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Review

Genetic polymorphisms in diabetes: Influence on therapy with oral antidiabetics

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Due to new genetic insights, etiologic classification of diabetes is under constant scrutiny. Hundreds, or even thousands, of genes are linked with type 2 diabetes. Three common variants (Lys23 of *KCNJ11*, Pro12 of *PPARG*, and the T allele at rs7903146 of *TCF7L2*) have been shown to be predisposed to type 2 diabetes mellitus across many large studies. Individually, each of these polymorphisms is only moderately predisposed to type 2 diabetes. On the other hand, monogenic forms of diabetes such as MODY and neonatal diabetes are characterized by unique clinical features and the possibility of applying a tailored treatment.

Genetic polymorphisms in drug-metabolizing enzymes, transporters, receptors, and other drug targets have been linked to interindividual differences in the efficacy and toxicity of a number of medications. Mutations in genes important in drug absorption, distribution, metabolism and excretion (ADME) play a critical role in pharmacogenetics of diabetes.

There are currently five major classes of oral pharmacological agents available to treat type 2 diabetes: sulfonylureas, meglitinides, metformin (a biguanide), thiazolidinediones, and α-glucosidase inhibitors. Other classes are also mentioned in literature.

In this work, different types of genetic mutations (mutations of the gene for glucokinase, HNF 1α, HNF1β and Kir6.2 and SUR1 subunit of K_{ATP} channel, *PPAR-γ*, *OCT1* and *OCT2*, cytochromes, direct drug-receptor (*KCNJ11*), as well as the factors that influence the development of the disease (*TCF7L2*) and variants of genes that lead to hepatosteatosis caused by thiazolidinediones) and their influence on the response to therapy with oral antidiabetics will be reviewed.

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INTRODUCTION

Type 2 diabetes genes

Diabetes mellitus has reached epidemic proportions and affects more than 170 million individuals worldwide. Some 90 % of diabetic individuals have type 2 (non-insulin-dependent) diabetes mellitus, and within this category no more than 10 % account for monogenic forms (1). In 1999, a classification of diabetes based on the etiology of individual types was proposed by the Experts Committee of the World Health Organization, and is now commonly accepted. Etiologic classification was gradually extended in the last decade with the progress of knowledge, in particular with the successes of researchers in the field of genetics (2). The detailed human genome sequence information now available will lead to identification of more candidate genes for type 2 diabetes. Despite several major family and population studies, the intervals linked with type 2 diabetes are large and may contain hundreds, or even thousands, of genes. More than 60 potential candidate genes involved in insulin action, insulin secretion and adipose metabolism (since both obesity and lipoatrophy are linked to diabetes) have been examined in the search for type 2 diabetes susceptibility genes. Although variants have been identified in many of these, only a few have been shown to be associated with diabetes or impaired protein function. Thus, mutations or polymorphisms that cause only modest deficits in gene/protein function may become clinically significant when coupled with other genetic or acquired defects. The resulting imperfect correlation between the genotype and phenotype makes the task of finding diabetogenes a formidable one (3).

Type 2 diabetes is a typical complex, polygenic disease for which several common risk alleles have been identified. Three common variants (Lys23 of *KCNJ11*, Pro12 of *PPARG*, and the T allele at rs7903146 of *TCF7L2*) have been shown to be predisposed to type 2 diabetes mellitus across many large studies. Individually, each of these polymorphisms is only moderately predisposed to type 2 diabetes (4). Thus far, most of the success in defining type 2 diabetes genes (diabetogenes) has been achieved by studying relatively rare forms of the disease (3).

Monogenic forms of diabetes are characterized by unique clinical features and the possibility of applying a tailored treatment, assuring optimal correction of the genetically conditioned metabolic defect. Differential diagnostics of the diseases types is playing an increasing role in diabetology, since it enables selection of optimal treatment methods, as well as assessment of the prognosis of the diabetes course and occurrence of complications (2).

Since 1992, numerous genetic subtypes of diabetes have been described in which gene mutations result in diabetes primarily through β-cell dysfunction. This knowledge means that patients who were previously categorized clinically as having maturity-onset diabetes of the young (MODY), permanent neonatal diabetes mellitus (PNDM) or transient neonatal diabetes mellitus (TNDM) can mostly be classified by genetic subgroup. Identification of the genetic subgroup can result in appropriate treatment, genetic counseling and prognostic information. MODY used to be clinically defined as autosomal, dominantly inherited, non-insulin-dependent, early-onset diabetes, but now there are at least eight genetic subgroups of MODY, most of which have a discrete phenotype

(5). These eight genetic subgroups of MODY include HNF4A, GCK, HNF1A, HNF1B, NEUROD1, KLF11, CEL and PAX4 subtypes (6).

