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Personalized pharmacotherapy for Type 2 diabetes mellitus

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Abstract

Genome-wide linkage and association studies have been applied to Type 2 diabetes in order to discover common genetic variation that contributes to disease risk. While there has been progress in understanding how genetic variation predisposes to diabetes, there is less of an understanding of how genetics can alter drug response. The hope is that in the future, pharmacogenetics can help guide the treatment of diabetes, thereby improving control while minimizing side effects in a large group of patients.

Keywords

OCT 1; pharmacogenetics; sulfonylureas; TCF7L2; Type 2 diabetes mellitus

The application of high-throughput genotyping techniques and the availability of large case–control cohorts have enabled the elucidation of multiple common genetic variants that increase the risk of developing Type 2 diabetes. In general, such data is of little use in predicting the future risk of diabetes in individual patients. By deciphering biological pathways in disease pathogenesis, genetics has provided a greater understanding of the pathophysiology of Type 2 diabetes and has identified new drug targets for the treatment of the disease. At the present time, knowledge of loci conferring the risk of diabetes is limited to rare variants conferring risk in a highly penetrant, autosomal dominant fashion, or to multiple common variants with weak-to-modest effects on disease predisposition. The discovery of less common, more penetrant variants awaits the application of whole-genome sequencing to large kindreds with a high prevalence of the disease.

On the other hand, less attention has been paid to determine how common genetic variation influences the response to pharmacotherapy for diabetes. In part, this is owing to the nature of the disease itself. Successful treatment is dependent on compliance with pharmacologic and nonpharmacologic intervention. Furthermore, response to treatment is affected by the duration of the disease and other parameters, such as weight and physical activity. Consequently, this has hampered the establishment of cohorts in which genetic effects on treatment can be adequately studied. Here, we review the pathophysiology of diabetes, the current state of knowledge regarding the role of genetic variation in determining treatment response and how this could lead to an individualized therapy for diabetes. The challenge of using pharmacogenetics in diabetes treatment is that additional confounding factors exist that influence treatment efficacy, including diet and lifestyle.

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Diabetes: disease course & management

More than 150 million people worldwide are affected by diabetes [1]. In the USA, a total of 23.6 million people (7.8% of the population) have diabetes and incidence has been increasing. Approximately 5.7 million of these individuals are undiagnosed. Across different ethnic groups, although the prevalence of diabetes varies, the main factors contributing to this dramatic increase are high caloric diets, reduced physical activity and a sedentary lifestyle [2]. A total of 1.6 million new cases of diabetes were diagnosed in individuals aged 20 years or older in 2007 [101].

Type 2 diabetes is a metabolic disorder arising from a complex interaction between genes and the environment. It is characterized by defects in insulin secretion and insulin action which leads to hyperglycemia [3]. Diabetes is defined on the basis of a fasting hyperglycemia (≥126 mg/dl), glucose levels being greater or equal to 200 mg/dl at 120 min after an oral glucose tolerance challenge or a random glucose test showing levels to be greater or equal to 200 mg/dl on two or more occasions.

Impaired fasting glucose (IFG) typically precedes diabetes and is defined by fasting blood glucose being in the 100–125 mg/dl range. Individuals with IFG have increased cardiovascular risk and estimates suggest that at least 57 million American adults had IFG in 2007 [101].

Significant morbidity and mortality is associated with diabetes [101]. In addition to increased cardiovascular risk, patients with diabetes are at risk of microvascular complications such as retinopathy, nephropathy and neuropathy. A total of 12,000–24,000 new cases of blindness are caused by diabetic retinopathy each year. In 2005, over 46,000 individuals with diabetes in the USA and Puerto Rico began treatment for end-stage renal disease, and 178,689 individuals with diabetes were living on chronic dialysis or with a kidney transplant [101]. More than 60% of nontraumatic lower-limb amputations occur in individuals with diabetes [101].

