Precision medicine in the management of type 2 diabetes

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The study of type 2 diabetes has been driven by advances in human genetics, epigenetics, biomarkers, mechanistic studies, and large clinical trials, enabling new insights into disease susceptibility, pathophysiology, progression, and development of complications. Simultaneously, several new drug classes with different mechanisms of action have been introduced over the past two decades, accompanied by data about cardiovascular safety and non-glycaemic outcomes. In this Review, we critically examine the progress and integration of this new science into clinical practice, and review opportunities for enabling the use of precision medicine in the diagnosis and treatment of type 2 diabetes. We contrast the success in delivering personalised medicine for monogenic diabetes with the greater challenge of providing a precision medicine approach for type 2 diabetes, highlighting gaps, limitations, and areas requiring further study.

Lancet Diabetes Endocrinol 2018

Published Online
April 23, 2018
http://dx.doi.org/10.1016/S2213-8587(18)30052-4

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Introduction

There has been much interest in our increased ability to incorporate data from human genetics, along with lifestyle and environmental information, to individualise treatment decisions. Although not a novel concept, the technological advancements that have driven the omics revolution have provided the impetus and expectation that a new dawn in precision medicine is approaching. In this Review, we use the term precision medicine to describe the stratification of patients into groups on the basis of molecular and genetic biomarkers and clinical characteristics to optimise therapeutic outcomes. The scope of precision medicine has appropriately been broadened to not only include genetics but also environmental and lifestyle factors, with recommendations targeting groups rather than individual patients. In this Review, we examine the evidence for precision medicine in diabetes, focusing on its success in monogenic diabetes, the emerging evidence for type 2 diabetes, and identifying challenges for enabling improved individualised treatment recommendations in the future.

Precision medicine in monogenic versus polygenic diabetes

The past 10 years have seen unprecedented progress in our understanding of the genetic basis of diabetes. With this progress has come an expectation among the clinical community that our ability to diagnose, characterise, and treat patients with diabetes will be transformed. Given the well documented success in rapid translation of gene discovery efforts for monogenic varieties of diabetes into changes in clinical care pathways, this belief is understandable. Up to 3% of cases of diabetes diagnosed in children have a monogenic basis, with the most common cause being mutations in the transcription factor gene *HNF1A*.[1] Individuals with rare penetrant mutations in *HNF1A* typically present before age 25 years with non-insulin-dependent diabetes, are slim, and have a strong family history of diabetes. Clinical investigation usually reveals that such individuals are autoantibody negative but C-peptide positive. An early case study[2] showed that individuals with diabetes due to an *HNF1A* mutation had a marked sensitivity to sulfonylureas, a finding that was elegantly substantiated in a randomised controlled trial that provided the first example of personalised medicine in diabetes.[3] The precise molecular mechanism for sensitivity to this class of oral hypoglycaemic drugs in patients with *HNF1A* mutations remains elusive but it has been argued that closure of the ATP-sensitive potassium (K_{ATP}) channel by sulfonylureas bypasses the major sites of β-cell dysfunction, which are upstream of the K_{ATP} channel, thus reigniting insulin secretion. Sulfonylureas are also the first-line treatment for individuals with neonatal diabetes due to activating mutations in the *KCNJ11* and *ABCC8* genes, which prevent the K_{ATP} channels from closing in response to ATP generated by glycolysis.[4–7] Closure of the channel by an ATP-independent mechanism circumvents the cause of the β-cell dysfunction, restoring insulin secretion in these individuals and, remarkably, improving their glycaemic control.

Personalised medicine in monogenic diabetes extends beyond treatment response: for example, individuals with loss-of-function mutations in the *GCK* gene have stable fasting hyperglycaemia and are unlikely to develop diabetic complications.[8] For neonatal diabetes, non-selective genetic testing now provides information about the future development of additional clinical features, disease management, and likelihood of disease remission.[9]

To date, however, genetic discovery efforts for type 2 diabetes have had limited translational benefits. Reconciling the different bench-to-bedside trajectories of monogenic versus complex forms of diabetes can be achieved by appreciating the differences in the genetic contributions to the development of diabetes, which makes the eventual classification of type 2 diabetes into multiple discrete subtypes less likely than into monogenic forms of diabetes (figure). As researchers have tried to understand how genetics might be used to support precision medicine, several theories have been proposed for complex diseases such as type 2 diabetes and coronary artery disease. Two untested models[10,11] that have garnered interest propose that patients with type 2 diabetes or coronary artery disease are likely to have a diverse set of overlapping mechanisms for their inability to regulate