Diabetes diagnosed before 6 months of age is likely to be one of the monogenic forms of neonatal diabetes (5). Neonatal diabetes mellitus can be either transient (TNDM) or permanent (PNDM) (7, 8). TNDM is a developmental disorder of insulin production that resolves postnatally and accounts for 50 to 60 % of cases of neonatal diabetes. In PNDM, insulin secretory failure occurs in the late fetal or early post-natal period and does not go into remission (9). The genetic origin has been established for more than 90 % of TNDM cases. The majority of cases (68 %) are due to abnormalities in the 6q24 region, whereas 10 and 13 % of cases are attributable to mutations in *KCNJ11* and *ABCC8*, respectively. Ten genes involved in pancreatic development, β-cell apoptosis, or dysfunction have been identified as being able to give rise to PNDM (8).

Pharmacogenetics and pharmacogenomics

Clinical observations of inherited differences in drug effects were first documented in the 1950s, giving rise to the field of pharmacogenetics, and later pharmacogenomics. Although the two terms are synonymous for all practical purposes, pharmacogenomics uses genome-wide approaches to elucidate the inherited basis of differences between individuals in their response to drugs (10). Pharmacogenetics originated as a result of the observation that there are clinically important inherited variations in drug metabolism. However, similar principles apply to clinically significant inherited variation in the transport and distribution of drugs and their interaction with their therapeutic targets (11). Genetic polymorphisms in drug-metabolizing enzymes, transporters, receptors, and other drug targets have been linked to interindividual differences in the efficacy and toxicity of a number of medications. Pharmacogenomic studies are rapidly elucidating the inherited nature of these differences in drug disposition and effects, thereby enhancing drug discovery and providing a stronger scientific basis for optimizing drug therapy on the basis of each patient's genetic constitution (12).

Among many potential causes of adverse drug reactions, genetic variants that cause susceptibility to a drug reaction stand out. Identification of such variants is expected to improve the management of patient care by determining which patients should avoid a specific drug and which patients should take a modified dose of the drug. This strategy could potentially reduce medical costs and improve the process of drug development (13).

Drug-induced liver injury (DILI) is a major reason for regulatory actions against marketing approval, removal from the place and restrictions to prescribing indications. Risk factors for DILI involve polymorphisms in two major categories of genes: the highly polymorphic genes in the major histocompatibility locus on chromosome 6, which encode antigen-presenting proteins; and various polymorphic genes that encode drug metabolizing enzymes (14).

The existence of large population differences with small intrapatient variability is consistent with inheritance as a determinant of drug response it is estimated that genetics can account for 20 to 95 percent of variability in drug disposition and effects (10, 15).

Unlike other factors influencing drug response, inherited determinants generally remain stable throughout a person's lifetime (10).

PHARMACOGENETICS OF ORAL ANTIDIABETICS

There are currently five major classes of oral pharmacological agents available to treat type 2 diabetes.

Sulfonylureas, insulin secretogogues, close the ATP-sensitive potassium channel (K_{ATP}) on the plasma membrane. First generation sulfonylureas (acetohexomide, chlorpropamide, tolazamide, and tolbutamide) possess lower binding affinity for the ATP-sensitive potassium channel and thus require higher doses to achieve efficacy. Second generation sulfonylureas, including glyburide (glibenclamide), glipizide, gliclazide and glimepiride, are now widely used. The second generation sulfonylureas are much more potent compounds (~100-fold), possess a more rapid onset of action, and generally have shorter plasma half-lives and longer duration of action compared to the first generation agents (16).

Meglitinides (repaglinide, nateglinide) are a novel class of non-sulfonylurea insulin secretogogues characterized by very rapid onset and abbreviated duration of action (17). They stimulate first-phase insulin release in a glucose-sensitive manner, theoretically reducing the risk of hypoglycemic events (16).

Metformin (a biguanide) has a glucoregulatory effect only in the presence of endogenous insulin by decreasing endogenous glucose production and reducing peripheral resistance to insulin (approximately 20–30 %) (17). It also increases the utilization of glucose and most likely decreases appetite (18). The European Association for the Study of Diabetes (EASD) guidelines recommend metformin as initial pharmacotherapy for type 2 diabetes (19).

Thiazolidinediones (pioglitazone, rosiglitazone – withdrawn from the the EU market in September 2010 because of an increased cardiovascular risk) are insulin sensitizing compounds. They have glucose- and lipid-lowering activity. They are selective agonists for the peroxisome proliferator-activated receptor γ (PPARγ) and exhibit a characteristic delay from 4–12 weeks in the onset of their therapeutic benefits. These compounds decrease insulin resistance and enhance the biological response to endogenously produced insulin, as well as insulin administered by injection (16). The European Medicines Agency today recommends suspension of marketing authorizations for the rosiglitazone-containing antidiabetes medicines.

α-Glucosidase inhibitors (acarbose and miglitol) block the enzymatic degradation of complex carbohydrates in the small intestine. These compounds lower post-prandial glucose and improve glycemic control without increasing the risk for weight gain or hypoglycemia (16).

