Individualizing care in type 2 diabetes mellitus

**Abbreviations:** T2DM, type 2 diabetes mellitus; SNPs, single nucleotide polymorphisms; OCTs, organic cation transporters; TZDs, Thiazolidinediones; PPARG-γ, peroxisome proliferator-activated receptor gamma; GLP-1, glucagon-like peptide-1; DPP-IV, dipeptidyl peptidase IV

**Editorial**

Today’s therapy for type 2 diabetes mellitus (T2DM) is vastly different than even a few years ago, being able to rely on a wider number of options, along with the possibility of a more effective personalized medicine, based on individual’s unique genetic makeup. So far, with few exceptions, antihyperglycaemic therapy in T2DM has not taken into account the individual genetic diversity that may contribute for the heterogeneity in treatment outcomes across diabetic patients, representing this as a substantial limitation of the conventional antidiabetic therapy.

More than 99% of the DNA is exactly the same in all humans. Therefore, phenotypic variability, including disease susceptibility and variable drug response, are the result of inherited sequence variations that affect less than 1% of human DNA. The most common inherited sequence variations are single nucleotide polymorphisms (SNPs), which modify single bases of the DNA sequence. SNPs in genes involved in the pharmacokinetics and pharmacodynamics of antidiabetic medications may influence the efficacy and safety of these drugs. Thus, identification of genetic biomarkers that predict antidiabetic treatment response can advance current clinical practice in diabetes care. This is one of the goals of pharmacogenomics, an emerging field of medical therapy, which studies the inherited genetic factors that cause interindividual differences in drug response. Recent studies on pharmacogenetics of antidiabetic drugs have implicated new candidate genes that may predict better treatment response for patients with T2DM. By reviewing these studies, I hope this editorial will serve as a guide for clinicians practicing diabetology and taking part in clinically oriented research.

Metformin is the first line medication for T2DM. However, the therapeutic response to metformin is highly variable and genetic heterogeneity may be a factor contributing to this variability. In fact, less than two-third of metformin-treated patients achieve glycemic control, leaving to assume that identifying SNPs associated with such variability would significantly contribute to improve the present day therapeutic regimens for drug treatment of these patients. Most of the studies in this area focus on the organic cation transporters (OCTs) of the SLC22 gene family, which are critically involved in the uptake, distribution and elimination of Metformin. Polymorphisms of OCTs can alter the hypoglycemic response to metformin in individuals carriers of these variants. Variants of the SLC22A2 gene, being able to induce a functional deficiency of OCT2, can reduce the clearance of metformin, resulting in an increase in plasma metformin concentrations and risk of hypoglycemia. Interindividual variation in the response to metformin has been observed in individuals with genetic variations in the genes coding for MATE1 (SLC47A1) and MATE2 (SLC47A2), which are involved in the extrusion of metformin through the urine. Whereas a greater response to metformin, with reduced levels of HbA1c, was found in association with the rs2252281 variant in the SLC47A1 gene, a reduced response to metformin was observed in patients carriers of the SLC47A2 rs12943590 polymorphism. Globally, these observations indicate that genetic variants of the OCTs are important in the therapeutic efficacy of metformin, being able to contribute to the interindividual variation in metformin response. Thus, genotyping of OCT genes is useful to predict the therapeutic efficacy of metformin.

Sulfonylureas are used for the treatment of T2DM as they help to lower blood glucose by closing the pancreatic β-cell ATP-sensitive potassium (KATP) channel, leading to insulin secretion. In Caucasians, sulfonylureas are metabolized primarily in the liver by the cytochrome P-450 CYP2C9 enzyme. Polymorphisms of the CYP2C9 gene significantly affect the pharmacological response of diabetic patients to sulfonylureas, because of the reduced metabolism of these drugs, which is followed by an increase in drug bioavailability and risk of hypoglycemia. The risk of hypoglycemia in sulphonylurea treated patients was confirmed in a study with a large population, in which genetic variations of CYP2C9 were associated with the improvement in glycemic control. Therefore, genotyping of the CYP2C9 gene may provide important information in predicting the adverse effects of these drugs and to assist physicians in prescribing sulfonylureas to diabetic patients.

