New Insights Into the Genetics of Glycemic Response to Metformin

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Commentary on Baojun et al. Genome-wide association study identifies pharmacogenomic variants associated with metformin glycemic response in African American patients with type-2 diabetes

Title: New insights into the genetics of glycaemic response to metformin

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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 from https://openprescribing.net) for a population of 56 Million people. Metformin has been in clinical use for over 60 years yet despite this, or probably because of this, the mechanism(s) for how metformin lowers glucose remain unclear. Population genetic studies have transformed our understanding of the aetiology of most common and rare diseases. It follows that population pharmacogenetic studies should provide insight into variation in glycaemic 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 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, 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 ADRs, drug metabolism, and anti-cancer treatments where pharmacogenetics is increasingly making its way into clinical care. For metformin, there have been three genome wide association studies published to date reporting on HbA1c 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 edition of *Diabetes Care*, Baojun et al report a further GWAS of glycaemic 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 a 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 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 in intronic in a gene, *ARFGEF3*, that has a plausible connection to glucose metabolism - it is expressed in alpha and beta-cells and 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 is working to lower glucose in humans.

One area highlighted by this study that has important implications for pharmacogenetic studies is the challenge of the defining a phenotype of 'drug response' in diabetes studies. The focus here is specifically on glycaemic response in patients with type 2 diabetes rather than acute response or prevention of diabetes. As outlined in the figure, the UKPDS and other subsequent studies like ADOPT [6] and GRADE [7] show that when a new medication is started there is a reduction in HbA1c to a nadir between 6 and 12 months and then an inexorable deterioration in glycaemic 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 pre-treatment value to an on-treatment value measured at or close to the HbA1c nadir (~6-12 months) and to adjust for the baseline HBA1c in a regression model. This has the merits that it is capturing the short-term response that is only minimally confounded by underlying disease progression and is a simple definition that can be applied across populations. But 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 as this is often started at or close to diabetes diagnosis, and it will be affected by regression to the mean [8]. Another approach would be to model time to failure of a medication, although this is difficult to disentangle drug effect from underlying disease progression. Probably the best approach, if sufficient data is available longitudinally, is to use a linear mixed model with many HBA1c measures before and after the medication initiation as used by McGurnaghan et al for modelling Dapagliflozin response [9]. In the study by Baojun et al, two on-treatment HBA1c measures are used at least 120 days apart, taking the closest such pair to metformin initiation. This definition was largely determined by the lack of pre-treatment HBA1c measures but does show how, even without pre-treatment measures, a measure of drug response can be derived from observational data. Supplementary figure S9 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 those patients with the first HBA1c measure before 146 days after starting metformin which explains why the overall HBA1c 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 Baojun et al. go on to investigate the interaction between drug dose (exposure) and HBA1c change and report a significant interaction for rs143276236 and metformin exposure; the SNP effect was only observed in those with >425mg/day of metformin. The use of such an interaction analysis provides strong support that the SNP is working to alter metformin response, not independently of metformin.

The challenges of defining drug response are largely overcome by randomised controlled trials – where the randomisation removes the baseline differences and the ability to assess the genetic effect in an interaction with treatment allocation ensures that findings do truly reflect a pharmacogenetic effect. To date, there has been limited RCT trial data with genotyping made available to researchers, but this is changing. A recent pharmacogenetic study of glycaemic response to GLP-1RA included data from the HARMONY studies (albiglutide) and the AWARD studies (Dulaglutide) [10]; and the pharmacogenetic study of GRADE [7] is ongoing. These open up the possibility of undertaking metanalysis of GWAS studies for RCTs of newer medications where genetic data is available, but these are likely to still be underpowered (10's of thousands only) and don't help us with older medications like metformin and sulphonylureas. With increasing availability of large biobanks, we should be able to supplement any RCTs with large cohorts (potentially reaching up to 100K individuals) where drug response is defined from electronic medical record data which capture longitudinal drug exposure, HbA1c, 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 mechanism and support a precision approach to diabetes care.

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References

1. GoDarts, et al., *Common variants near ATM are associated with glycemic response to metformin in type 2 diabetes.* Nat Genet, 2011. **43**(2): p. 117-20.
2. Rotroff, D.M., et al., *Genetic Variants in CPA6 and PRPF31 Are Associated With Variation in Response to Metformin in Individuals With Type 2 Diabetes.* Diabetes, 2018. **67**(7): p. 1428-1440.
3. Zhou, K., et al., *Variation in the glucose transporter gene SLC2A2 is associated with glycemic response to metformin.* Nat Genet, 2016. **48**(9): p. 1055-1059.
4. Li, J.H., et al., *Identification of Genetic Variation Influencing Metformin Response in a Multiancestry Genome-Wide Association Study in the Diabetes Prevention Program (DPP).* Diabetes, 2023. **72**(8): p. 1161-1172.
5. Li, J.H., et al., *Genome-wide association analysis identifies ancestry-specific genetic variation associated with acute response to metformin and glipizide in SUGAR-MGH.* Diabetologia, 2023. **66**(7): p. 1260-1272.
6. Kahn, S.E., et al., *Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy.* N Engl J Med, 2006. **355**(23): p. 2427-43.
7. Group, G.S.R., et al., *Glycemia Reduction in Type 2 Diabetes - Glycemic Outcomes.* N Engl J Med, 2022. **387**(12): p. 1063-1074.
8. Jones, A.G., et al., *Should Studies of Diabetes Treatment Stratification Correct for Baseline HbA1c?* PLoS One, 2016. **11**(4): p. e0152428.
9. McGurnaghan, S.J., et al., *The effect of dapagliflozin on glycaemic control and other cardiovascular disease risk factors in type 2 diabetes mellitus: a real-world observational study.* Diabetologia, 2019. **62**(4): p. 621-632.
10. Dawed, A.Y., et al., *Pharmacogenomics of GLP-1 receptor agonists: a genome-wide analysis of observational data and large randomised controlled trials.* Lancet Diabetes Endocrinol, 2023. **11**(1): p. 33-41.

Figure legend

An illustration of how HBA1c changes over time, with initiation of new treatment. Each letter depicts different definitions of drug response: A) Difference between a pre-treatment HbA1c and on-treatment HbA1c at 6-12 months; B) The approach used by Baojun et al. The difference between two on treatment HbA1cs at least 120 days apart, closest to initiation of medication; C) time to failure of medication defined as initiation of next medication, or a threshold HBA1c reached; D) A linear mixed model allowing for within person slope prior to medication initiation (ref x)