The development pipeline for new oral therapeutic agents for type 2 diabetes is encouraging and continues to expand. Thus, there are new approaches like dipeptidyl peptidase IV (DPP-IV) inhibition and selective cannabinoid-1 receptor (CB-1) antagonism (16). Glucagon-like peptide 1 mimetics and amylin mimetics are also mentioned in literature (20). Identification of the underlying molecular genetics opens the possibility of understanding the genetic architecture of clinically defined categories of diabetes, new biological insights, new clinical insights, and new clinical applications (21). Understanding the pathways that result in β cell dysfunction at physiological and molecular levels is critical for improved understanding and treatment of type 2 diabetes.

Rare types of diabetes in which a single gene defect results in severe β cell dysfunction offer a chance to gain new insights into this disease if the responsible gene can be defined (22). Monogenic β-cell disorders, which are clinically recognized as MODY or neonatal diabetes, are good examples that the therapeutic response both reflects and improves our understanding of pathophysiology. Examples of these diseases illustrate how different etiology of damage of β-cells can react very differently to therapy. The greatest attention is paid to mutations of the genes for glucokinase, HNF 1α, HNF1β and Kir6.2 subunit of K_{ATP} channel of β-cell (23). The number of researches related to different genes that influence the emergence of diabetes and parallel researches to investigate pharmacogenetical parameters and factors affecting the response of the body to applied medicines is constantly growing (Fig. 1). Researchers pay attention to genetic variations that affect the drug ADME (absorption, distribution, metabolism, excretion), where *OCT1*, cytochromes, direct drug-receptor (*KCNJ11*) are the factors that influence the development of the disease (*TCF7L2*) (20).

Mutations in the glucokinase gene

Thus far, about 200 glucokinase (GCK) mutations have been reported (24). Patients with heterozygous glucokinase mutations do not need any treatment, because they have only mild hyperglycemia, as reflected in the hemoglobin A_{1c} (HbA_{1c}) level that is at or slightly above the upper limit of normal (23). Both the severity of the GCK mutation and the genetic background seem to play a relevant role in the GCK MODY phenotype (25).

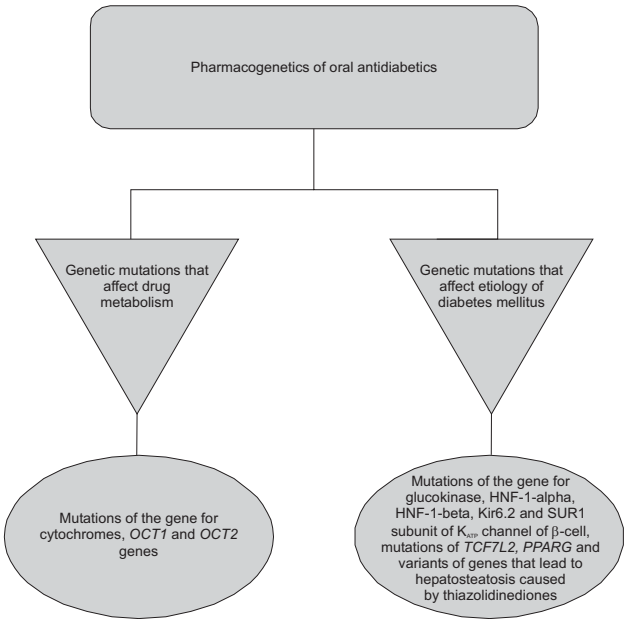

Fig. 1. Pharmacogenetics of oral antidiabetics.

Heterozygous, inactivating mutations in the glucokinase gene result in life-long mild fasting hyperglycemia, which deteriorates very little with age. This is primarily due to compensation through overexpression of the normal, nonmutated allele (23).

Diabetes due to mutations in glucokinase appears to be relatively mild, as indicated by the number of affected subjects who did not have overt diabetes and by the fact that the disease was treated by the diet alone in most subjects. The fact that most were lean, having a normal body weight was sufficient to maintain fasting plasma glucose concentrations around 125 mg per deciliter (6.9 mmol L^{-1}) (26).

Mutations in the HNF1α gene

Subjects with mutations in the HNF-1α gene usually develop diabetes in adolescence or early adulthood (27, 28). Mutations in HNF-1α result in progressive β-cell dysfunction with increasing treatment requirements and a higher risk of complications with age (29). Deterioration of fasting glucose with age is a result of a faster deteriorating β-cell function with the HNF-1α than with the GCK mutation (27).

Progressive β-cell failure leads to increasing hyperglycemia due to reduced insulin secretion in response to hyperglycemia (28). The ability of glucose to induce closure of K_{ATP} channels in the HNF-1α (–/–) mouse β-cells is significantly reduced. Since the K_{ATP} current is blocked by the addition of ATP and NADH to the cell, the failure to generate ATP appears to account for reduced glucose responsiveness of the K_{ATP} channel in HNF-1α (–/–) mouse β-cells (30).

