EDITORIAL (SEE HERMAN ET AL., P. 2453)

A1C: Does One Size Fit All?

Diabetes specialists almost uniformly nod their heads when I ask whether they see patients whose A1C results don't match their blood glucose monitoring data. Providers used to attribute that to unreliability of the monitors or the patient records, but technological advances overcame those barriers. Some mismatches can be attributed to inadequate temporal distribution of glucose sampling, and those will be easier to define as continuous glucose monitoring is used more widely, but a substantial number still remain unexplained. That has led to a controversy as to the role of remaining sources of variation in A1C in the routine patient in whom there is no obvious condition known to influence A1C values, i.e., hemoglobinopathy, red cell disorder, or renal failure known to alter either mean age of circulating red cells or hemoglobin chromatographic properties; or the rare drug that modifies A1C by a variety of mechanisms. Without such pathology, does the fact that such variation remains suggest that our standard A1C goals for glycemic control do not in fact fit all individuals with diabetes? Is it indeed valid to equate A1C and mean blood glucose as has become common?

There is one view that proposes a "high glycator–low glycator" hypothesis (1–9) to explain how apparently equivalent glycemic control could result in differing A1C values. The hypothesis is based on the observation that while most individuals in a population with a given mean blood glucose will have A1C within a fairly narrow expected range, there are subsets who have a consistently higher or consistently lower value. These could be due to corresponding alterations either in the relative rate of intracellular glycation or deglycation or in the rate of hemoglobin (red cell) turnover. How large a problem does this have to be to have widespread clinical implications? Even if only 5% of all people in the U.S. with diabetes exhibited this, it would conservatively represent >1 million people. From my own patients, I suspect it is far more common.

Our lab has established a paradigm not in terms of comparison of A1C with a direct measure of glucose but rather of A1C with another integrated measure of glycemic control, glycated serum proteins measured as fructosamine, to overcome the limitations of blood glucose sampling frequency and time distribution. While we have been taught that A1C and glycated serum proteins are measures that reflect glycemic control over different time periods, when patients are at steady state—as they probably are most of the time—the temporal factors cancel out, and there can be an extraordinarily tight correlation within an individual (8). When looked at in this way, 23% of subjects had A1C >1 percentage point higher and 17% had A1C >1 percentage point lower than the value predicted from simultaneously drawn glycated serum proteins. Results within individuals are fairly consistent over time. We referred to this as a glycation gap between the results of an intracellular (A1C) and an extracellular (fructosamine) protein target of glycation or an integrated measure of glycemic control. The within-subject inconsistency of two precise measures of glycemic control supports the validity of the high glycator–low glycator hypothesis, i.e., physiologic as opposed to technical causes for differences in A1C. We have shown the glycation gap to be linked to nephropathy status in a small population in which we did not detect an association with A1C.

Others suggest that the remaining variation in A1C is relatively small (10) and technical in nature such that by improved standardization of the A1C assay, coupled with continuous glucose monitoring, one size should fit all. Indeed, the A1C, when measured accurately, is a close reflection of glycemia in the vast majority of otherwise normal patients. This school of thought has expressed skepticism of the high glycator–low glycator hypothesis and questions the need for this concept (11,12). If they are right for 85% of people, that leaves 3 million in the U.S. with diabetes whose A1C does not fit the one size.

As pointed out by Genuth et al. (11) and Lachin et al. (12), it is not valid to look on glycation gap or hemoglobin glycation index, which autocorrelate with A1C, as determinants themselves of risk for diabetes complications unless they can be shown to be independent of A1C in a particular analysis. However, they are measures of the variance in the predictor of complications, A1C, which are not shared between A1C and another test of glycemic control. Some of the underlying mechanisms could potentially be shared in common between A1C determination and the pathophysiology of diabetes complications and some not, and that distinction is critical to how it affects A1C interpretation. We have argued that glycation gap permits assignment of the source of risk associated with A1C between glucose- and nonglucose-related mechanisms (9). At the American Diabetes Association's 67th Scientific Sessions (22–26 June 2007, Chicago, IL), our laboratory showed data demonstrating, with a new highly precise technique for red cell survival determination, that much more variation in A1C in hematologically normal people can be explained by differences in the mean age of circulating red cells than is currently appreciated (13). We have also shown data suggesting interindividual differences in how the steady-state concentration of sugar in the red cell relative to that outside the red cell relates to differences in the level of hemoglobin glycation (14). Either of these findings—the first seemingly not linked to the mechanisms of complications and the latter potentially linked—would lead to the expectation of subtle but clinically important variations in the relationship of mean blood glucose to A1C. It is intriguing to speculate, if they become delinked in GLUT1-regulated (noninsulin-regulated) tissues, which would be the more valid biological determinant: the measure of extracellular glucose or of intracellular glucose?