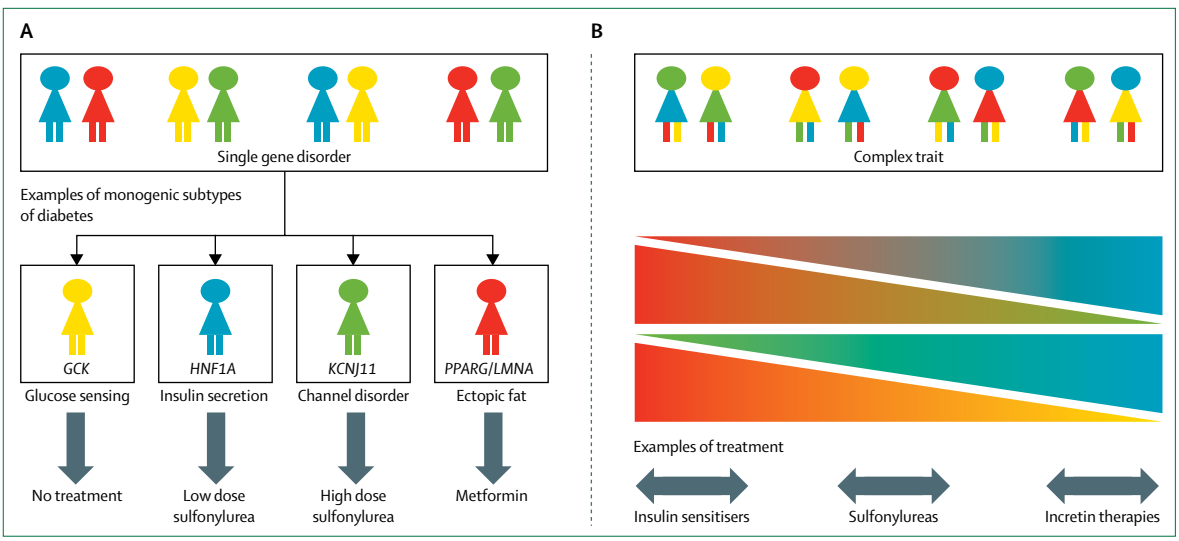

Figure: **Precision medicine approaches for the treatment of type 2 diabetes**
(A) Treatment of patients with selected monogenic subtypes of diabetes. (B) Individuals with complex genetic determinants of type 2 diabetes. Monogenic diabetes subtypes have specific treatments whereas complex trait type 2 diabetes is a sliding scale making individualised treatment more difficult. Many subtypes of monogenic diabetes can be treated with specific pharmcological agents, whereas individuals with type 2 diabetes have a heterogeneous phenotype, with different degrees of abnormalities in multiple pathways.

their blood glucose or lipid concentrations, respectively, and that these combinations will be difficult to tease apart into discrete subtypes. Both models propose that what matters is where an individual is on a series of hypothetical sliding scales of intermediate phenotypes for particular pathophysiological processes (eg, β-cell mass, insulin sensitivity, and incretin response in patients with type 2 diabetes, or LDL cholesterol concentrations in patients with coronary artery disease).[10,11] If we can understand the composition of the pallette or blend and where individuals are located on these sliding scales then we can make more tailored treatment choices, particularly when identifying patients who are unlikely to respond to a particular therapy. For example, people with diabetes largely due to loss of β-cell mass are unlikely to respond to drugs that increase insulin secretion. There is already evidence for this hypothesis from studies showing the reduced efficacy of glucagon-like peptide-1 (GLP-1) receptor agonists in insulin-treated patients with low C-peptide concentrations and autoantibodies.[12] Encouraging evidence for the clinical utility of genetic risk profiling has emerged from efforts to understand the frequency of type 1 diabetes in individuals presenting with diabetes in adulthood. Distinguishing these patients from those with type 2 diabetes is important as individuals with type 1 diabetes will rapidly require insulin therapy.[13]

Stratification of diabetes into multiple subtypes

A 2018 study[14] from Scandinavia has shown that identifying discrete subtypes of diabetes that have different pathophysiology might provide information about disease trajectory. By doing hierarchical clustering in about 9000 newly diagnosed patients with diabetes, the researchers were able to identify five subtypes of diabetes based on clinical variables (autoantibodies, age at diagnosis, BMI, HbA_{1c}, and estimates of β-cell function and insulin resistance), which were replicated in independent cohorts. In support of the presence of different pathophysiological features, the clustering of established genetic associations differed between these subtypes. In line with different degrees of shared pathophysiology, the risks of complications differed across the subtypes. Notably, diabetic retinopathy was identified earlier in patients with relative insulin deficiency, whereas patients with insulin-resistant diabetes showed an increased risk of developing diabetic kidney disease.[14] These findings, if replicated in ethnically diverse populations across a range of age groups, might be of potential value for clinical trial enrolment or for early treatment stratification, perhaps with drugs such as sodium-glucose cotransporter 2 (SGLT2) inhibitors, which show potential for modification of renal outcomes.[15] Future studies will now need to establish whether treatment response with different drug classes differs across these subtypes of diabetes and whether this classification can further be improved and refined by additional prospective omics and clinical data.