Studies in β-cell models investigated the impact of human HNF-1α mutations on β-cell function. The most common mutation of HNF-1α has dominant negative effects on the expression of genes involved in glucose transport and glycolysis. Also, it has been discovered that there is a common mitochondrial defect substained by diminished ATP generation and substrate oxidation (31). This form of diabetes frequently requires treatment with oral agents or insulin (27).

Sulfonylureas can dramatically improve glycemic control and should be considered as the initial treatment for patients with poor glycemic control on an appropriate diet (32). Marked sensitivity to the hypoglycemic effect of sulfonylureas in HNF-1α subjects has been observed, which could be explained, at least in part, by increased insulin sensitivity (27, 28, 33). The key feature of all these defects is that they are upstream of the K_{ATP} channel. This means that as long as some ATP is present within the β-cell, sulfonylureas would be able to close the channel, because this is downstream of the primary defect. This explains why these patients are sensitive to the hypoglycemic effects of sulfonylureas, but does not explain the progressive deterioration in β-cell function that results in increasing hyperglycemia with age. The precise mechanisms of chronic reduction in β-cell mass are uncertain (23).

Glibenclamide is one of the most widely used orally active sulfonylureas in the treatment of type 2 diabetes. Hypoglycemia is the most important and most often fatal adverse effect of sulfonylureas (34).

In studies of the HNF1α knockout animals, researchers hypothesized that the reduced clearance of glibenclamide was due to a decrease in hepatic uptake or impaired metabolism of the sulfonylurea. Hypoglycemia may occur more frequently in subjects with

HNF-1 α deficiency treated with glibenclamide because of delayed disappearance of the drug from the blood. Very low doses of short-acting sulfonylureas should therefore be used initially in the treatment of patients with HNF-1α deficiency, and these drugs should be discontinued in subjects with liver disease. Monitoring sulfonylurea plasma concentration in HNF-1α deficiency patients may also be useful for avoiding hypoglycemia (34). Cessation of sulfonylureas should be undertaken cautiously as there may be marked deterioration in glycemic control (32).

In a randomized crossover trial of gliclazide and metformin in 36 patients, either with diabetes caused by HNF-1α mutations or type 2 diabetes, who were matched for body-mass index and fasting plasma glucose, Pearson *et al.* (33) found that patients with HNF-1α diabetes had a stronger response to gliclazide than to metformin and also stronger response to gliclazide than those with type 2 diabetes. Patients with HNF-1α diabetes had a strong insulin secretory response to intravenous tolbutamide despite a weak response to intravenous glucose, and were more insulin sensitive than those with type 2 diabetes. Sulfonylurea metabolism was similar in both patient groups.

Mutations in the HNF-1α gene make up the majority of cases that might be mistaken for type 1 diabetes (35, 36).

One study was made on eight UK Caucasian patients with median age of 34 years (range 17–48), median age of diagnosis 14 years (range 8–17), and median time on insulin 20 years (range 4–35); four patients had been on insulin for more than 27 years. All patients were able to discontinue insulin and were maintained on sulfonylureas without developing ketonuria or marked hyperglycemia. There was heterogeneity in response of the majority of patients (6 of 8), showing an improvement in control. In short-term studies, when patients with *HNF-1α* mutations were transferred from insulin to sulfonylureas, good glycemic control was achieved, even when patients had been on prolonged insulin treatment before transferring. These preliminary short-term data needs to be repeated in larger series with long-term follow-up. Many of these patients may require insulin again in the future (37).

Mutations in the HNF1β *gene*

The syndrome of mild diabetes mellitus, progressive non-diabetic renal disease and severe genital tract abnormalities with vaginal aplasia and rudimentary uterus are associated with a heterozygous mutation in the *HNF-1β* gene (38). The low insulin sensitivity in HNF-1β subjects suggests that an insulin sensitizer such as metformin or a peroxisome proliferator-activated receptor-γ agonist would be the oral agent of choice. HNF-1β patients have a different diabetes phenotype than HNF-1α patients. The difference in both the pancreatic and extrapancreatic phenotypes of HNF-1α and HNF-1β mutations is striking, particularly in view of the close homology of these transcription factors and their shared binding site (39). It was found that HNF-1β defines a cellular population that forms primitive pancreatic ducts. Such embryonic duct HNF-1β$^+$ cells are phenotypically distinct from earlier pancreatic bud cells and present evidence that they are direct precursors of endocrine progenitor cells (40).

