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Dorothy Hodgkin Lecture 2021: Drugs, genes and diabetes

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Abstract

Glycaemic response to metformin and sulphonylureas is heritable – with ~34%–37% of variation explainable by common genetic variation. The premise of this review is that by understanding how genetic variation contributes to drug response we can gain insights into the mechanisms of action of diabetes drugs. Here, I focus on two old drugs, metformin and sulphonylureas, where I would suggest we still have a lot to learn about their mechanism of action or their optimal use in clinical care. The fact that reduced function variants of the key transporter that takes metformin into the liver (OCT1) do not alter glycaemic response to metformin suggests that metformin does not need to get into the liver to work. A subsequent GWAS of metformin response identifies a robust variant that alters GLUT2 expression – which may support increasing evidence that metformin works primarily in the gut. For sulphonylureas, observation from patients with neonatal diabetes due to activating K_{ATP} channel mutations treated with sulphonylureas identified a novel role for sulphonylureas to enable β-cell incretin response. This work led to recent studies of low-dose sulphonylurea (20 mg gliclazide) in T2DM, which identified that at this dose sulphonylureas augment the incretin effect and increase β-cell glucose sensitivity, without increasing hypoglycaemia risk. This work, prompted by studies in monogenic diabetes, suggests that we have historically been using sulphonylureas at too high a dose. With increasing availability of genetic data pharmacogenomic studies in patients with diabetes should reveal mechanistic insights into old and new diabetes drugs, with the potential for optimized use and novel therapies.

KEYWORDS
genetics of type 2 diabetes, metformin, pharmacology, sulphonylurea

Dorothy Hodgkin solved the crystal structure for porcine insulin in 1969, work that paved the way for the development of human and analogue insulins that have transformed care for patients with insulin-treated diabetes. At this time, there were two classes of drugs used to treat diabetes: biguanides and sulphonylureas. Both the biguanide, metformin,[1] and sulphonylureas[2] were introduced into clinical practice in the 1950s and were the only diabetes treatment other than insulin until the 1990s – when acarbose (1995), miglitol (1996), troglitazone (1996) and repaglinide (1997) were approved.[3] In the last 6 years, several large randomised controlled trials have established the beneficial cardiovascular (CV) and renal effects of two of the newer classes of agent – Sodium Glucose Transporter 2 inhibitors (SGLT2i) (2012) and Glucagon-like Peptide 1 Receptor Agonists (GLP-1RA) (2005) – and these are now

indicated second line after metformin in those at high CV risk or with chronic kidney disease.[4] Yet more than 60 years after their introduction, metformin remains the most widely used diabetes treatment, and sulphonylureas are still used extensively.[5] For both metformin and sulphonylureas the glucose-lowering effect was an incidental finding; the drugs were not designed to inhibit or activate a particular receptor or transporter. Whilst sulphonylureas have subsequently been shown to have a largely targeted mechanism – inhibition of the β-cell K_{ATP} channel – the molecular targets of metformin remain uncertain. In this review, I will revisit these two stalwarts of diabetes therapy, highlighting how we can gain insights from human genetics into the molecular and physiological mechanisms of action of metformin and sulphonylureas.

Patients treated with glucose-lowering treatment vary in their response – some gain considerable benefit, whereas others have no benefit; some get limiting side effects, but many do not. There are many factors that impact on this variation, but we know this is a heritable trait (i.e. some of the variation is genetic): the SNP-based heritability for glycaemic response to metformin is 34%,[6] with similar estimates for sulphonylureas (37%, *Diabetes Care in press*). For comparison, the SNP-based heritability of height, a highly heritable trait, is ~55%. Thus, the study of pharmacogenomics, that is, how this genetic variation impacts on drug efficacy, has the potential to provide a tool to investigate the biological mechanisms of drug action. Diabetes pharmacogenomics can be approached from two directions. The first approach considers genetic variation that alters diabetes risk, on the assumption that the genetic processes whereby someone develops diabetes may alter how they respond to a diabetes drug. This can be seen in the extreme example of HNF1A MODY – the monogenic defect that causes diabetes impacts on β-cell mechanisms in such a way as to make patients with this diabetes exquisitely sensitive to sulphonylureas,[7,8] or in neonatal diabetes (NDM) as will be discussed later with respect to sulphonylureas. The second approach is to consider a drug intervention as an exposure and address how patient genotype alters response to diabetes treatment – this may identify not only the aetiological variation but also the mechanisms of drug action that are independent of aetiology. I will expand upon this approach when considering genetic insights into metformin response.