Pharmacogenomics and clinical trial data to inform personalised treatment recommendations

Overview

Notwithstanding tremendous advances in the application of genetics to the characterisation of diabetes pathogenesis and treatment, the precise aetiology of type 2 diabetes is not currently informed by genetic testing or

available biomarkers. Ideally, evidence would include a cost-effective genetic test, coupled with robust prospective validation of the predictive value of incorporating genetic information into the treatment algorithm. Currently, the extent to which genetic variation in the *G6PD* locus underestimates the baseline HbA_{1c} in some African Americans[16] mandates consideration of routine genotyping at this locus for individuals in whom interpretation of HbA_{1c} values is assumed to be clinically relevant. Despite substantial progress in the integrated analysis of tissue and systemic metabolic networks perturbed in the settings of obesity, insulin resistance, and type 2 diabetes,[17] a uniform set of genetic information or biomarkers providing clinically useful information enabling individualised therapeutic choices has not yet been validated in randomised prospective clinical trials. Hence, a personalised approach to therapy requires consideration of the available evidence from clinical trials, complemented by decisions surrounding affordability and patient goals and preferences.

It is important to be as critical of the emerging data from pharmacogenetic studies as we are of association studies of the risk of type 2 diabetes and to recognise the importance of replication. Most of the scientific literature is focused on small studies of candidate genes or single nucleotide polymorphisms, as opposed to unbiased genome-wide assessments of the impact of genetic variation on therapy response. Thus, although many studies report associations between type 2 diabetes risk alleles and response to treatment, most of these associations have not yet been replicated in larger prospective studies.

Metformin

Metformin is the most widely used and intensively studied drug that is recommended for first-line therapy in the treatment of type 2 diabetes. Indeed, the study of metformin includes a large pharmacogenomics effort, analysis of genetic determinants of metformin transport, and molecular targets transducing metformin action. Genetic determinants of variability in metformin pharmacokinetics, tissue uptake, and clearance have been identified (*SLC22A1, SLC22A2,* and *SLC47A*), but their clinical utility in predicting response to metformin in patients with type 2 diabetes remains suboptimal.[18] Some studies have also identified genetic variation within *SLC22A1*, together with the use of medications that inhibit the OCT1 protein, as factors predicting up to a four-times higher rate of gastrointestinal metformin intolerance.[18] Genetic variation (rs11212617) near the *ATM* gene locus is associated with glycaemic response to metformin in some but not all populations, but the effect size is modest, precluding current use in the clinic. More encouraging data, including analyses of gene expression in human liver samples, have implicated variation within an intron (rs8192675) of *SLC2A2* (encoding GLUT2), together with hepatic *SLC2A2* expression, informing the therapeutic response to metformin in individuals of European ancestry (up to a 0·33% [2·1 mmol/L] difference in HbA_{1c} reduction).[18] Nevertheless, no association of variation within *ATM* or *SLC2A2* and therapeutic response to metformin was detected in individuals with prediabetes followed up in the Diabetes Prevention Program (DPP) trial, highlighting the challenges of extrapolating genetic findings from an analysis of established type 2 diabetes to different study populations and metabolic states.[19] Moreover, treatment with metformin or lifestyle modification improved insulin sensitivity in the DPP study, independently of the genetic burden for insulin resistance, based on the presence or absence of 17 established genetic variants that are associated with insulin sensitivity.[20] Hence, although considerable progress has been made in understanding the genetic basis underlying therapeutic response to metformin, the predictive insights have been modest. Considering that metformin is inexpensive and associated with a low risk of major side-effects, broad implementation of pharmacogenomic analyses for clinical prediction of metformin efficacy and tolerability is currently neither practical nor cost-effective. Continued efforts to understand the genetic factors underlying differences in therapeutic responses between individuals might, however, shed light on the mechanisms by which metformin improves glycaemic control, which continue to be debated.[21]

Sulfonylureas

The historical and ongoing extensive use of sulfonylureas and insulin as second-line glucose-lowering drugs, recommended in many type 2 diabetes guidelines, reflects decades of research and clinical experience. Moreover, intensive glucose control for several years in regimens that include these treatments is generally associated with a reduction in microvascular outcomes in the short term, with a reduction in cardiovascular events and, in some trials, decreased all-cause mortality during longer-term follow-up (up to 10 years).[22,23] Nevertheless, the reduction in rates of microvascular disease might vary considerably depending on the population that is studied, the precise treatment regimens, and the duration of observation.[24,25] The use and benefits associated with sulfonylureas and insulin are offset by increased rates of hypoglycaemia and weight gain.[25–27] Indeed, the risk of severe hypoglycaemia with these treatments can be characterised by loss of consciousness, seizures, changes in mental status, and associated neurological and cardiovascular sequelae, resulting in increased emergency room visits, hospital admissions, morbidity, and mortality, particularly in older patients.[28,29]