Pathophysiology of Type 2 diabetes

Type 2 diabetes is characterized by impaired insulin secretion and action (defined as the ability of insulin to suppress glucose production and stimulate glucose uptake). In addition, glucose effectiveness (the ability of glucose *per se* to stimulate its own uptake and suppress its own release) is also impaired. Excess caloric intake and obesity seem to exacerbate the physiological derangements that underlie diabetes. In the postprandial situation, defective suppression of glucagon secretion as well as accelerated gastric emptying may contribute to the postprandial hyperglycemia observed in diabetes.

Monogenic disorders, such as maturity onset diabetes of the young, have been helpful in illustrating the contribution of specific genes and their associated pathways to glucose homeostasis. For example, mutations in the glucokinase gene alter the set point at which insulin secretion occurs, although insulin secretion and action are unimpaired in affected patients. As progress is made in understanding the genetic predisposition to diabetes, it may be possible to discern different pathophysiological mechanisms within the heterogenous grouping of Type 2 diabetes. In such situations, a given therapy may be more effective in one subgroup of patients than in another. Certainly in some subtypes of maturity onset diabetes of the young, insulin secretagogues seem to be more effective than insulin sensitizers or insulin [4].

Treatment of diabetes

Diet, exercise and weight loss form the cornerstone of diabetic management. In addition, various classes of medications including sulfonylureas, meglitinides, biguanides, thiazolidinediones (TZDs), α-glucosidase inhibitor, glucagon-like peptide-1 (GLP-1) receptor

agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors exist. Insulin therapy also plays an important role after the primary or secondary failure of oral agents.

It is, of course, important to remember that aggressive treatment of other cardiovascular risk factors, such as hyperlipidemia or hypertension, is an important part of the management of patients with diabetes.

The presence of complications or comorbidities also has an important role in determining therapy – for example, the presence of microvascular complications may provide a stimulus for tighter control to delay progression – especially in the presence of a family history of complications. On the other hand, hypoglycemia unawareness may lead to a loosening of glycemic targets in an individual patient.

Intensive glycemic control can decrease or delay the onset and progression of microvascular complications. Of interest is the observation noted in the follow-up of the Diabetes Control and Complications Trial (DCCT), the Epidemiology of Diabetes Interventions and Complications (EDIC) that demonstrated, despite similar hemoglobin A1c (HbA1c) values, patients who were initially treated intensively continued to demonstrate a reduction in the risk of retinopathy, nephropathy and neuropathy. In addition, surrogate markers of cardiovascular disease (CVD), including carotid intimal medial thickness and coronary calcification, were reduced in the intensive treatment group. This carry-over effect has been referred to as glycemic memory [5-8]. The applicability of these findings to patients who are newly diagnosed with diabetes is uncertain. However, if it were possible to predetermine the risk of microvascular complications, the subset of patients at high risk could benefit from early, aggressive polypharmacy to improve glycemic control.

Tight glycemic control may have adverse consequences as well. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) was a large randomized trial studying subjects with a history of either CVD or substantial CVD risk to intensive control (HbA1c < 6.0%) or standard control (HbA1c: 7.0–7.9%). The study was terminated owing to the finding of an increased rate of mortality in the intensive arm compared with the standard arm [9,10].

Effect of genetic variation on response to treatment

Sulfonylureas & meglitinides

Sulfonylureas bind to their receptor complex on the pancreatic β-cell surface leading to the closure of potassium channels and thus, resulting in depolarization of the cell with subsequent calcium influx and insulin release that is unrelated to glucose concentration. These drugs should be used with caution in patients with CVD and in whom hypoglycemia may be an issue [11]. Compared with placebo, sulfonylurea therapy leads to a mean decrease of A1c by approximately 1–2%. In addition to hypoglycemia, another common adverse effect is weight gain [12]. Meglitinides have a similar mechanism of action but produce a less sustained rise in insulin secretion. Meglitinides have a shorter half-life and because of this, these agents may be useful in elderly patients at risk of adverse events from hypoglycemia.