1 | INSIGHTS FROM GENETICS: HOW DOES METFORMIN WORK TO LOWER GLUCOSE?

Metformin is a potent glucose-lowering agent, that has many potential non-glucose benefits – reviewed in a series of linked articles released to celebrate 60 years of metformin.[9,10] The mechanisms of action for metformin in glucose lowering are much debated and a detailed discussion is beyond the scope of this review; for more detail see Reference [11].Metformin is absorbed from the gut (where it is the most highly concentrated compared with any other tissue due to active transport by a range of organic cation transporters); it is actively transported into the liver, before being taken up and excreted via the kidneys. Concentrations of metformin outside of these three tissues are very low and as such it seems likely that metformin lowers glucose by acting at the gut, liver or kidneys (or a combination of these tissues).

Human genetic variation provides a useful tool to investigate the site of metformin action. A widely proposed mechanism of action for metformin is that it acts on the liver to lower hepatic glucose output.[12] Metformin is a cation and as such is actively transported into tissues, with minimal passive diffusion. The main transporter taking metformin into the liver is OCT1[13] – encoded by *SCL22A1*. In European ethnic populations, two genetic variants that reduce OCT1 function are relatively common (rs72552763, M420Del, MAF (minor allele frequency) 19%; rs12208357, R61C, MAF 6%). A recent paper using ^{11}C-metformin and PET/CT imaging established that carriage of either the 420del or 61C variant reduced metformin uptake into the liver in humans (Figure 1).[14] Given this, we hypothesised that if metformin lowers glucose by acting on the liver, then patients carrying reduced function OCT1 variants should not respond so well to metformin treatment as those with normal function (wildtype) OCT1. We first undertook a study in a Scottish cohort (Genetics of Diabetes Audit and Research Tayside Scotland; GoDARTS) in ~1500 patients with type 2 diabetes treated with metformin,[15] and then in a larger Metformin genetics consortium (MetGen) cohort of ~4500 patients[16] and showed no effect of carriage of either the 420del or the 61C variant of OCT1; the point estimate when looking at the variants in combination was slightly in favour of metformin benefit in these patients (Figure 2). This genetic data would suggest that metformin does not need to enter the liver to lower glucose in patients with diabetes, and is supported by recent tracer studies in patients with recent onset T2D[17] or those without diabetes[18,19] that metformin treatment results in an *increase* in hepatic glucose production rather than a reduction, likely secondary to an increase in glucose clearance.

An alternative approach to use human genetics to gain insight into metformin action is to utilise a genome-wide association study (GWAS). This tests ~3 M variants distributed across the genome to see if any variants are associated with altered glycaemic response to metformin, and as such makes no prior assumption about the biological mechanism. In the largest GWAS of glycaemic response

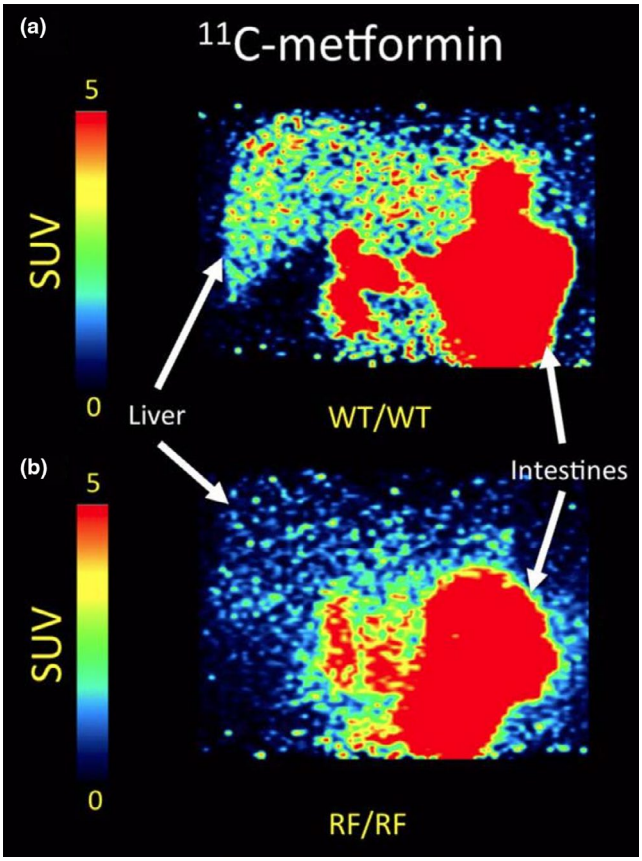

FIGURE 1 Hepatic metformin exposure after oral ingestion of ^{11}C-Metformin. Summed ^{11}C-metformin PET images from a person wildtype for *SLC22A1* genotype (a) and a person with two reduced function variants of *SLC22A1* (b). The uptake into the liver seen in (a) is markedly attenuated in (b). Reproduced with permission from Reference [14]