Probably the best studied example of genetics informing pharmacological responses is variation at the *TCF7L2* gene locus; data from the GoDARTS study[30] showed that carriers of the *TCF7L2* type 2 diabetes risk allele are less likely to achieve glycaemic goals in response to sulfonylureas than non-carriers, a treatment effect that was not seen for

metformin. Other pharmacogenetic determinants contributing to therapeutic response to sulfonylureas have also been studied, including genetic variation within genes important for sulfonylurea metabolism and the sulfonylurea receptor, β-cell function, and insulin action, including *CYP2C9*, *ABCC8*, *KCNJ11*, *IRS1*, *CDKAL1*, *CDKN2A*, *CDKN2B*, *KCNQ1*, and *NOS1AP*.[18,31] Of particular interest is the case of genetic variation in the genes encoding the sulfonylurea receptor itself, where a number of studies have investigated whether coding variants in the *KCNJ11* and *ABCC8* genes, which are themselves associated with risk of type 2 diabetes, also affect response to sulfonylurea treatment.[32–34] There are data from functional studies to support pharmacogenetic effects on treatment with a particular subclass of sulfonylureas (gliclazide, an A-site sulfonylurea) in carriers of the *ABCC8* A1369AS variant.[35] Nevertheless, the importance of determining these genotypes for guiding individual sulfonylurea selection or dose to optimise achievement of clinical type 2 diabetes outcomes has not been sufficiently validated in prospective randomised studies.

Thiazolidinediones

Notwithstanding concerns surrounding relative benefits versus risks of thiazolidinediones for glucose control in individuals with type 2 diabetes, these drugs attenuate disease progression in subsets of patients with non-alcoholic fatty liver disease and non-alcoholic steatosis in studies of up to 24 months' duration.[36] Furthermore, in the IRIS trial, pioglitazone reduced the development of new type 2 diabetes and decreased the rate of fatal or non-fatal stroke or myocardial infarction over 4·8 years in individuals with insulin resistance and established cerebrovascular disease.[37] Nevertheless, our understanding of the genetic determinants underlying beneficial or adverse therapeutic responses to thiazolidinediones, principally rosiglitazone and pioglitazone, remains narrow. Variants within *SLCO1B1*, encoding the organic anion transporting polypeptide 1B1 (OATP1B1), affected glycaemic response to rosiglitazone in 833 patients assessed from 1 to 18 months of therapy, whereas variation within *CYP2C8*, encoding cytochrome P450 2C8 metabolising enzyme, was associated with glycaemic response and weight gain.[38] Surprisingly, the presence of these genetic variants did not similarly affect the response to pioglitazone therapy.[38] Moreover, the findings that genetic variation with *PPARG*, specifically P12A, is associated with decreased responsivity to thiazolidinediones in some small Asian cohorts[18] have not been independently verified in larger heterogeneous populations followed up for longer periods of time. Hence, the broad clinical relevance of these associations remains uncertain.

Acarbose

Acarbose, an α-glucosidase inhibitor widely used in some parts of Asia (particularly China) and to a lesser extent elsewhere, reduces development of new incident type 2 diabetes in patients with impaired glucose tolerance, and a secondary analysis of the STOP-NIDDM trial suggested a possible association between acarbose therapy in this population and a reduction in cardiovascular events.[39] Findings from the STOP-NIDDM trial revealed associations between genetic variations in *PPARA*, *HNF4A*, *LIPC*, *PPARG2*, and *PPARGC1A* and the response to acarbose in subsets of individuals with impaired glucose tolerance.[40] Nevertheless, these associations were quantitatively modest, have not yet been confirmed in independent populations, and have not been examined in acarbose-treated individuals with established type 2 diabetes. Moreover, an independent study (6522 individuals, median follow-up of 5 years) assessing the effect of acarbose versus placebo in individuals with impaired glucose tolerance and established coronary artery disease did not reveal differences in rates of cardiovascular disease, all-cause mortality, hospital admission for heart failure, or impaired renal function.[41]

Genetic risk scores

The use of patient-appropriate HbA_{1c} targets remains a cornerstone of type 2 diabetes management; however, personalised treatment goals beyond HbA_{1c} based on available clinical evidence and expert opinion are increasingly within reach (panel). The failure to achieve uniform benefit in the ACCORD trial provides a note of caution regarding the formulation of HbA_{1c} targets and implementation of intensive treatment regimens for people older than 65 years with type 2 diabetes, notably those at risk for cardiovascular disease.[42]

Analysis of common genetic variants from white individuals with type 2 diabetes in the ACCORD trial identified two genetic variants that were significantly associated with cardiovascular mortality in response to intensive diabetes therapy.[43] A genetic risk score based on these variants was further validated in the clinical care of patients with type 2 diabetes at the Joslin Diabetes Center (Boston, MA, USA) and patients who participated in the ORIGIN outcomes trial of insulin glargine.[27] Remarkably, a 22% increase in plasma GLP-1 concentrations in a subset of intensively treated participants in the ACCORD trial was associated with a favourable genetic risk score (driven by homozygous carriers of the C allele at rs57933) and cardiovascular benefit.[44] The implications of these findings and the applicability of this risk score to individualisation of type 2 diabetes therapy for younger patients using treatment regimens that minimise incidence of hypoglycaemia remains uncertain and requires prospective validation.