There are no useful models of the role of HNF-1β in the β-cell because the HNF-1β$^{-/-}$ mouse dies at an early embryonic stage and there is no published literature on HNF-1β in pancreatic cell lines (39). Despite considerable homology of HNF-1α and

HNF-1β, differences in associated diabetes phenotypes exist in MODY. Despite the evidence suggestive of insulin resistance, insulin requirements in patients with diabetes due to HNF-1β tend to be low. These low requirements could indicate that patients still have considerable endogenous insulin secretion. This suggests that the β-cell defects in diabetic subjects caused by HNF-1β mutations are qualitatively different from HNF-1α with different sites or severity of defects. In HNF-1β mutation carriers diabetes may develop during embriogenesis, a consequence of which is reduced β-cell mass. HNF-1β patients do not respond particularly well to sulfonylureas, and this is consistent with the PEAKtolb--to-PEAKgluc ratio being similar to type 2 diabetes (39).

Mutations in the gene for Kir6.2 (KCNJ11) and SUR1 (ABCC8)

To date, more than 30 heterozygous, activating mutations in K_{ATP} channels have been reported (41). K_{ATP} channel is composed of four small subunits Kir6.2 that surround the central cavity and four major subunits that build SUR1 (42). Every subunit can be in opened and closed conformation (43). Numerous factors can modulate the activity of K_{ATP} channels. This can happen at the level of Kir6.2 and SUR subunits. The most important factors that inhibit the Kir6.2 are ATP and ADP, and the most important factors that inhibit SUR are sulfonylureas. The most important factors that activate Kir6.2 are fatty acid metabolites, PIP2 (phosphatidylinositol phosphate) and SUR diazoxide, Mg-ATP and Mg--ADP. Glucose and amino acids can regulate the secretion of insulin. Glucose and amino acids are metabolized in β cells in which ATP is created, which leads to closure of K_{ATP} channels, accumulation of intracellular potassium, membrane depolarization, opening voltage dependent calcium channel that stimulates insulin exocytosis (42).

KCNJ11 (coding Kir6.2 subunit of K_{ATP} channel) mutations that cause a small decrease in the ATP sensitivity of heterozygous K_{ATP} channels result in neonatal diabetes alone, whereas those which produce a greater reduction in ATP-sensitivity are associated with additional symptoms. The molecular mechanism by which a mutation affects the channel ATP sensitivity determines the severity of its effect in the heterozygous state, with the mutations that influence gating producing larger effects on ATP sensitivity, and a more severe disease phenotype, than those that lie in the putative ATP-binding site (44). Of the 49 patients with heterozygous activating mutations in the *KCNJ11* gene, who were treated with an adequate dose of sulfonylureas, 44 were able to stop insulin treatment. The switch to sulfonylureas was successful regardless of the type of sulfonylurea used, suggesting a class effect (45). Efficacy of sulfonylurea therapy is likely to depend on the nature of the Kir6.2 mutation. Functional characterization of additional mutations in Kir6.2, as well as additional clinical studies, will provide essential data regarding the efficacy of sulfonylurea therapy in treating K_{ATP}-induced diabetes and the possibility of tailoring individual therapy based on the underlying Kir6.2 mutation. Careful attention should be paid to the degree to which neonatal diabetes mutations cause a loss of ATP sensitivity by an increase in open-state stability. The greater is the mutational effect on open-state stability, the higher will be the sulfonylurea dose necessary to achieve a given degree of channel inhibition. Thus, to achieve the same therapeutic effect (sufficient closure of K_{ATP} under appropriate physiological conditions), proportionally higher doses of an sulfonylurea may be clinically required. Models of the K_{ATP} channel gating and nucleotide and sulfonylurea sensitivity have been developed. To have predictive

use, such models should account for channel gating (in the absence of ATP), nucleotide sensitivity, and drug sensitivity, and by adjusting relevant parameters, they should be able to account for the effects of mutations on channel function (46).

Heterozygous activating mutations in *ABCC8*, encoding the SUR1 regulatory subunit of the ATP-sensitive potassium channels found in beta cells, cause both permanent and transient neonatal diabetes. Although molecular mechanisms of the *ABCC8* and *KCNJ11* mutations are distinct, the cellular mechanism reducing insulin release is common to both. Treatment with sulfonylureas, glyburide or glipizide was initiated in patients with permanent neonatal diabetes and transient neonatal diabetes and has proved effective (47). Oral sulfonylurea therapy is safe and effective for a short term in most patients with diabetes due to SUR1 mutations and may successfully replace treatment with insulin injections. A different treatment protocol needs to be developed for this group of patients because they require lower doses of sulfonylureas than those required by Kir6.2 patients (48).

Zung *et al.* (49) observed near-normal postprandial glucose values although glibenclamide administration was not synchronized with meals, which contained significant amounts of simple carbohydrates. This overcame the initial concern that sulfonylurea therapy might result in unregulated insulin secretion, because sulfonylurea receptor 1-mediated K_{ATP} channel closure might prevent the channel from responding to altered ATP concentrations resulting from varying glucose concentrations through the classical pathway.