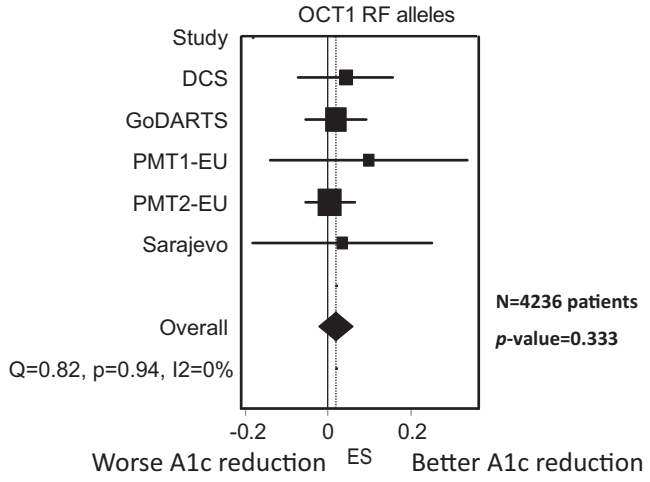

FIGURE 2 Forrest plot representing the association of carriage of one or more reduced function OCT1 variants (R61C, M420del) on glycaemic response to metformin. Data are shown for individual cohorts (DCS, GoDARTS, PMT1-EU, PMT2-EU, Sarajevo) along with an overall effect following meta-analysis. A positive result represents better glycaemic response to metformin. Modified from Reference [16]

to metformin to date, the MetGen consortium reported a large, robust signal at an intronic locus within *SLC2A2*, encoding the glucose transporter GLUT2.[20] In this study we show that C-allele rs8192675 is associated with a greater glycaemic response to Metformin – with those with a CC genotype having a 4 mmol/mol (0.4%) greater HbA_{1c} reduction than those with a TT genotype (a dose equivalence of 550 mg metformin). We also show that this C-allele is associated with reduced GLUT2 expression in the liver and intestines. What does this tell us about how metformin is working and at what site? GLUT2 is an important glucose transporter in the liver, enabling bidirectional glucose flux in the fasting and prandial state, with deletion of glut2 reducing glucose uptake but not output by the liver.[21] However, our prior genetic data does not support an important role for metformin in the liver. GLUT2 is similarly a facilitative glucose transporter expressed in the basolateral membrane of intestinal enterocytes. Mice lacking GLUT2 do not have altered absorption of glucose following oral ingestion[21]; however, metformin increases uptake of glucose into enterocytes from the systemic circulation (across the basolateral membrane) rather than the lumen,[22] probably explaining the increase in glucose clearance observed in the tracer studies described above. We hypothesise that intestinal GLUT2 may be in part moderating metformin efficacy, although exactly how remains an important question. At the time of writing, colleagues in Dundee and Turku are undertaking studies on metformin treatment in mice with heterozygous glut2 knock out, and with intestinal specific glut2 knockout aiming to address this hypothesis.

2 | INSIGHTS FROM GENETICS: HOW DO SULPHONYLUREAS WORK? ARE WE USING THEM CORRECTLY?

Sulphonylureas were discovered in 1942 as severe hypoglycaemia was identified in patients treated with sulphonamides, used to treat typhoid fever. With clinical introduction in the 1950s, it was not until 1985 that the β-cell K_{ATP} channel was identified as the likely target of sulphonylureas.[23] Subsequently the mechanisms mediating this via binding of sulphonylureas to the SUR1 subunit of the K_{ATP} channel have been extensively characterised and are reviewed elsewhere (e.g. see Ref. [24–26]).