New classes of glucose-lowering drugs

Three new classes of glucose-lowering agents—GLP-1 receptor agonists, dipeptidyl peptidase-4 (DPP-4) inhibitors, and SGLT2 inhibitors—have been introduced in the past 13 years, extending the ability of clinicians to

treat type 2 diabetes with reduced rates of hypoglycaemia, less frequent self-monitoring of blood glucose, simplified dosing regimens, and without weight gain. These drugs were initially developed on the basis of metabolic physiology,[45–47] and the mechanisms of action and safety of SGLT2 inhibitors and GLP-1 receptor agonists were subsequently further validated by analysis of genetic variation at *SLC5A2* (the gene encoding SGLT2) and *GLP1R* in individuals[48] and large population studies.[49] Reinforcing the ability of human genetics to identify safe and effective therapeutic targets, array-based studies, focused on assessing coding variation exome-wide, identified a low-frequency non-synonymous variant A316T in the receptor for GLP-1, which is associated with fasting blood glucose concentrations.[50,51] The glucose-lowering allele at A316T is also associated with decreased type 2 diabetes risk and paradoxically a reduction in the early β-cell response to glucose, quantified by the insulinogenic index.[51] Furthermore, and pertinent to therapeutic response, the glucose-lowering allele at A316T is associated with protection against coronary heart disease.[49] Nevertheless, the extent to which genetic variation within the GLP-1 receptor contributes to glycaemic or non-glycaemic outcomes in clinical trials of GLP-1 receptor agonists is not yet known.

Even less is known about the pharmacogenetic determinants underlying the glycaemic response to DPP-4 inhibitors or SGLT2 inhibitors. Genetic variation at rs7202877 near *CTRB1/2*, a known diabetes risk locus, is associated with differential insulin secretory responses to acute GLP-1 infusion and a lower HbA_{1c} response to DPP-4 inhibitor treatment.[52] Genetic variation and clinical biomarkers that are associated with declining β-cell function also predict the response to GLP-1 receptor agonist therapy in some populations.[12] Recent findings from the PRIBA study,[51] validated independently by use of case records from the Clinical Practice Research Datalink, support the use of baseline clinical characteristics in decisions about incretin-based therapies. Individuals with markers of insulin resistance—such as high fasting C-peptide concentrations, homoeostatic model assessment 2 insulin resistance, and high triglyceride concentrations—responded less well than individuals without these conditions to DPP-4 inhibitor treatment in a 6-month treatment period, but their response to GLP-1 receptor agonists was unaffected.[53]

Surgical approaches

Considerable effort has been expended, by use of genetics, biomarkers, metabolomics, and gut microbial profiling, to prospectively identify ideal candidates for metabolic surgery with an increased likelihood of achieving sustained diabetes remission. Development of a Diabetes Remission (DiaRem) scoring system (comprising age, HbA_{1c}, and use of specific glucose-lowering medications) was followed by introduction of an Advanced DiaRem (Ad-DiaRem) score, which was refined through the addition of diabetes duration and number of glucose-lowering drugs to the scoring system. Ad-DiaRem enhanced predictive accuracy for diabetes remission at 1 year in people with severe obesity.[54] These clinical tools, although promising, require further validation in long-term prospective clinical trials because the rate of type 2 diabetes remission after surgery drops progressively with follow-up beyond 1 year. Moreover, extending these analyses from Roux-en-Y gastric bypass (RYGB) surgery to vertical sleeve gastrectomy, potentially incorporating indices reflecting β-cell function, tissue fibrosis, and additional metabolic profiling data, might enhance the performance and utility of emerging predictive scoring systems. The available observational data support a sustained improvement in blood pressure and control of dyslipidaemia and a 51% rate of type 2 diabetes remission assessed 12 years after RYGB surgery.[55] RYGB surgery reduced the rates of cardiovascular death in obese individuals followed up over 10·9 years in the Swedish Obese Subjects study; however,

Panel*: Evolving clinical considerations underlying personalised medicine recommendations for intensification of therapy after metformin in people with type 2 diabetes

Clinical characteristics influencing selection of glucose-lowering drugs

Older age, fragility
DPP-4 inhibitors, age-specific treatment goals

Severe or recurrent hypoglycaemia
DPP-4 inhibitors, SGLT2 inhibitors, GLP-1 receptor agonists, modern insulins

Poor, variable, or subotimal compliance
Once-weekly GLP-1 receptor agonists

Obesity
Bariatric surgery, GLP-1 receptor agonists, SGLT2 inhibitors

High HbA_{1c}, failure of oral antidiabetes drugs
Bariatric surgery, insulin, GLP-1 receptor agonists

Considerations based on non-glycaemic actions of glucose-lowering therapies and the reduction in rates of complications associated with diabetes

Non-alcoholic fatty liver disease, non-alcoholic steatohepatitis
Thiazolidinediones, GLP-1 receptor agonists

Heart failure
SGLT2 inhibitors

Coronary artery disease
GLP-1 receptor agonists

Stroke
Thiazolidinediones, GLP-1 receptor agonists

Chronic kidney disease
SGLT2 inhibitors

*Recommendations are based on available clinical evidence and expert opinion.