Sulfonylureas cause partial closure of the K_{ATP} channel, which means that the β-cell membrane is no longer fully depolarized, and is therefore able to respond to other stimuli, particularly glucagon-like peptide-1, which is released with food. Additional studies are needed, but early results strongly support the idea that incretins and other alternative pathways that stimulate insulin secretion are required for excellent glycemic control (23).

According to pharmacokinetic data, chronic glibenclamide treatment *in vivo* causes loss of insulin secretory capacity due to β-cell hyperexcitability, but also reveals rapid reversibility of this secretory failure, arguing against β-cell apoptosis or other cell death induced by sulfonylureas. These *in vivo* studies may help explain why patients with type 2 diabetes can show long-term secondary failure to secrete insulin in response to sulfonylurea, but experience restoration of insulin secretion after a drug resting period, without permanent damage to β-cells. This finding suggests that novel treatment regimens may succeed in prolonging pharmacological therapies in susceptible individuals (50).

The common E23K polymorphism in *KCNJ11* has been most extensively studied in the classical form of type 2 diabetes. E23K variant in the candidate gene *KCNJ11* may impair insulin secretion stimulated by sulfonylureas, thus increasing the risk of developing secondary failure to these oral agents (51).

Mutations of the cytochrome p450 system

The polymorphic enzyme cytochrome P450 (CYP) 2C9 is the main enzyme that catalyzes the biotransformation of sulfonylureas (52). Although not the most prominent risk factor, *CYP2C9* genotypes predictive of low enzyme activity (*CYP2C9*3/*3* and **2/*3*) should be considered as one but not the main risk factor for severe hypoglycemia resulting from treatment with sulfonylurea oral hypoglycemic agents. Furthermore, comedication with

agents that inhibit CYP2C9 might be an additional risk factor for hypoglycemia by increasing the concentrations of oral hypoglycemic drugs that are metabolized by this enzyme. Genotyping of *CYP2C9* allelic variants is a relatively easy and inexpensive test that might help prevent adverse reactions to CYP2C9 substrates (53).

Pharmacokinetics of glyburide depended significantly on CYP2C9 genotypes. In homozygous carriers of genotype *3/*3, total oral clearance was less than half that of the wild-type genotype *1/*1. The corresponding differences in insulin plasma levels indicated that dose adjustment based on CYP2C9 genotype may improve antidiabetic treatment (54).

Tolbutamide was confirmed as a substrate of the genetically polymorphic enzyme CYP2C9. The pronounced differences in pharmacokinetics due to amino acid variants did not significantly affect plasma insulin and glucose concentrations in healthy volunteers (55).

The meglitinide class drug nateglinide is metabolized by CYP2C9. According to pharmacokinetic data, moderate dose adjustments based on CYP2C9 genotypes may help in reducing interindividual variability in the anti hyperglycemic effects of nateglinide (52). Significantly reduced oral nateglinide clearance was found in carriers of CYP2C9*3 alleles, whereas carriers of CYP2C9*2 alleles had kinetic parameters similar to those of the wild-type allele carriers. Carriers of the CYP2C9*3/*3 genotype may be at a slightly higher risk of hypoglycemia compared to carriers of CYP2C9*1, particularly when taking nateglinide doses above 120 mg (56).

Repaglinide is metabolized by CYP2C8 and, according to clinical studies, CYP2C8*3 carriers had higher clearance than carriers of the wild-type genotypes; however, this was not consistent with *in vitro* data and therefore further studies are needed. CYP2C8*3 is closely linked with CYP2C9*2 (52). An association of insulin-like growth factor 2 mRNA--binding protein 2 (IGF2BP2) rs1470579 and rs4402960 polymorphisms and development of type 2 diabetes, and therapeutic efficacy of repaglinide in Chinese type 2 diabetes patients was reported (57).

Bozkurt *et al.* (58) published 37 studies between 1966 and 2007 reporting data on genetic polymorphisms and responses to glucose-lowering drugs. Most studies involving cytochrome P450 (CYP) genes had small sample sizes (21 studies < 50 subjects) and included healthy volunteers. They found that CYP2C9*3 allele was associated with a decreased clearance of meglitinides.

CYP2C8 and CYP3A4 are the main enzymes that catalyze biotransformation of the thiazolidinediones troglitazone and pioglitazone, whereas rosiglitazone is metabolized by CYP2C9 and CYP2C8.

Pharmacogenetic variability plays an important role in the pharmacokinetics of oral antidiabetic drugs; however, the impact of this variability on clinical outcomes in patients is still mostly unknown and prospective studies on the medical benefit of CYP genotyping are required (52).

Mutations in the OCT1 *and* OCT2 *gene*

OCT1 deletion results in reduced metformin uptake and response in primary mouse hepatocytes. OCT1 appears to play a key role in determining one of the major pharmaco-

logic effects of metformin, inhibition of hepatic gluconeogenesis. OCT1 polymorphisms modulate metformin uptake and response in cells. Seven OCT1 variants exhibited reduced metformin uptake compared to the OCT1-reference. The tissue-specific action of metformin may be related to expression of influx transporters such as OCTs that can deliver metformin intracellularly (59).