It is necessary here to briefly review the physiology of glucose-stimulated insulin secretion by the pancreatic β-cell. Two important pathways are recognised, as described by Henquin[27] – the triggering pathway and the amplifying

pathways. The triggering pathway is mediated via the K_{ATP} channel, closure of which results in a rise in membrane potential sufficient to trigger calcium influx and insulin secretion. Insulin secretion is amplified by glucose, incretins, charged amino acids and other nutrients. The amplifying pathways are only evident when the triggering pathway is active – as when the K_{ATP} channel is not closed the large potassium currents dominate, and the other mechanisms have little effect. Sulphonylurea binding to SUR1 brings about closure of the K_{ATP} channel independent of glucose metabolism and triggers insulin secretion. Importantly, at the doses used to treat patients with T2D, closure of the K_{ATP} channel results in triggering of insulin secretion even when the blood glucose is low, resulting in increased risk of hypoglycaemia. Figure 3a shows a schematic representation of insulin secretion against glucose for patients with T2D treated with sulphonylureas. At a given glucose concentration there is an increase in insulin secretion. Note that there is an increase in the slope (the glucose sensitivity) as once triggered by K_{ATP} channel closure the amplifying mechanisms, including glucose, can operate to increase insulin secretion, and sulphonylureas are reported to act via a non-K_{ATP} mechanism to augment the amplifying pathway.[28] The ideal secretagogue would increase β-cell glucose sensitivity while maintaining glucose dependency so when the glucose concentrations drop below 4 mmol/L there is no insulin secretion. This is shown schematically in Figure 3b and is seen with drugs that act via the incretin system, for example, DPP-4 inhibitors and GLP-1RA.

The human genetic insights into the mechanism of action of sulphonylureas come from patients with NDM due to activating mutations in either the *KCNJ11*[29] or *ABCC8*[30] genes, encoding the Kir6.2 and SUR1 components of the K_{ATP} channels. These patients develop insulin-requiring diabetes often with ketoacidosis in the early neonatal period (up to 6 months of age). Following the discovery of the genetic aetiology in these patients, we established that patients who had been on lifelong insulin treatment were able to successfully transition off insulin on to (high-dose) oral sulphonylurea treatment.[31] Many patients with NDM treated with sulphonylureas can achieve near normalisation of their glucose, with HbA_{1c} in the non-diabetic range, yet have little to no hypoglycaemia. Physiological studies undertaken before and after transition to sulphonylureas are striking (Figure 4). Before treatment with sulphonylureas, there is no insulin secretion in response to intravenous (iv) or oral glucose. In patients treated with sulphonylureas, there is a small measurable insulin secretory response to IV glucose, yet there is a large insulin secretory response to oral glucose. This greater insulin secretion with oral versus iv glucose is a measure of the incretin effect – in patients with NDM due to K_{ATP} channel mutations, sulphonylureas are enabling the β-cell to respond to incretins (amplifying pathway) with minimal effect on the direct (triggering) pathway. So, for these patients, in contrast to that seen in T2DM, sulphonylureas are acting as the perfect secretagogue.

How can sulphonylureas promote meal-regulated insulin secretion in patients with NDM? Elegant work from Fran Ashcroft's lab provides a clue to this. They studied isolated β-cells from mice with the V59M mutation in Kir6.2 and compared with wildtype mice.[32] In whole-cell patch clamp studies, glibenclamide resulted in a rapid and near complete reduction in membrane conductance in normal (wildtype) β-cells. By contrast, in β-cells from mice carrying the V59M mutation, higher doses of glibenclamide were needed to reduce the conductance, and

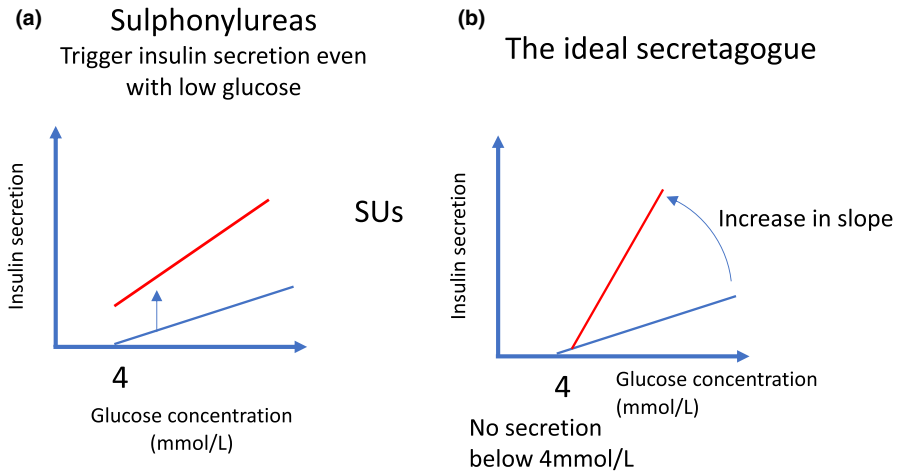

FIGURE 3 A schematic representation of insulin secretion against glucose. (a) shows the effect of sulphonylureas – an increase in insulin secretion even at low glucose and a probable increase in glucose sensitivity (the slope). (b) shows the ideal secretagogue – an increase in the slope, but with no increased insulin secretion below a glucose of 4 mmol/L. The blue lines are without secretagogue, the red lines are with secretagogue