The KATP channel plays a central role in mediating glucose-stimulated insulin release from pancreatic β-cells. Variants in the KATP channel genes, KCNJ11 and ABCC8, are the most common cause of neonatal diabetes accounting for ~40% of all cases. As an example of pharmacogenetics applied to clinical practice, recent evidence has shown that diabetic patients with mutations of the KATP genes do much better on treatment with sulfonylureas than with insulin. Additional results, in this context, have been obtained from the study of the TCF7L2 gene, which appears to play a role in β-cell function. Two genetic variants of this gene, rs7903146 (G>T) and rs7903146 (C>T), show variation in the therapeutic response to sulfonylureas, as the reduction in both fasting plasma glucose and HbA1c was higher in diabetic patients carrying the GG or CC allele, and lower in patients with the TT genotype, in which the risk for sulfonylurea treatment failure was higher.

Thiazolidinediones (TZDs), such as pioglitazone and rosiglitazone, are highly effective oral medications for T2DM, which act through...
the nuclear receptor peroxisome proliferator-activated receptor gamma (PPAR-γ). Genetic variants of PPAR-γ have been associated with increased risk for T2DM,\textsuperscript{11,12} a finding that suggested this gene as a candidate for pharmacogenetic studies predicting outcome to TZDs in diabetes. Despite this, pharmacogenetic studies in this area have yielded mixed results, and the clinical value of the PPAR-γ polymorphisms remains unsettled. TZDs can cause fluid retention and peripheral edema formation, which may exacerbate or precipitate heart failure. Recently, sequence variants have been identified in genes such as AQP2 and SLC12A4, which are related to sodium and water reabsorption. Two genetic variants in AQP2 (rs296766) and SLC12A1 (rs12994216) have been associated with TZD-related edema, suggesting these variants represent a risk factor in TZD-treated patients with T2DM.\textsuperscript{15}

Metiglinides (nateglinide and repaglinide) are short-acting insulin secretagogues acting by inhibiting the KATP channel on β-cells. They are similar to sulfonylureas, in that they force the pancreas to make more insulin. The association of CYP2C9 genetic variants with variability in glucose-lowering effect of nateglinide has been documented,\textsuperscript{16} together with the results from other related studies indicating that genetic polymorphisms of CYP2C9 might increase clearance of repaglinide.\textsuperscript{17} The SLC01B1 gene is critical to the body’s uptake and metabolism of various drugs. Specific variations in the SLC01B1 gene have been implicated in patient’s responses to metiglinides.\textsuperscript{18}

GLP-1 (glucagon-like peptide-1) is a potent insulin secretagogue which is inactivated rapidly by dipeptidyl peptidase IV (DPP-IV) and can significantly lower plasma glucose in the majority of patients with T2DM. There are two types of incretin-based medications: GLP-1 agonists (liraglutide and exenatide) and DPP-IV inhibitors (gliptins). Variation in GLP-1 receptor gene that may alter insulin secretion in response to exogenous GLP-1 has been reported in response to hyperglycemia and to infused GLP-1 in non diabetic subjects. It is not certain, however, whether such variation may account for interindividual differences in response to GLP-1-based therapy. Also in this context, a common variant in TCF7L2 gene (rs7903146) has been shown to affect response to exogenous GLP-1,\textsuperscript{19} while variants in KCNQ1 (rs151290, rs2237892, rs2237895) alter endogenous GLP-1 secretion.\textsuperscript{20} Nevertheless, other studies showed no effect of these variants on these parameters, underlining the necessity for further investigations.

To sum up: To date, with few exceptions, medical treatment of T2DM has not taken into account the individual genetic diversity of affected patients, which represents a major limitation of current therapies for T2DM. Clinical implementation of pharmacogenetics in the treatment of T2DM may contribute to identify new personalized medical solutions, shifting from the actual therapeutic empiricism to evidence-based management, thereby helping to avoid treatment failure and ensure treatment success. Taking in consideration the wide interindividual variability in the response to oral antidiabetic drugs, more data on this selected topic are needed to expand our knowledge on this phenomenon and to improve clinical practice in T2DM.

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Conflict of interest

Author declares that there is no conflict of interest.

References
