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Race Differences in Long-Term Diabetes Management in an HMO

Response to Hart

We read Dr. Hart's (1) response to our article with great interest. The issue of racial differences in the presence of variant hemoglobins that may affect HbA_{1c} (A1C) test results is certainly an important one. Ours (2) was a retrospective analysis using electronic medical record data that did not contain information on either the presence of sickle hemoglobin or the results of patient self-monitoring of blood glucose (SMBG) testing. However, because we found persistent differences in A1C lab values by race, even when controlling for individual-level A1C at baseline in our multivariate analyses, we do not believe the presence of sickle hemoglobin in 8% of our population would eliminate the racial disparities we observed. Still, the issue of measurement raised by Dr. Hart is worthy of discussion. Because of possible variations in the calculation of A1C over time, we ran several diagnostic tests on our A1C measures to test for systematic differences in measurement over time by race. While we did not identify shifts in A1C by race, we did find a shift in A1C values for the entire cohort midway through our study period due to a change in the calculation of A1C by an external vendor. As stated in our article (2), we adjusted for this change using statistical techniques and found no race-based differences in the effect of this adjustment.

We agree with Dr. Hart that a combination of patient SMBG and A1C results represents a better standard for assessing actual control. Unfortunately, rates of SMBG testing in this population were below optimal and were particularly low for black patients. Furthermore, information from patient SMBG is not consistently recorded in the medical record. For this reason, we are now exploring strategies for increasing SMBG among all diabetic patients, especially black patients. We are also exploring interventions that would incorporate patient data from both lab A1C testing and SMBG values in clinical decisions.

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Testing the Accelerator Hypothesis: Body Size, β-Cell Function, and Age at Onset of Type 1 (Autoimmune) Diabetes

Response to Dabelea et al.

The contribution by Dabelea et al. (1) to the growing debate on the accelerator hypothesis is an important one, but I wonder if there is a confounder that has not been accounted for in the reasoning. The report revolves principally around Fig. 2, which shows, after appropriate adjustments, a clear inverse relationship between age at diagnosis and BMI (the acceleration predicted) among those whose fasting C-peptide (FCP) levels lay below the median, but none among those whose FCP lay above. The difference is interpreted to mean that any relationship to insulin resistance applies only to a subset of type 1 diabetic children with low β-cell reserve.

The accelerator hypothesis argues that "type 1 and type 2 diabetes are the same disorder of insulin resistance, set against different genetic backgrounds" (2). It predicts a general inverse relationship between BMI (surrogate for insulin resistance) and age at diagnosis and identifies three accelerators that determine the rate at which the β-cell mass declines during life: constitution (genes/gestation), insulin resistance (lipotoxity and antigenicity), and immune response (HLA) genotype (response to insulin resistance–induced antigenicity).

The one adjustment that was not made to the regressions in Fig. 2 of Dabelea et al.'s report may be the crucial one: the HLA genotype. Those children who

fulfilled the prediction were younger than those who did not. The younger the type 1 diabetic child at diagnosis, the more likely he/she is to carry high-susceptibility HLA genes (3), and so it is possible, even probable, that the proportion of children carrying high-susceptibility HLA genes was greater in the younger group than in the older group. Reactive HLA genes are the third accelerator of β-cell loss, and presenting the data in this way may serve to support the hypothesis for the entire group, rather than qualify it according to FCP.

The only difference between the behavior of the two groups in Fig. 2 may be one of tempo, and while the age range studied was sufficient to demonstrate the predicted inverse relationship in the younger group carrying more intensely reactive HLA genes, it may not have been wide enough to demonstrate the corresponding relationship for the older group carrying less reactive genes. An age range spanning many decades may be needed where the tempo is slower. DNA is available to the SEARCH study, and it will be interesting to learn in due course whether the distribution of HLA genotypes was indeed different between the two groups.

The accelerator hypothesis has now been subject to the scrutiny of several independent cohort studies. The Birmingham study mentioned by Dabelea et al. was small and of mixed race. (The relationship between BMI and insulin resistance is different between children of Asian and European descent [4].) The racial distribution of the children in Dabelea et al.'s study is not detailed but may be important. Two other U.K. studies of almost exclusively white children (5,6) and a large European study involving many thousands of predominantly white children (7) have all shown the predicted inverse relationship between age at onset and BMI on simple univariate regression. Furthermore, a German study involving 920 children with type 1 diabetes shows the same (8), and a study of pre–type 1 diabetic children from Australia suggests that the more insulin resistant the child, the more rapidly he/she progresses to type 1 diabetes (9). Longitudinal studies will be important to further elucidate the accelerator hypothesis, as Dabelea et al. suggest, but the real test will be a randomized controlled trial to reduce insulin resistance in at-risk children of type 1 diabetes.

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Testing the Accelerator Hypothesis: Body Size, β-Cell Function, and Age at Onset of Type 1 (Autoimmune) Diabetes

Response to Wilkin

We thank Dr. Wilkin (1) for his valuable comments. Overall, we (2) did not observe the hypothesized association between increasing BMI and younger age at onset of diabetes among U.S. youth with autoimmune diabetes. Our results were similar to a report from Birmingham, U.K. (3), and one from Philadelphia (4). They were in contrast to three previous European studies (5–7). However, we did observe the inverse association among youth with low residual insulin secretion at diagnosis (fasting C-peptide [FCP] <0.5 ng/ml). We hypothesize that obesity is "accelerating" the onset of the disease at a later stage in the natural history of the diabetes process, after substantial autoimmune destruction of β-cells has occurred.

The discrepancy between our results and those of the European studies may be due to several factors. It is possible that youth in Europe are diagnosed at a later stage in their natural history, when most have low residual FCP. This cannot be addressed, since these studies did not measure FCP. In the U.S., diagnosis may occur at an earlier stage in the natural history, before complete β-cell destruction occurs. Evidence for this exists, since a lower proportion of cases now present in diabetic ketoacidosis than previously reported (8,9). In these youth, acceleration, as assessed using age at clinical diagnosis, may be impossible to document since the time of true disease onset is uncertain.

Dr. Wilkin suggests that the two groups of youth in our Fig. 2 have different HLA genes. According to Dr. Wilkin, a higher proportion of high-risk HLA genes would trigger a more intense insulin resistance–induced autoimmune destruction. This hypothesis is testable in longitudinal studies starting before the onset of autoimmunity. We have collected HLA genotype data in SEARCH; however, none of the previous cross-sectional reports, including the current