The sulfonylurea complex is encoded by multiple genes, including the inwardly rectifying potassium channel (*KCNJ11*) and the ATP-binding cassette transporter sub-family C member 8 (*ABCC8*). A nonsynonymous SNP in *KCNJ11* is associated with Type 2 diabetes. It has been suggested that carriers of the Lys23 variant of the *KCNJ11* Glu23Lys polymorphism are more susceptible to secondary failure (defined as those requiring insulin owing to a rise in fasting plasma glucose above 300 mg/dl despite sulfonylurea–metformin combined therapy, appropriate diet and the absence of any independent conditions causing hyperglycemia) when

treated with a sulfonylurea. Carriers of the lysine allele have a relative risk of secondary failure of 1.45 (95% CI: 1.01–2.09; p = 0.04) compared with Glu23Glu homozygotes [13].

Other polymorphisms associated with differential response to these compounds include a haplotype in *ABCC8* (*SUR1*) that may alter the affinity of sulfonylurea binding to its receptor. In those carrying this haplotype, there was demonstrated to be a 50% reduction in serum C-peptide and a 40% reduction in serum insulin response in diabetic subjects carrying the combined genotype to tolbutamide [14]. Another locus that may alter the response to sulfonylureas is in the insulin receptor substrate 1 (*IRS1*), the Arg 972 allele of the *IRS1* Gly972Arg polymorphism. The genotype frequency of the Arg(972) IRS1 variant was demonstrated to be 8.7% among diabetic patients being well controlled with oral therapy and 16.7% among patients with secondary failure to sulfonylurea (odds ratio: 2.1; 95% CI: 1.18–3.70; p = 0.01). In this study, secondary failure was defined as those patients requiring insulin [15].

In the Diabetes Prevention Program cohort, *KCJN11* Lys23 carriers progressed to diabetes at a higher rate when treated with metformin for 1 year than the Glu/Glu homozygotes [16].

Biguanides

Metformin reduces hepatic gluconeogenesis but its mechanism of action is uncertain [12]. The organic cation transporter 1 (OCT 1), which is expressed in hepatocytes [17], mediates the uptake of the drug and is essential for its action. Owing to the absence of hypoglycemia and an effect promoting weight loss, metformin is often used as a first-line therapy in many patients with diabetes. Metformin improves both fasting and post-prandial hyperglycemia. The most frequent side effects are anorexia, diarrhea, nausea, vomiting and abdominal discomfort [12]. Hypoglycemia does not occur with metformin monotherapy [12]. Owing to the potential for lactic acidosis, metformin is contraindicated in patients with renal or hepatic insufficiency or congestive heart failure [12]. Metformin therapy leads to a mean decrease in A1c of approximately 1–2% [12].

Shu *et al.* studied the response to a 75 g oral glucose tolerance test in nondiabetic human subjects at baseline and after receiving two doses of metformin. The test subjects were characterized by the presence or absence of polymorphisms that decreased or abrogated *OCT1* function *in vitro* and *in vivo*. Metformin lowered glycemic excursion by 7.5% with intact *OCT1* function. However, in those with polymorphisms in *OCT1* that caused decreased uptake of metformin, the glycemic excursion was not altered by metformin [17].

Thiazolidinediones

The nuclear peroxisome proliferator-activated receptor (PPAR) is activated by fatty acids and fatty acid-derived eicosanoids. It exists in three isoforms (α, γ and δ) with differing tissue specificity. Activation of PPAR leads to the formation of heterodimers with retinoid-X receptors. These bind to DNA sequences that act as PPAR-response elements which act as transcriptional regulators of PPAR-regulated genes. PPAR-γ is mainly expressed in white and brown adipose tissue although it is also expressed in cardiac and skeletal muscle, macrophages and foam cells as well as the vasculature [18]. TZD therapy leads to a mean decrease in A1c of approximately 1–2% [12].

