Editorial

It's Not Black and White: Individualizing Metformin Treatment in Type 2 Diabetes

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The treatment of type 2 diabetes is algorithmic. Given a new diagnosis of type 2 diabetes, professional organizations offer a series of competing guidelines which share, as a common denominator, suggestions for both the initiation of therapy and subsequent escalation, depending on the ability of the prescribed regimen to achieve prespecified treatment goals (1, 2). At the top of all algorithms stands the generic drug metformin, which is safe, cheap, and effective; therefore, it is universally prescribed as the first-line agent in the treatment of type 2 diabetes, barring unusual contraindications. More recent recommendations have attempted to individualize treatment based on personal characteristics (3), but metformin remains in a pre-eminent position, and the prescriber's assessment of suitability is necessarily subjective. This practice persists despite emerging evidence that metformin is not equally effective in everyone (4, 5). Thus, there is an urgent need to increase our granularity in type 2 diabetes therapeutics, so that precision medicine can guide the right prescription for the right patient at the right time. The paper by Williams et al (6) in this issue of the *JCEM* represents one step in that direction.

Williams et al (6) examined whether response to metformin differs in European American or African American patients with type 2 diabetes by comparing change in glycated hemoglobin (HbA_{1C}) in enrollees in the Henry Ford Health System in southern Michigan. They made use of the electronic health records to identify 19 672 patients with diabetes taking metformin, among whom 7429 individuals self-identified as being African American and 8783 identified themselves as being European American. Participants had to have at least two HbA_{1C} measurements while on metformin. The authors calculated the total daily dose of metformin exposure based on prescription information, normalized it to the allowed maximal dose (850 mg thrice daily, or 2550 mg), and derived 120-day windows to reflect the average lifespan of a red blood cell. They then used a variety of statistical models based on generalized estimating equations with repeated measures to examine the impact of metformin exposure on the outcome HbA_{1C}, before and after adjustment for several relevant covariates such as patient age, sex, race/ethnicity, duration of time on treatment, baseline HbA_{1C} level, and concomitant use of other diabetes medications (ie, similarly obtained exposure measures for meglitinides, sulfonylureas, thiazolidinediones, fast-acting insulin, and slow-acting insulin). They included interaction terms for self-reported ethnicity and conducted additional stratified analyses to confirm the observed effects. The authors found that African American patients were younger and had a higher HbA_{1C} at baseline; a greater proportion of African American patients were women. They were also less likely to receive dipeptidyl peptidase-4 inhibitors and more likely to receive insulin. In every statistical model, African Americans were shown to be more responsive to metformin in terms of a change in HbA_{1C}, even after adjusting for all relevant covariates.

This provocative finding, if confirmed, would define African Americans as more likely metformin responders when compared to European Americans. Given the retrospective and uncontrolled nature of this exploration, however, great caution must be exercised to ensure that the observed differences are not the result of unmeasured confounders, and the authors take this valid concern to heart.

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Abbreviations: BMI, body mass index; HbA_{1C}, glycated hemoglobin.

One potential confounder relates to the initial glycemic state of the participants. It is well known that response to metformin is dependent on glycemic state, with greater response shown by those with higher glucose levels, greater insulin resistance, or heavier body mass index (BMI). The authors attempt to account for this by adjusting for baseline BMI and HbA_{1C}, which was higher in African American participants (BMI was measured only in a small subset). However, it is possible that such adjustments are not sufficient to capture the overall glycemic status (eg, insulin resistance, or fasting glucose), such that the observed effect is still driven by glycemia and not race/ethnicity. In this scenario, race/ethnicity may be serving as a proxy for a level of glycemia or metabolic state that is imperfectly captured by baseline HbA_{1C}, and thereby subject to residual confounding. Indeed, in population cohorts, African Americans have been found to have a higher average HbA_{1C} than their White counterparts (7, 8), a difference that is ascribed to glycemic factors (7). Nevertheless, the consistency of the observed differences at every stratum of HbA_{1C} in the current study suggests that the phenomenon is not just driven by initial glycemic state.

A second crucial potential confounder concerns concomitant antidiabetic therapy. The authors adjusted their analyses for all other antihyperglycemic medications, but European American and African American participants differed in their use of insulin. Incorporating insulin use derived from electronic medical records or prescription data into statistical models is inherently difficult, because insulin has an essentially continuous distribution of dosages and a variable number of daily injections; thus, it remains possible that African American participants had a greater HbA_{1C} reduction because of more intense concomitant insulin use, not fully captured by the authors' statistical adjustments. To address this possibility (as well as the issue of disparate baseline HbA_{1C} raised above), the authors conducted a sensitivity analysis in which only patients on monotherapy were studied, and they were further matched for baseline HbA_{1C} and duration of follow-up. Although the sample size was greatly reduced when defining this narrow cohort, and thus statistical power was limited, the magnitude and direction of the observed differences were consistent with the results obtained in the full cohort.