Liver concentration of metformin was approximately 30 times higher in Oct1(+/+) mice than Oct(–/–) mice. A 3- to 7-fold higher distribution in Oct1(+/+) than in Oct(–/–) mice was also observed in the duodenum, jejunum, and ileum. On the other hand, the distribution of metformin to the kidney was almost identical for the two types of mice and the difference in the distribution to the colon was minimal (60). Metformin is dominantly transported by OCT2 compared to OCT1. The *in vivo* tissue uptake clearance of metformin in male rat kidney was about 6 times higher than that in male liver, and therefore the plasma flow rate in the kidney might be a limiting factor for metformin renal distribution (61).

Mutations in the TCF7L2 *gene*

Pearson *et al.* (62) studied the influence of variation within TCF7L2 on the early response to sulfonylureas and metformin in 1,846 patients with type 2 diabetes in Tayside, Scotland. Variation in TCF7L2 influences the initial treatment success with sulfonylurea therapy in patients with type 2 diabetes. This is seen for both SNPs (rs12255372 and rs7903146) that were reported to be associated with diabetes risk and is an addition to the effect of dose, adherence, sex, and baseline glycemia. Compared with the monogenic examples, the effect of TCF7L2 variation on the response is modest, although a twofold greater likelihood of treatment failure in 12% of the population who are TT homozygote at rs1225372 is striking.

There was a weak association between metformin treatment success and TCF7L2 genotype. This study is a robust example of pharmacogenetics within an unselected polygenic type 2 population (62).

Mutations in the PPARG *gene*

Five haplotype blocks in *PPARG* and its surrounding regions were identified, and association results based on the response to troglitazone suggests that three of these may independently, or jointly, be involved in mediating the response to troglitazone. Individual SNPs in blocks 1, 3, and 5, plus SNP rs1152003, showed association with 3-month changes in phenotypes, suggesting that these regions may be of importance in mediating troglitazone response. Sequence variation in *PPARG* that may contribute to different insulin-sensitizing responses to troglitazone therapy in Hispanic women with previous gestational diabetes was identified (63). Genetic variants within two haplotype blocks may help determine the response. Whether the inability to respond to troglitazone therapy is due to an effect of these variants on troglitazone binding to PPARG or an impairment of the agonistic activity of troglitazone through disruption of interactions between *PPARG* and critical *PPARG* cofactors (*e.g.*, retinoid X receptor-α) will require functional characterization studies. Response to thiazolidinediones therapy may not be accurately predicted by genotyping one or two variants within *PPARG*. Instead, prediction of the response

may require assessment of a cluster of genotypes, possibly across different genes. Nonetheless, our results provide the first evidence supporting the concept that variation within *PPARG* partly accounts for the response to therapy with thiazolidinediones (63).

The Pro12Ala variant in the PPARG gene does not affect the efficacy of pioglitazone therapy, suggesting that the drug-treatment response is independent of pharmacogenetic effects between PPARG and its ligand pioglitazone. Whether the Ala12Ala genotype plays a role in the response rate to thiazolidinedione therapy remains to be determined (64).

Among young Hispanic women at high risk of type 2 diabetes, the Pro12Ala variant of the PPARG receptor gene did not explain the failure of 1/3 of subjects to increase their insulin sensitivity when placed on troglitazone at a dose of 400 mg/day (65).

Peroxisome proliferator activated receptor-γ coactivator-1α (PGC-1α) Thr394Thr and Gly482Ser polymorphisms were associated with the therapeutic efficacy of multiple-dose rosiglitazone in Chinese patients with type 2 diabetes mellitus (66).