Thiazolidinediones bind to PPAR-γ. This isoform is important in adipocyte differentiation and also mediates the expression of glucose transporters GLUT-1 and GLUT-4, thereby increasing glucose uptake by the liver and skeletal muscle. At present, two thiazolidinediones are available for clinical use – pioglitazone and rosiglitazone. These agents enhance insulin action primarily

in the periphery but also, to a certain extent, in the liver [19]. *In vitro*, they inhibit gluconeogenesis in isolated hepatocytes.

Clinical use of these agents has been associated with weight gain. This is, in part, due to the stimulation of adipocyte differentiation as well as fluid retention. Often, this can be to a degree that results in hemodilution. For this reason, thiazolidinediones are contraindicated in situations where fluid retention is a problem – for example, congestive cardiac failure [20]. PPAR-γ agonists promote the uptake of free fatty acids in subcutaneous adipose tissue rather than in visceral adipose tissue. This may be the reason for the paradoxical improvement in insulin action despite the weight gain observed in clinical studies. In addition, they stimulate adiponectin and inhibit resistin secretion from the adipocyte, which may also contribute to improved insulin action.

A nonsynonymous SNP in *PPARG (*proline 12alanine) was one of the first common genetic variants to be associated with a predisposition to Type 2 diabetes. There has been some discordant data as to whether the alanine allele was thought to be protective. In a German study, 131 patients with Type 2 diabetes mellitus used 45 mg pioglitazone once daily for at least 26 weeks. There was no difference (defined as a greater than 15% decrease in HbA1c and/or a greater than 20% decrease in fasting plasma glucose after 12 or 26 weeks) in those who had Pro/Pro genotype versus those who carried an Ala allele [21]. However, in a study by Kang *et al.*, the response rate to 4 mg rosiglitazone once daily for 12 weeks was significantly higher in patients with the Pro/Ala genotype compared with the Pro/Pro genotype. Response was defined as a greater than 15% decrease in HbA1c and/or a 20% decrease in fasting plasma glucose after 12 weeks of therapy [22].

The presence of a defective allele in the lipoprotein lipase (*LPL*) polymorphisms, the Ser447X polymorphism, was associated with lower response rate to pioglitazone. Using the criteria of observing a greater than 10% relative reduction in fasting glucose after 10 weeks of pioglitazone treatment, response to pioglitazone treatment in the Ser447Ser genotype group was significantly higher (odds ratio: 0.538 [0.298–0.974]; p = 0.0403) than in the Ser447X genotype group [23]. LPL catalyzes the hydrolysis of triglycerides, providing free fatty acids for cells and affecting the maturation of circulating lipoproteins.

In a study of Hispanic women with previous gestational diabetes and are therefore, at high risk of progression to diabetes, genetic variants within two haplotype blocks of the *PPARG* locus altered response to troglitazone [24]. Dense genotyping of the locus suggested that response to TZD therapy may not be accurately assessed by genotyping one or two variants. Construction of a dense SNP map may be required to correctly identify variants or haplotypes associated with variation in drug response [24].

GLP-1-based therapy

The administration of glucose via the gut results in greater insulin secretion than when an equivalent amount of glucose is administered intra venously. This has been attributed to ‘incretins’ – hormones released by the gut in response to nutrient ingestion that aid in the postabsorptive assimilation of these nutrients [25]. GLP-1 is one such hormone. It arises from post-transcriptional processing of proglucagon in intestinal L-cells by prohormone convertase-1, which leads to the formation of GLP-1. Although it has a short half-life in the circulation (secondary to its rapid inactivation by DPP-4, an enzyme which is widely distributed and cleaves all peptides whose second N-terminal amino acid is a proline or alanine), it is a potent insulin secretagogue. It inhibits glucagon secretion and also delays gastric emptying [26].

Exenatide is a GLP-1 receptor agonist administered twice daily subcutaneously. It has a 53% sequence similarity to human GLP-1 and is resistant to the actions of DPP-4. In addition to improved glycemic control, its use is associated with weight loss of approximately 2–3 kg after 30 weeks of treatment [27,28]. Inhibition of DPP-4 activity leads to prolongation of the action of endogenously released GLP-1. Sitagliptin and vildaglipitin are clinically-available compounds that inhibit DPP-4, leading to enhanced glucose-induced insulin secretion and inhibition of glucagon release [2,29].