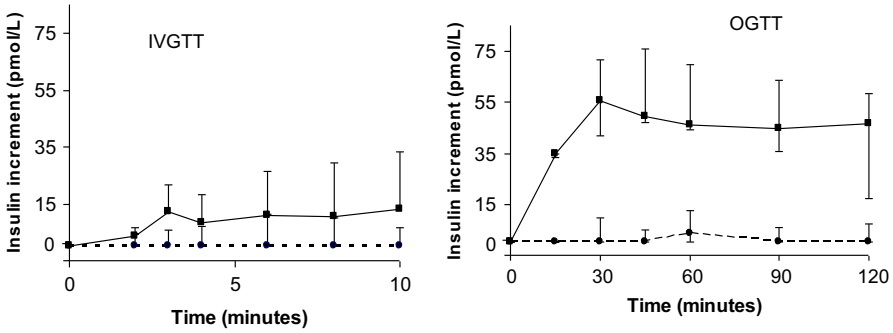

FIGURE 4 Physiological studies in patients with neonatal diabetes due to activating KCNJ11 mutations. The left panel shows the plasma insulin concentrations over 10 min after an iv glucose bolus in patients before being treated with sulphonylureas (dashed line) and after transitioning onto sulphonylurea treatment (solid line). The right panel shows the insulin concentrations over 120 min after an oral glucose challenge in patients before (dashed line) and after (solid line) transition to sulphonylurea treatment. Reproduced with permission from Reference [31]

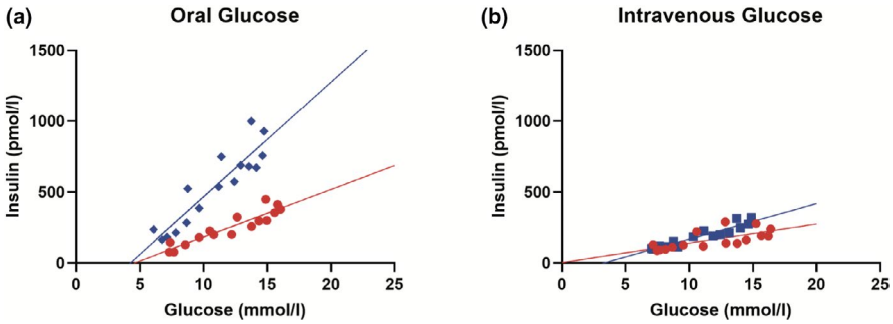

FIGURE 5 Effects of low-dose (20 mg) gliclazide in patients with T2DM. The left panel shows the insulin secretion plotted against glucose following oral glucose challenge with (blue) and without (red) gliclazide; the right panel shows the insulin secretion plotted against glucose following an isoglycaemic intravenous glucose with (blue) and without (red) gliclazide. Reproduced with permission from Reference [33]

even with very high concentrations there was never complete closure of the K_{ATP} channels (i.e. conductance did not reduce to zero). It is this latter property that probably means that patients do not develop hypoglycaemia despite high doses of SU. The residual K_{ATP} conductance in the presence of SU holds the pancreatic β-cell at a subthreshold voltage insufficient to trigger insulin secretion directly, thus minimising hypoglycaemia, but at a level where only small changes in non-K_{ATP} conductance can trigger insulin release, resulting in postprandial insulin secretion.