study participants were aged at least 37 years at the time of surgery and only 7·4% of individuals had type 2 diabetes.[56] Nevertheless, the incidence of myocardial infarction, but not stroke, was reduced after bariatric surgery in individuals with obesity and type 2 diabetes.[57]

Evidence guiding therapeutic recommendations for type 2 diabetes

Optimisation of diet and exercise remain key initial therapeutic recommendations for almost all patients with type 2 diabetes, together with treatment of coexisting hypertension and dyslipidaemia, and consideration of antiplatelet therapy. Despite the proliferation of genetic and biomarker information refining our understanding of the underlying characteristics of the disease in different populations, regulatory guidance currently embodies only a single precision medicine recommendation: health-care providers should consider genetic testing for glucose-6-phosphate dehydrogenase (G6PD) deficiency before the use of some sulfonylureas,[58] given the risk of haemolytic anaemia. Hence, a personalised medicine approach to type 2 diabetes mandates extensive consideration of clinical trial data, in the context of individual patient goals and characteristics.

In the absence of robust comparative effectiveness data, and few insights from prospective use of genetic and biomarker studies to inform long-term therapeutic efficacy, evidence-based formulation of personalised treatment recommendations for patients with type 2 diabetes is challenging. Randomised controlled trials comparing individualised treatment regimens with traditional sequential therapy based on HbA_{1c} targets are scarce. Each patient is unique, with different goals, medical history, and expectations (panel). Moreover, medication access and costs vary widely, and substantially influence individual treatment recommendations. Although some expert guidance advocates initial therapy with two or more glucose-lowering drugs for individuals with higher levels of HbA_{1c} to counteract clinical inertia, long-term studies and evidence supporting early initial combination therapy with sequential addition of further medications is scarce.[59]

Application of cardiovascular outcome trial findings to clinical practice

Two classes of drugs, the SGLT2 inhibitors and GLP-1 receptor agonists (notably liraglutide), have been associated with reductions in major adverse cardiac events and reduced mortality in individuals with type 2 diabetes in randomised cardiovascular outcome trials. Such effects were first seen in the EMPA-REG OUTCOME trial,[60] which examined the effects of the SGLT2 inhibitor empagliflozin in individuals older than 18 years (mean age 63 years) with type 2 diabetes and established cardiovascular disease. Cardiovascular benefit was also seen in the CANVAS trial programme assessing the SGLT2 inhbitor canagliflozin, in which the mean age was 63 years and 65·6% of the study population had a history of cardiovascular disease.[61] The population studied in the LEADER trial of the liraglutide, the first of the GLP-1 receptor agonists to show cardiovascular benefit, was aged at least 50 years (mean age 64 years) at the time of study enrolment, with around 80% of enrolled patients having prior cardiovascular disease.[62] In the SUSTAIN-6 trial, the cardiovascular safety of the once-weekly GLP-1 receptor agonist semaglutide (0·5 mg or 1·0 mg once per week) was studied in 3297 patients with type 2 diabetes and established cardiovascular disease (83%) or cardiovascular risk factors and a mean HbA_{1c} of 8·7% (70·6 mmol/mol), followed up for a median of 2·1 years. Semaglutide was associated with a reduction in major adverse cardiac events, predominantly strokes.[63] Cardiovascular safety, but not a reduction of major adverse cardiovascular events, was noted in the EXSCEL trial of once-weekly exenatide in 14752 patients with type 2 diabetes and established cardiovascular disease (73%) or without previous cardiovascular events and a median HbA_{1c} of 8·0%, followed up for 3·2 years. However, a nominally significant reduction in all-cause mortality was noted in patients treated with once-weekly exenatide.[63]

Subgroup analyses of EMPA-REG OUTCOME revealed that, as a group, African-American individuals, individuals younger than 65 years, or those with a BMI greater than 30 kg/m² did not show reductions in the primary cardiovascular outcome, but all three subgroups had a reduced rate of cardiovascular death.[60] Less than 4% of individuals enrolled in the CANVAS trial assessing the cardiovascular effects of canagliflozin were black or African American, and individuals younger than 50 years were not included in the primary prevention cohort.[61] Nevertheless, the reduction in cardiovascular events that occurred with the use of canagliflozin provides reassuring evidence for the cardiovascular safety associated with SGLT2 inhibitor therapy.