In this issue, Herman et al. (15) use an extremely valuable population to extend this observation about variability that clinicians make empirically everyday on A1C to a systematic comparison among racial and ethnic groups. They found that A1C values among those who met oral glucose tolerance test screening criteria for entry into the recent type 2 Diabetes Prevention Program differed by race between whites, blacks, Hispanics, American Indians, and Asians, even after accounting for the effects of a host of potential covariates. The authors make a key

rhetorical point early in RESULTS that, while certain of the covariates were higher in one group and lower in another group than in whites, A1C was consistently lower in whites than in any of the other groups; the biggest difference from the mean ± SD white A1C (5.80 ± 0.44%) was in blacks (6.19 ± 0.59%)—0.4 percentage points that would affect clinical decisions with notable frequency—with lesser differences in Hispanics (5.89 ± 0.46%), Asians (5.96 ± 0.45%), and American Indians (5.96 ± 0.46%).

While studies have compared A1C among races before, this is really the most unequivocal comparison claiming differences by race that cannot be explained by either glycemic control or socioeconomic or demographic variables likely linked through glycemic control. Before we examine the details, I want to point out that this finding really represents a triumph for the NIH (National Institutes of Health) policy over the last 10–15 years, requiring substantial representation of racial and ethnic groups—where appropriate for the disease process—in NIH-sponsored large clinical studies. Without that, this study likely would not have had the prerequisite population. This scientific benefit from the federal diversity policy portends other important evidence about racial differences in biology as other such analyses reach fruition.

Still, regardless of whether the variance is associated with race or with one or several of the other covariates, it is critical to convert this clinical correlation to mechanism(s) for the various sources to logically translate the clinical guidelines for glycemic control arising from predominantly white (the Diabetes Control and Complications Trial and the UK Prospective Diabetes Study) and Japanese (the Kumamoto Study) populations to all people.

What are the strengths and limitations of these findings? Strengths of the study include the large size and diversity of the population with the use of a common protocol and core lab. Limitations include the small number of glucose data points from a single day on each subject, although interday variation should be less in this population than in one with frank diabetes. Further limitations result from the difficulty in parsing the covariates (age, BMI, and blood pressure) for whether they are mediated through a glycemic control–related versus nonglycemic control–related mechanism. The glucose and insulin parameters most clearly reflect the plasma glucose to which the red cell was exposed, whereas sex most likely does not.

What do these racial differences mean in practice, and how do these results relate to the clinical issues set out earlier in this editorial? Understanding that some differences in A1C by race are not explainable by glycemic control is critical to evaluating an individual A1C result and interpreting studies where A1C has been used as the sole measure of glycemic control; a between-group difference in A1C may not necessarily be explained by a difference in glycemic control. These results also provide additional evidence that factors besides glucose are important determinants of A1C in many individuals with diabetes even without specific confounders. Racial differences imply an extension of the findings of Snieder et al. (16), who reported that a substantial portion of the variance in A1C is heritable within a predominantly white U.K. population. In contrast, glycated serum protein levels are not heritable, speaking to the difference from A1C in their underlying determinants (9). As a result, the glycation gap provides a means for narrowing down what fraction of A1C is heritable. This will not affect the ability to interpret longitudinal changes in A1C, which is the linchpin of the Diabetes Control and Complications Trial, the UK Prospective Diabetes Study, and the Kumamoto Study. However, differences in A1C between people have to be looked on with increasing skepticism.

Is it as simple as taking the results concerning race from a study like this and superimposing them on the results of previous glycemic control versus complications studies to achieve new guidelines? No. While race is significant, it accounts for only about one-third of the variance in A1C represented by the covariates and race together. Again, it will become far easier to understand these issues when the mechanisms accounting for the variance associated with race and the other markers are clearer.

In summary, the work by Herman et al. is an exceedingly important contribution to a field where there is controversy that has largely flown below the radar but has important clinical and public policy implications: How hard do we push each person with diabetes toward the tightest control, and should we use the same guidelines in all? We currently individualize goals of glycemic control for subsets of the population, the very young, the elderly, and those with a heavy burden of other intercurrent illness. It remains to be seen whether we need to refine this by race or whether perhaps simple tests will become available as the key mechanisms become clear and prove necessary to simplify A1C interpretation and its implications for each of our patients, whatever their size.

ROBERT M. COHEN, MD

From the Division of Endocrinology, Metabolism, and Diabetes, Department of Medicine, University of Cincinnati, Cincinnati, Ohio; and Medical Service, Cincinnati Veterans Affairs Medical Center, Cincinnati, Ohio.

Address correspondence to Robert M. Cohen, MD, University of Cincinnati Medical Center, P.O. Box 670547, Cincinnati, OH 45267-0547. E-mail: robert.cohen@uc.edu.

R.M.C. holds stock in Novartis and Medtronic.

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