A third obvious potential confounder might arise from the known differences in medication adherence between ethnic groups, because these same authors have noted that African American patients in their health care system tend to have lower measures of adherence (9). Here, the authors obtained measures of metformin exposure based on the timing, number of pills, and doses of each metformin prescription and have thus performed a reasonable job of trying to account for these differences. In any case, given the lower documented adherence level shown for African American patients in previous studies, if there were any residual confounding, their greater glycemic response shown here would indicate an underestimation of the true effect.

This study's strengths include the focus on a single, clinically relevant hypothesis; the availability of a very large cohort in which to carry out these analyses with adequate statistical power; the examination of a single health care system to ensure homogeneity of measurements; similar numbers in both ethnic groups; a thoughtful inclusion of appropriate covariates; and the use of a variety of statistical approaches to test the robustness of the findings. To bolster the authors' contention that their finding is real, they note that in the Diabetes Prevention Program, African American participants randomized to metformin had a greater reduction in diabetes incidence than White participants (44 vs 24%), although the differences were not statistically significant (10).

Assuming that the finding is real, a key question still remains: what is the nature of the mechanism for these differences? Are they due to environmental (social, cultural) or biological (genetic, metabolic) factors? This distinction is critical in health disparities research, in that the former might be more amenable to public health interventions, whereas understanding the latter might guide fundamental lines of physiological investigation. In this regard, the population history of African Americans represents a research opportunity. African Americans constitute a classical admixed population, where both African and European ancestries contribute to varying degrees in each individual, with the proportion of African ancestry typically ranging from 50 to 100%, and reaching 80–85% on average. Furthermore, each African American person's genome is a mosaic, where the segments derived from African or European descent vary in their location, as they are defined by that person's lineage and specific recombination history. Thus, if the greater response to metformin is driven by genetic factors that correlate with African descent and not by the environmental circumstances of African Americans, one could perform a study in African American participants only, with individual global proportion of African ancestry as the independent variable and metformin response as the outcome. Such ancestry proportions can now be estimated from a limited number of ancestry-informative markers, or genetic polymorphisms that display large allele frequency differences across continental groups (11); this could then be combined with admixture mapping to identify the areas of the genome responsible for the observed association (12, 13).

The first element of this approach has been attempted for a related measure, basal HbA_{1C} in nondiabetic African Americans (14). Although the proportion of European ancestry was inversely correlated to the HbA_{1C} level, it explained < 1% of the total variance in the trait. Whether the effects on *treated* HbA_{1C} (ie, affected by metformin response) will be much larger than those observed on *native* HbA_{1C} remains to be seen. Emerging evidence suggests that metformin response is approximately 30% heritable (15), and genetic polymorphisms associated with metformin response are beginning to be identified (16). Establishing that the improved metformin response in African Americans is due to specific genetic variants that are more prevalent in people of African descent could shed light on the elusive molecular target of metformin, illuminate its mechanism of action, and guide the development of related therapeutic agents. Furthermore, it could also serve to stratify the population into high and low responders a priori; identifying low responders to metformin could direct therapeutics, by adding (or substituting) a second agent upfront, or testing whether such low responders might tolerate higher doses of metformin while achieving comparable efficacy (17).

If the improved response to metformin in African Americans is confirmed, whatever its mechanism, two other clinical corollaries come to mind: first, given that the association of HbA_{1C} with hard clinical endpoints is comparable in people of European or African ancestry (18, 19), metformin may have a more beneficial impact on preventing diabetic complications in the latter group; and second, metformin might be particularly effective in African American youth with type 2 diabetes, although a sub-analysis of the TODAY study indicates that this may not be the case, perhaps due to differences in the genetic architecture of type 2 diabetes in this age group (5).

In the end, practitioners should remember that the differences observed here were not black and white: it is not as if Blacks experienced a complete response to metformin whereas Whites had a null response. African Americans had an average reduction in HbA_{1C} of 0.9% compared to 0.42% in European Americans, such that metformin was also effective in this latter population. In addition, self-reported race/ethnicity (or the prescriber's perception of such a construct) is a poor proxy for the biological or genetic determinants of drug response, because many African Americans could carry the variant that predicts a poor response and vice versa, as shown recently for the use of interferon-α in hepatitis C (20). Therefore, an intelligent deployment of precision medicine will require confirmation that this differential effect is real, determination of the factors underlying the difference, and direct measurement of such factors beyond the simple use of self-reported race/ethnicity as the proxy variable on which to base clinical decision-making.

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