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Implications for Glucose Measures in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study

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Each day in the U.S. approximately 5,200 people are diagnosed with diabetes. Thirty-three people with diabetes progress to end-stage renal disease, 230 will have diabetes-related amputations, and 55 will become blind (1). There is a substantial loss of life expectancy, mostly from cardiovascular disease (CVD) (1–3). While it is generally accepted that elevations in glucose concentration (e.g., hyperglycemia) predict micro- and macrovascular outcomes in both type 1 and type 2 diabetes, it is unclear what measure of hyperglycemia is most strongly related to adverse outcomes (1–4). Over the last two decades, there has been much work to define various strategies that reduce the risk of these complications and to what extent targets may maximally reduce the risk of complications such as retinopathy, nephropathy, or CVD. However, the majority of this work used glycated hemoglobin (HbA_{1c}) as a biomarker of the degree of hyperglycemia to predict long-term outcomes such as proteinuria, proliferative retinopathy, myocardial infarction, heart failure, or stroke. Recently, there has been an increasing interest in exploring other biomarkers of glycemia in risk prediction for complications related to morbidity and mortality in people with diabetes (5–8). In this regard, there has been work to explore the relative merits of glycated albumin versus measurement of HbA_{1c} in risk prediction for morbidity and mortality in those with kidney disease (5) and in comparing traditional fasting glucose measures with HbA_{1c} biomarkers for prediction of CVD (6). This has led to the natural question regarding how various measures of glycemia predict risk for both micro- and macrovascular complications related to diabetes.

In this issue, Nathan et al. (7) report data from the Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) study on the interrelationship of various glucose biomarkers of short-, intermediate-, and long-term glycemia on microvascular and macrovascular complications (8). The authors used a case-control design derived from subjects enrolled in the DCCT/EDIC, wherein 497 subjects of the original 1,441 had shorter term glycemic measures obtained in addition to HbA_{1c}. The study was powered for a net risk reduction of 36% and yielded a need for 145 incident cases of albuminuria as defined by urine albumin excretion rate >40 mg/day, retinopathy as defined by a validated scale through the Early Therapy Diabetic Retinopathy Scale research group, or CVD as previously defined outcomes for EDIC (8). The modeling approach employed various techniques to explore the interrelationships of HbA_{1c}, glycated albumin, and data derived from a seven-point blood glucose profile for glucose variability among the individual measures and then with each of the a priori designated outcomes. In essence, the authors report that within the individual glycemic measures glycated albumin and HbA_{1c} were strongly associated, while glycated albumin, but not

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See accompanying original article, p. 282.

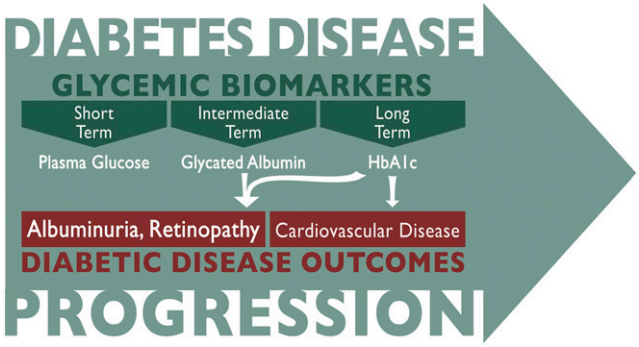

Figure 1—Nathan et al. (7) provide compelling data to suggest the combination of glycated albumin and HbA_{1c} strengthens the association with microvascular end points such as nephropathy (e.g., albuminuria) and retinopathy (e.g., nonproliferative retinopathy). The strength of this association was stronger than that for CVD and implies that a glycemic staging system may be especially useful for understanding diabetes microvascular disease progression such as kidney and eye disease.

HbA_{1c} alone, tended to trend with individual glucose profiles. The findings of the interrelationships are not entirely surprising, but exploration of the various measures with the various outcomes provides new and provocative information.

Nathan et al. report that HbA_{1c} and albumin predict retinopathy and nephropathy to a greater extent than mean blood glucose values derived from the profile and the combination strengthened the association with retinopathy but not nephropathy. The authors suggest these differences may be a result of the inherent differences in disease progression and/or their response to sustained hyperglycemia. One potential confounder in the studies of HbA_{1c} could potentially be the inclusion of individuals with kidney disease and the reduced cycling of hemoglobin. However, DCCT/EDIC controlled for this with a primary or secondary prevention strategy targeting individuals with either no albuminuria at baseline or with microalbuminuria (e.g., albumin excretion rate $<$40 mg/day or $<$200 mg/day, respectively). Consequently, no individuals with advanced kidney disease were included.

Another point of interest is the finding that HbA_{1c} as well as mean blood glucose, but not glycated albumin, were associated with CVD outcomes. It is not surprising that HbA_{1c} had a strong association with CVD, but it is rather intriguing that mean blood glucose was also associated with this adverse outcome. D'Antonio et al. (4) suggest glucose measures do not predict long-term CVD outcomes to the degree HbA_{1c} does. These results are more likely due to a sampling issue wherein only a few incident cases of CVD occurred during the DCCT where both glycated products were measured (7). This was appropriately acknowledged by the authors in the context of the weaker association of glycated products (e.g., hemoglobin and albumin) with CVD relative to retinopathy and nephropathy. Further, the authors suggest the very compelling notion that glycated products may have more to do with intrinsic diabetes disease progression (e.g., retinopathy and nephropathy) than glycemia has in its relationship to CVD, where powerful CVD risk factors such as hypertension, obesity, or dyslipidemia may dilute the impact of hyperglycemia. Here again, this weaker association, in part, might also be due to a sampling size issue as the authors point out. Indeed, readers should realize that the current results are based on a passive secondary analysis and that prospective validation is needed to more definitively explore the difference in glucose measures and even glucose variability on diabetes complications.

A novel and potentially translational finding of this investigation is the notion that the type of glucose biomarker measurement has some intrinsic relationship to metabolic memory in understanding the natural micro- and macrovascular disease progression in patients with type 1 diabetes (Fig. 1). In this regard, the fact that glycated products (e.g., albumin and hemoglobin) reflect disease activity and progression is not surprising given the adverse impact of glycation of proteins (5,9). However, the results of this study should remind us of similar data from the UK Prospective Diabetes Study (UKPDS) wherein the strength of the association of HbA_{1c} with macrovascular end points was greatly attenuated compared with the risk associated with microvascular end points (10). We now have two studies that would suggest the strength of HbA_{1c} to predict long-term CVD outcomes is not as great as the strength to predict shorter term microvascular outcomes such as retinopathy or kidney disease. The observation in Nathan et al. (7) that the addition of glycated albumin to that of HbA_{1c} improved the association of hyperglycemia to retinopathy and nephropathy mirrors findings in type 2 diabetic patients where the addition of glomerular filtration rate to albuminuria enhances the prediction of chronic kidney disease progression (11). Indeed, including both albuminuria and estimated glomerular filtration rate augments risk prediction, and the combination of both biomarker risks is useful in staging chronic kidney disease progression (12). This might suggest the

consideration that adding glycated albumin to clinical care may improve risk stratification of diabetes to a similar extent to that observed in stratification of those with kidney disease. Further, this work might set the stage for consideration of a glycemic staging system for diabetes.

In summary, despite a secondary analysis of a cohort using an analytic approach that is limited to demonstrate a correlation with no understanding of population attributable risk, Nathan et al. (7) provide a unique insight into how various glucose measures may predict disease progression. Further, findings from the investigation suggest the utility of using two markers in assessing risk prediction and possible stratification of disease progression.

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