Polymorphisms in the GLP-1 receptor, in which threonine 149 is substituted with a methionine residue, have been demonstrated to alter response to GLP-1 *in vitro* [30]. However, the role of genetic variation in explaining interindividual differences in response to such compounds has not been actively explored. This finding may affect the response to agents such as exenatide.

Other variation that may alter response to intervention

TCF7L2 encodes a transcription factor that is part of the *Wnt*-signaling cascade. A common polymorphism within this locus increases susceptibility to Type 2 diabetes [31]. Carriers of the risk allele (TT genotype at rs7903146) appear to secrete less insulin in response to oral glucose [32].

Consistent with this observation, such individuals are less likely to respond to sulfonylurea treatment and are at a higher risk of sulfonylurea treatment failure. A total of 53% of rs7903146 TT individuals failed to reach target (A1c < 7%) on sulfonylurea compared with 40% of CC allele carriers [33].

Intriguingly, Schafer *et al.* demonstrated that GLP-1 induced insulin secretion in carriers of the *TCF7L2* risk allele (rs7903146 and rs12255372) who were impaired despite having a normal insulin response to intravenous glucose [34]. This observation, if independently replicated, is of importance since it suggests that diabetes-associated gene variation in *TCF7L2* does not produce a global defect in insulin secretion, but rather a defect that is specific to incretin-based responses. However, other investigators have demonstrated an impaired response to intravenous glucose in individuals with the diabetes-associated allele (T) of rs7903146 in *TCF7L2*.

Although it stands to reason that any variant impairing insulin secretion is likely to negatively influence the response to secretagogues or, indeed, insulin sensitizers, carriers of the T allele at rs7903146 seemed to respond dramatically to life-style intervention in the Diabetes Prevention Program. On the other hand, in the Diabetes Prevention Program, the diabetes-associated variant, rs10811661 at the CDKN2A/B locus, was associated with impaired insulin secretion and led to decreased benefit from pharmacological intervention with an insulin sensitizer or lifestyle modification compared with subjects without the diabetes-associated allele [35]

Future perspective

In the future, pharmacogenetics will have a significant impact on individualizing medical care. Owing to of the progress that has been made with genetic association studies and diabetes, we may see some of the first advances in the field of pharmacogenetics applied to the treatment of diabetes. Advances in pharmacogenetics may help to further define the role of genetics in variable response to glucose-lowering drugs. Of course, replication of these studies is important. We know that there is inter individual variation in response to diabetes treatment. The initial data from population-based genome-wide screening for pharmacogenetic data has been promising. In addition, we know that factors such as obesity, diet and activity play a role in diabetes and diabetic treatment options and there are genetic components that influence these

factors as well. Continued work investigating SNPs in multiple candidate genes will help to study interactions between oral antidiabetic agents and genetic polymorphisms. Although initial implementation of these tests may be difficult, both economically and logistically, with increased use of these tests, they may become more readily implemented in the clinic. While there is no replacement for the physician–patient interaction for eliciting nuances in a patient's life and routine that will affect their diabetic care and treatment decisions, pharmacogenetics may play a role in helping us to identify which agents to use in order to cater our treatment for a particular individual.

Executive summary

Diabetes: disease course & management

- Almost 8% of the US population has diabetes.
- Type 2 diabetes is a metabolic disorder arising from a complex interaction between genes and the environment.
- Classes of medications including sulfonylureas, meglitinides, biguanides, thiazolidinediones, acarbose, glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors exist for the treatment of diabetes in addition to insulin.

Effect of genetic variation on response to treatment

- Pharmacogenetics is likely to have a significant impact on individualizing care in Type 2 diabetes mellitus.
- There is already initial evidence in multiple candidate genes, including *OCT 1*, *PPARG*, *KCNJ11*, *TCF7L2* and *CDKAL1*, suggesting variation in response to oral hypoglycemic agents.

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