Although results of cardiovascular outcome trials have provided substantial insight into the benefits and safety of some new antidiabetes drugs, extrapolation of these results to other type 2 diabetes populations is problematic. It is unknown whether initiation of long-term therapy with SGLT2 inhibitors or GLP-1 receptor agonists in patients with type 2 diabetes, but without known cardiovascular disease, earlier in the disease course will provide substantial cardiovascular benefits. Indeed, subgroup analysis in the LEADER trial showed no benefit in the cohort of patients who were older than 60 years without established cardiovascular disease.[62] Many cardiovascular outcome trials enrolled few female patients older than 75 years and included few patients older than 80 years. Ideally, treatment recommendations and targets for elderly patients need to be adjusted on the basis of life expectancy and individualised on the basis of the relative risk of developing new diabetes complications over defined time periods.[64] The development of polygenic risk scores enabling identification of individuals at high risk of developing coronary artery disease[65] might prove

useful for the selection of individuals without known cardiovascular disease for early treatment with SGLT2 inhibitors or GLP-1 receptors agonists; however, information about the predictive value of these scores in large populations of patients with type 2 diabetes, independent of aggressive treatment of blood pressure and dyslipidaemia, is currently scarce.

Targeting glycaemic outcomes and complications beyond HbA_{1c}

Current evaluation of therapeutic effectiveness remains predominantly focused on a single glycaemic measure, HbA_{1c}; however, it seems likely that this approach will change in the future. The expanding use of continuous glucose monitoring to refine understanding of the importance of glycaemic parameters beyond HbA_{1c}, including rates of hypoglycaemia and proportion of time within target glucose ranges, is receiving increasing attention in the management of both type 1 diabetes and type 2 diabetes. Notably, HbA_{1c} might not always reflect or predict the burden of disease, and continuous glucose monitoring might be particularly useful for individuals with unexplained recurrent hypoglycaemia or substantial glycaemic variability. A limited assessment, comprising several capillary blood glucose determinations each month, showed correlation between the extent of glycaemic variability and rates of severe hypoglycaemia in the DEVOTE trial, which assessed the cardiovascular safety of insulin degludec compared with insulin glargine in patients with type 2 diabetes at high risk of cardiovascular events.[66] Moreover, the development of severe hypoglycaemia was correlated temporally with rates of all-cause mortality in patients in the DEVOTE trial.[67] More information about the potential clinical importance of severe hypoglycaemia is probably forthcoming from results of the CAROLINA trial (comparing cardiovascular outcomes in patients treated with linagliptin or glimepiride),[68] which might further shift the type 2 diabetes treatment approach away from drugs that are associated with an increased risk of severe hypoglycaemia, particularly in elderly patients and those at high risk for cardiovascular events (panel). Hence, future precision diabetes initiatives will probably encompass new goals and non-glycaemic targets, once these become prospectively validated.

Individualisation of therapeutic options beyond metformin, as outlined in the panel, is largely influenced by expert opinion, not prospective validation in randomised trials. The finding that two SGLT2 inhibitors and two GLP-1 receptor agonists reduced major adverse cardiac events further refines current options for reduction of heart failure (SGLT2 inhibitors) and complications related to major adverse cardiac events (GLP-1 receptor agonists and SGLT2 inhibitors) in patients with type 2 diabetes. Although heart failure has not been a traditional focus for adjudication of cardiovascular disease events in cardiovascular outcome trials involving patients with type 2 diabetes, a reduction in hospital admission for heart failure was reported in both the EMPA-REG OUTCOME and CANVAS trials, highlighting the importance of heart failure as an independent outcome in patients with type 2 diabetes.[60,61] Moreover, a reduction in progression of diabetic nephropathy, including doubling of serum creatinine, and time to renal replacement was detected in patients treated with empagliflozin in the EMPA-REG OUTCOME trial.[15] Although a decreased number of renal events was reported in patients treated with canagliflozin in the CANVAS trial, this finding was not significant, based on the hierarchical statistical analysis plan.[61]

Less compelling than evidence from cardiovascular outcome trials, but equally intriguing, are findings from exploratory studies showing reduction of liver fat and attenuation of liver inflammation and fibrosis in patients with prediabetes or type 2 diabetes treated with 45 mg daily of pioglitazone for 18–36 months.[69] Moreover, a double-blind, randomised controlled trial in which 26 out of 52 patients were treated with liraglutide 1·8 mg daily for 48 weeks, including nine (35%) individuals with type 2 diabetes, revealed a reduction in the extent of non-alcoholic steatohepatitis and fibrosis with liraglutide.[70] Although much larger registration studies will be needed to validate the preliminary findings for these putative non-glycaemic indications, it seems likely that therapeutic recommendations for the management of type 2 diabetes will increasingly be based on a personalised combination of goals encompassing both glycaemic and non-glycaemic targets (panel), which in turn will be based on accumulating evidence from outcome and registration studies.

Addressing the gap in personalised medicine

Despite the introduction of several new drug classes for the treatment of type 2 diabetes, data from real-world health-care audits show that population HbA_{1c} concentrations have failed to decline as much as might be expected according to analysis of clinical trial data. Although many explanations, including barriers to medication and health-care access, contribute to this discrepancy, poor medication adherence underlies the challenge in achieving target HbA_{1c} concentrations for many patients.[71] Despite substantial differences in HbA_{1c} outcomes favouring GLP-1 receptor agonists over DPP-4 inhibitors in multiple clinical trials, a retrospective claims analysis revealed similar (and disappointing) HbA_{1c} reductions of around 0·51% for both classes, with low rates of medication adherence (29% for GLP-1 receptor agonists *vs* 37% for DPP-4 inhibitors).[72] The introduction of medications taken once weekly or even less frequently might theoretically improve compliance with diabetes therapies; however this concept requires rigorous prospective validation in real-world studies.

