New Insights Into the Genetics of Glycemic Response to Metformin

Ewan R. Pearson

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Metformin is one of the most commonly prescribed medications in the world, with 25 million prescriptions in England in the last year alone (data are from https://openprescribing.net) for a population of 56 million people. Metformin has been in clinical use for >60 years, yet despite this, or probably because of this, the mechanism(s) for how metformin lowers glucose remains unclear. Population genetic studies have transformed our understanding of the etiology of most common and rare diseases. It follows that population pharmacogenetic studies should provide insight into variation in glycemic response to metformin, which can be attributed to variation in pharmacokinetics and pharmacodynamics of the medication. This might allow us to better understand how metformin works, enabling more targeted drug treatments or the identification of who is likely to respond or not respond.

Unlike common disease and trait genetics, where it is now not uncommon to see genetic studies of more than 1 million people, pharmacogenetic studies in general are much smaller, are less powered, and have had limited success when considering common diseases and medications. It should be noted that this is not the case for genetics of rare disease, severe adverse drug reactions, drug metabolism, and anticancer treatments, where pharmacogenetics is increasingly making its way into clinical care. For metformin, there have been three genome-wide association studies (GWAS) published to date reporting on HbA_{1c} change in people with type 2 diabetes (1–3), with additional GWAS reporting on the genetic interaction with metformin and diabetes prevention (4) and acute response to metformin in people without diabetes (5). Of these, only the loci at *NPAT/ATM* and *SCL2A2* have been replicated.

In this issue of *Diabetes Care*, Wu et al. (6) report a further GWAS of glycemic response to metformin. The discovery GWAS used data from 447 African Americans, with replication undertaken in 353 African Americans and 466 European Americans. A genome-wide variant, rs143276236, in gene *ARFGEF3*, replicated in the African American cohort but not in the European American population. This is the first GWAS to focus discovery on an African American population, with previous metformin GWAS being predominantly in populations of White European or mixed ethnicity. This, of course, is important to ensure precision medicine findings are not limited to the European population and may identify ancestry-specific variants that would not be detected in a White European population. The variant identified is an intronic single nucleotide polymorphism (SNP) in a gene, *ARFGEF3*, that has a plausible connection to glucose metabolism, as it is expressed in α-cells and β-cells and its knockout in mice is associated with increased insulin granule content and increased insulin secretion. The mechanism whereby rs143276236 alters metformin response is unclear and follow-on mechanistic studies are needed, but this study, like the previous GWAS, provides potential novel insights into how metformin works to lower glucose in humans.

One area highlighted by this study that has important implications for pharmacogenetic studies is the challenge of defining a phenotype of drug response in diabetes studies. The focus here is specifically on glycemic response in patients with type 2 diabetes rather than acute response or prevention of diabetes. As outlined in Fig. 1, the U.K. Prospective Diabetes Study (UKPDS) and subsequent studies, like A Diabetes Outcome Progression Trial (ADOPT) (7) and Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE) (8), show that when a new medication is started there is a reduction in HbA_{1c} to a nadir between 6 and 12 months and then an inexorable deterioration in glycemic control that reflects the underlying diabetes disease progression, resulting in what is commonly referred to as the "Nike tick." The most-used measure of drug response is to simply measure the change from a pretreatment value to an on-treatment value measured at or close to the HbA_{1c} nadir (∼6–12 months) and to adjust for the baseline HbA_{1c} in a regression model. This method has merit because it captures the short-term response, which is only minimally confounded by underlying disease progression, and it is a simple definition that can be applied across populations. However, it is far from perfect: it will be confounded by lifestyle change at the time of medication initiation, which may well be marked for metformin, because it is often started at or close to diabetes diagnosis and will be affected by regression to the mean (9). Another approach would be to model

Division of Population Health & Genomics, University of Dundee, Dundee, U.K.

Corresponding author: Ewan R. Pearson, e.z.pearson@dundee.ac.uk

See accompanying article, p. 208.