Given that patients with NDM on high-dose SU with normal HbA_{1c} are able to fast for 24 h without hypoglycaemia, is it possible for this effect to be mimicked in T2DM? The key question here is whether, in the context of only mildly impaired K_{ATP} channel function, it is possible to use a low enough dose of SU to partially lower K_{ATP} conductance to a similar level as seen in NDM and high-dose SU. To address this question, we have recently undertaken a series of studies of low-dose SU in patients with T2DM. The usual starting dose of gliclazide is 40–80 mg; after an initial dose ranging study, we used 20 mg. We first investigated the effect of low-dose gliclazide on β-cell physiology and specifically on the incretin effect.[33] To assess the incretin effect, we undertook 'isoglycaemic clamp' studies. In these, a paired oral glucose tolerance test and isoglycaemic iv glucose infusion are given on different days – with the difference in insulin secretion between the iv and oral stimulus reflecting the gut secreted incretins. We showed that the incretin effect is increased from 35.5% to 55% ($p = 0.049$) by 20 mg oral gliclazide. Interestingly, when we plot the insulin concentration for a given glucose in response to oral and iv glucose (Figure 5), there is minimal augmentation of insulin secretion with sulphonylurea treatment for an iv glucose stimulus, but in response to an oral glucose stimulus, 20 mg gliclazide augments insulin secretion by augmentation of the slope (glucose sensitivity) but with no direct effect at low glucose levels – in other words, at a dose of 20 mg gliclazide can act as the ideal secretagogue (Figure 3b). In a second study we have undertaken a crossover trial of placebo, 20 mg of

gliclazide, 100 mg of sitagliptin and the combination of low-dose gliclazide and sitagliptin, undertaking mixed-meal tolerance tests on each arm. This 'Sulphonylureas synergistic with sitagliptin study' (SSS) (NCT04192292) investigated the glucose-lowering effect at mixed meal, as well as undertaking continuous glucose monitoring to look for evidence of hypoglycaemia, aiming to establish the efficacy of low-dose gliclazide relative to sitagliptin, and to investigate if low-dose gliclazide, that increases the incretin effect, works synergistically with DPP-4i, that increase circulating endogenous incretins. This trial will be reported separately to this review.

To conclude, using human monogenic diabetes an exemplar, we have established that sulphonylureas used at high dose in NDM are highly effective largely by enabling the β-cell to respond to non-glucose stimuli and do not cause hypoglycaemia as the mutant channels cannot fully close. Leading directly from these observations we have now established that 20 mg of gliclazide works, at least in part, by augmenting the incretin effect and at this dose are potent and do not cause hypoglycaemia. Sulphonylureas are dropping out of current guidelines, with the latest ADA/EASD guidelines relegating them to 'where cost is an issue'. The main concerns with sulphonylureas are weight gain, hypoglycaemia, reduced durability and lack of CV benefit. I believe that the first three of these concerns reflect the doses and types of sulphonylureas used (see Ref. [2]). Low-dose gliclazide should cause minimal weight gain and no hypoglycaemia due to the greater role of the incretin effect at these doses, and there should be no persistent β-cell hyperpolarisation that causes loss of β-cell function (at least in mice[34]) and reduced durability of action. In short, we have historically been using sulphonylureas at far too high a dose and need to revisit how this cheap effective drug is used.

3 | INSIGHTS INTO MECHANISMS OF DRUG ACTION: NEWER AGENTS

What about the newer diabetes treatments like GLP-1RA or SGLT2i – can we learn from human genetics? We already have – genetics tells us that people with genetic loss of SGLT2i are healthy[35] and thus SGLT2i inhibitors should be safe, and that variants in GLP-1R that lower glucose and reduce diabetes risk and thus mimic GLP-1RA, have reduced CV risk.[36] But what about variability in response to these drugs? Why do some people have weight loss and minimal glucose lowering with GLP-1RA, or glucose lowering with minimal weight loss? What is the mechanism whereby SGLT2i reduce risk of heart failure or decline in renal function? With large, well-powered GWAS of glycaemic response, weight change and CV outcome I hope that human genetics will contribute to our understanding of the mechanisms of action for these drugs too in the near future.

4 | CONCLUSIONS

Identifying how genetic variation alters the response to the treatment serves two purposes – firstly, it may provide novel insights into drug mechanisms, that may not be apparent from studying drug action in vitro or in animal models; secondly, it may enable a targeted treatment approach in the clinic. This second aspect is addressed elsewhere[37] – but in brief, yes, I strongly believe that within 10 years genotyping will be embedded in the medical record and the size of genetic effects identified to date will inform on treatment decisions. In this review, given the basic science focus of the Diabetes UK Dorothy Hodgkin Lecture, I have focused on the role of human pharmacogenomics to provide insight into drug mechanism as I think this is an exciting and unrecognised potential for pharmacogenomics. With increasing availability of genetic data in large populations (e.g. UKBiobank, Our Future Health) and an increasing openness by industry to undertake and share genetic analyses of clinical trials, studying genetic impact on drug outcome and undertaking recruit by genotype physiological studies will provide a much deeper understanding of how the available diabetes drugs work, potentially enabling optimized use and a route to develop novel therapies.

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