Poor adherence is not limited to glucose-lowering drugs, but extends to therapies directed at reduction of blood pressure, platelet aggregation, and dyslipidaemia. As poor adherence is associated with increased rates of hospital

Search strategy and selection criteria

We searched PubMed for relevant journal articles published from Jan 1, 2000, to March 2, 2018, in English, using query terms including "diabetes", "genetics", "biomarkers", "pharmacogenomics", "precision medicine", and "personalised medicine". We also searched reference lists of key articles. After reviewing about 100 papers, a smaller list of references was selected for inclusion on the basis of the quality of the data, study sizes, and direct relevance to our topic.

admission and all-cause mortality in patients with type 2 diabetes,[73] understanding the myriad causes underlying poor adherence in different individuals is important for the successful application of personalised diabetes therapy. Intensification of efforts directed at identifying key factors underlying the success of randomised controlled trials (frequent interaction with health-care providers; finite, time-limited, and incentivised commitments to clinic visits and compliance; unencumbered access to medications; extensive provision of resources; and regular support) and implementing best practices in the clinic represents a major challenge and opportunity for improved delivery of effective diabetes care in clinical practice.

Several international studies investigating patient stratification or predictors of response to therapy in treatment-naive individuals are underway, including the Innovative Medicines Initiative-funded DIRECT study and the MASTERMIND and SUGAR-MGH studies.[74,75] These efforts will help to address some of the current gaps in our knowledge about the impact of metabolic state on response to treatment. Indeed, results from the SUGAR-MGH study show a role for the *TCF7L2*-type 2 diabetes risk alleles in the acute responses to both glipizide and metformin in people without diabetes.[76] Whether identification of these risk alleles provides similarly useful information about the long-term response to therapy in patients with type 2 diabetes remains uncertain.

For more on the **Innovative Medicines Initiative-funded DIRECT study** see http://www.direct-diabetes.org/

Future directions, limitations, recommendations, and areas of uncertainty

The available evidence strongly links early and sustained control of type 2 diabetes with long-term benefits and reductions in the rate of complications. Increased use of information generated from electronic medical records for monitoring achievement of blood pressure, glucose, bodyweight, and lipid targets, together with timely reminders for frequency of eye examinations and foot care, should reduce the morbidity and mortality associated with type 2 diabetes. We are at an early stage in our understanding of how genetic information can be used to stratify individuals for treatment response and it is almost certain that this information will need to be considered together with the clinical status of each individual along their disease progression path. The increasing availability and decreasing cost of human genetic analysis makes it likely that precise genome analyses will become routine in clinical medicine and used for diagnosis and therapeutic recommendations in multiple subspecialties beyond the diabetes clinic. Refinement of algorithms incorporating predictive genetic variation and biomarkers for drug responsiveness and the risk of complications, prospectively validated by clinical trial outcomes data in multiple populations with different ethnic backgrounds, should enhance our ability to transform diabetes care.

Successful deployment of a precision medicine approach to type 2 diabetes requires attention to gaps in our current knowledge base, which include a paucity of clinical trial data guiding treatment in adolescents, the elderly, and during pregnancy. Moreover, most patients in trials assessing the safety and cardiovascular benefit of new medications for type 2 diabetes were recruited with established cardiovascular disease. The available outcomes data for recommending type 2 diabetes therapy that is directed at primary prevention of macrovascular complications in young, healthier individuals are insufficient.

It seems certain that the increasing availability and improved accuracy and utility of genomic and clinical biomarkers will further enable precision treatment of diabetes. Simultaneously, information technology will continuously improve our capacity to do global, large-scale, and cost-effective clinical trials. Nevertheless, given the staggering numbers of patients with type 2 diabetes, critical evaluation of the cost versus benefit of the use of genomics, biomarkers, new technologies, and specific medications will be needed to support recommendations for clinical use in specific populations. Given the tremendous progress made over the past decade, it is reasonable to predict greater adoption of precision medicine approaches in the type 2 diabetes clinic in the years to come.

Contributors

The authors contributed equally to reviewing the scientific literature, writing and editing the Review, and generating the figure and panel.

Declaration of interests

DJD is a consultant to Intarcia, Merck, Novo Nordisk, and Pfizer. Mount Sinai Hospital receives funding for preclinical studies for work in the Drucker lab from GSK, Merck, and Novo Nordisk. ALG receives funding for preclinical studies from Novo Nordisk.

Acknowledgments

ALG is a Wellcome Trust Senior Fellow in Basic Biomedical Research (095101/Z/10/Z and 200837/Z/16/Z). DJD is supported by the Canada Research Chairs programme, a Banting and Best Diabetes Centre Novo Nordisk Chair in Incretin Biology, and CIHR grant 154321.

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