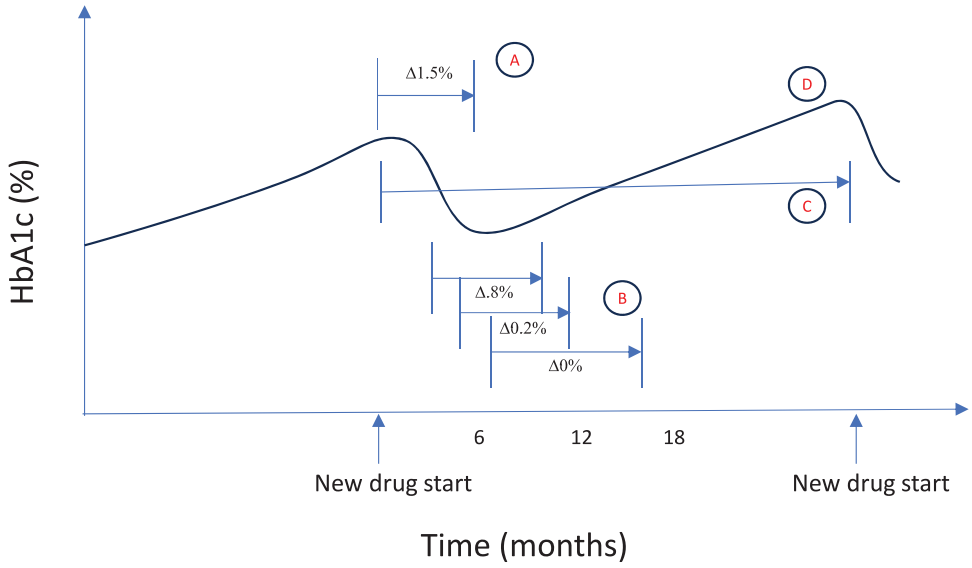

Figure 1—An illustration of how HbA_{1c} changes over time with initiation of new treatment. Each letter depicts different definitions of drug response: A, difference between pretreatment HbA_{1c} and on-treatment HbA_{1c} at 6–12 months; B, the approach used by Wu et al. (6), which relied on the difference between two on-treatment HbA_{1c} values at least 120 days apart and closest to initiation of medication; C, time to failure of medication, defined as initiation of next medication or a threshold HbA_{1c} reached; and D, a linear mixed model allowing for within-person slope prior to medication initiation.

time to failure of a medication, although it is difficult to disentangle drug effect from underlying disease progression. Probably the best approach, if sufficient data are available longitudinally, is to use a linear mixed model with many HbA_{1c} measures before and after medication initiation, as used by McGurnaghan et al. (10) for modeling dapagliflozin response. In the study by Wu et al. (6), two on-treatment HbA_{1c} measures are used at least 120 days apart, and the closest such pair to metformin initiation was used. This definition was largely determined by the lack of pretreatment HbA_{1c} measures but does show how, even without pretreatment measures, a measure of drug response can be derived from observational data. Supplementary Fig. 9 in their article nicely demonstrates how, as the window used to define metformin response shifts away from the initiation of metformin, the drug effect is attenuated, with much of the informative data coming from those patients with the first HbA_{1c} measure before 146 days after starting metformin, which explains why the overall HbA_{1c} reduction seen with metformin is low. The potential merits of this approach are that it may be less affected by regression to the mean caused by a randomly increased baseline measure. Importantly, Wu et al. (6) go on to investigate the interaction between drug dose (exposure) and HbA_{1c} change and report a significant interaction for rs143276236 and metformin exposure; the SNP effect was only observed in those receiving >425 mg/day of metformin. The use of such an interaction analysis provides strong support that the SNP is working to alter metformin response, and its effect is not independent of metformin.

The challenges of defining drug response are largely overcome by randomized controlled trials (RCTs), where the randomization removes the baseline differences and the ability to assess the genetic effect in an interaction with treatment allocation ensures that findings truly reflect a pharmacogenetic effect. To date, limited RCT trial data with genotyping have been made available to researchers, but this is changing. A recent pharmacogenetic study of glycemic response to glucagon-like peptide 1 receptor agonists included data from the Harmony trials (albiglutide) and the Assessment of Weekly Administration of LY2189265 (dulaglutide) in Diabetes (AWARD) studies (11), and the pharmacogenetic study of GRADE (8) is ongoing. These open the possibility of undertaking metanalysis of GWAS for RCTs of newer medications where genetic data are available, but these are likely to still be underpowered (only tens of thousands of individuals) and do not help us with older medications like metformin and sulfonylureas. With increasing availability of large biobanks, we should be able to supplement RCTs with large cohorts (potentially reaching up to 100,000 individuals) where drug response is defined from electronic medical record data that capture longitudinal drug exposure, HbA_{1c}, BMI, and other covariates. Hopefully the complementary meta-analyses of RCTs and large real-world data from biobanks will allow us to move diabetes pharmacogenetics closer to diabetes disease genetics, finding many robust replicated variants that inform on drug mechanisms and support a precision approach to diabetes care.

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