether and when additional refinement of recommendations (from an LDL focus to a broader, non-HDL focus) will become the standard or whether the interest in non-HDL cholesterol is just passing fashion. Regardless, given the cardiovascular morbidity in diabetes and the salutary effect of lowering cholesterol with statins in particular, attention to dyslipidemia must be a central focus of diabetes care and improvement initiatives [3,4].

Two such improvement initiatives are also highlighted in this issue of *Clinical Diabetes*. The authors call attention to a culturally tailored educational initiative targeting self-care behaviors and depression in an underserved Hispanic population and the authors describes a broader effort among family physicians in Florida to improve diabetes care. Both efforts share a desirable attribute of measuring outcomes beyond glycemic control (Shahady's group measures both LDL and non-HDL cholesterol, whereas Anderson's group measures only LDL cholesterol).

Another key attribute of both improvement initiatives, and of most effective quality improvement initiatives, is the systematic and continuous monitoring of important variables. One point Peters highlights is the difficulty of reliably and accurately measuring LDL cholesterol in the subset of diabetes patients who are not fasting and have substantial hypertriglyceridemia.

Although this point is rendered moot for clinics that directly measure LDL cholesterol, many laboratories do not routinely provide this service, or the cost of such service is considerable. This difficulty in measurement, for the subset of individuals with diabetes who are non-fasting with significant hyper triglyceridemia, is one of the more compelling reasons to consider non-HDL cholesterol as the marker of dyslipidemia in our patients. Conversely, the robustness of the interventional data (contrasted with the wealth of observational data cited in Peters' article) in support of efforts to lower LDL cholesterol argues for monitoring LDL cholesterol as the primary marker of dyslipidemia in diabetes. An approach that combines both by focusing on LDL first but defaulting to non-HDL cholesterol when patients are not fasting and have significant hyper triglyceridemia is also sensible.

No matter which argument or combination of arguments may seem compelling, attention to dyslipidemia at the individual and/or the population level is a crucial aspect of diabetes care. A focus on glycemic control alone is no longer de rigueur [5].

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