Variants of genes that lead to hepatosteatosis caused by thiazolidinediones

Obesity-associated diabetes (diabesity) also has a complex polygenic basis in mice. Admixing genomes of unrelated strains of inbred mice provides an insight into how a complex disease such as type 2 diabetes can become more common as genetic heterogeneity increases in an outbreeding human population. A panel of recombinant congenic strains (RCSs) with varying degrees of obesity and diabetes was generated. Availability of the panel of genetically characterized RCS models of diabesity with differential thiazolidinedione sensitivities is useful for understanding the genetic basis for susceptibility to adverse drug responses. Such pharmacogenetic knowledge might distinguish a small percentage of patients who should not take this class of compounds. RCS8 and RCS10 exhibit comparable levels of obesity and basal hepatic lipidosis with a control diet, but only RCS8 experiences a drug-exacerbated steatosis as extreme as originally described in F1. The most notable genetic difference distinguishing RCS8 is its NZO (New Zealand obese) origin of chromosome 16 in its entirety. The cholinephosphate cytidylyltransferase-α subunit is encoded on this chromosome. The active form of cholinephosphate cytidylyltransferase activity resides on cellular membranes. Subcellular fractionation showed that rosiglitazone-mediated reduction in the cholinephosphate cytidylyltransferase activity in total homogenate was primarily in a cytosol and, to a lesser extent, in the crude mitochondrial fraction. Genetic disruption of cholinephosphate cytidylyltransferase-α (CTα) produces a hepatic phenotype similar to that observed in rosiglitazone-treated F1 (67). In studies on mice in which the hepatic CT α gene was specifically inactivated it was observed that impairment in the hepatic CDP-choline pathway alters the metabolism of both hepatic and circulating lipids and lipoproteins (68). In RCS8, not only is cholinephosphate cytidylyltransferase activity reduced, but also this partial loss of cholinephosphate cytidylyltransferase activity is accompanied by significant losses in both choline kinase and PEMT (phosphatidylethanolamine methyltransferase) biosynthetic functions. At least four other loci on chromosome 16 associated with hepatic triglyceride metabolism and steatosis represent potential candidates. Rosiglitazone-mediated inhibition of enzymes in both arms of the phosphatidylcholine biosynthetic pathway would very likely impair lipoprotein assembly and export, and hence promote, the observed

hepatic triglyceride accumulation. Moreover, regardless of the mechanism of the decrease in cholinephosphate cytidylyltransferase and PEMT activity as a result of rosiglitazone treatment, less diacylglycerol would be used in the biosynthesis of phosphatidylcho-

Table I. Mutations of genes that can affect treatment with oral antidiabetics

Mutations of genes that can affect treatment	Effects
	Sulfonylureas
HNF-1α	Marked sensitivity to hypoglycemic effect of sulfonylureas (27, 28, 33). Transferring insulin-treated patients with HNF-1α mutations to sulfonylureas was safe for a short term (37).
HNF-1β	Do not respond particularly well to sulfonylureas (39).
KCNJ11	Of the 49 patients with heterozygous activating mutations in the *KCNJ11* gene who were treated with an adequate dose of sulfonylureas, 44 were able to stop insulin treatment. The switch to sulfonylureas was successful regardless of the type of sulfonylurea used (45). Efficacy of sulfonylurea therapy is likely to depend on the nature of the Kir6.2 mutation (46).
KCNJ11, E23K variant	May impair insulin secretion stimulated by sulfonylureas, thus increasing the risk to develop secondary failure to these oral agents (51).
ABCC8	Oral sulfonylurea therapy is safe and effective for a short term in most patients and may successfully replace treatment with insulin injections (48).
cytochrome P450 (CYP) 2C9	CYP2C9*3/*3 and *2/*3 should be considered as one but not the main risk factor for severe hypoglycemia resulting from treatment with sulfonylurea oral hypoglycemic agents (53).
TCF7L2 (rs12255372 and *rs7903146)*	Influences initial treatment success with sulfonylurea therapy in patients with type 2 diabetes (62).
	Meglitinides
*CYP2C9*3*	Significantly reduced oral nateglinide clearance (56).
*CYP2C8*3*	Repaglinide is metabolized by *CYP2C8* and, according to clinical studies, *CYP2C8*3* carriers had higher clearance than carriers of the wild-type genotypes (52).
IGF2BP2	Mutations can affect treatment with repaglinide treatment (58).
	Metformin
OCT1	Deletion results in reduced metformin uptake and response in primary mouse hepatocytes (59).
	Thiazolidinediones
PPARG	SNPs in blocks 1, 3, and 5, plus SNP rs1152003, showed association with 3-month changes in phenotypes, suggesting that these regions may be of importance in mediating troglitazone response (63).
PGC-1α	Mutations can affect treatment with rosiglitazone (66).

line. Under such conditions, the diacylglycerol would be acylated to triacylglycerol and this could lead to the observed hepatic steatosis. It remains to be established whether this unusual pharmacogenetic effect is mediated *via* direct effects of peroxisome proliferator-activated receptor-γ (PPAR γ) at the hepatocyte or indirectly by primary drug effects on another tissue, such as white fat. These results indicate a constitutive impairment of hepatic phosphatidylcholine biosynthetic enzyme functions, which is further exacerbated by thiazolidinedione treatment (67).

Other mutations that can affect therapy with oral antidiabetics

There have lately been new reports on polymorphisms that can influence therapy with oral antidiabetics. Carriers of A allele of Thr394Thr had high density lipoprotein--cholesterol, which was enhanced to a lesser degree and lower attenuated postprandial serum insulin compared to G alleles. Patients with PGC-1α Gly482Gly had fasting plasma glucose that was attenuated to a greater degree and postprandial serum insulin compared to Gly482Ser+Ser482Ser. After rosiglitazone treatment, carriers of A allele of Thr394Thr and Ser allele of Gly482Ser showed a worsening trend for GG and a significant therapeutic response to rosiglitazone for Gly/Gly. Huang *et al.* (68) found that the effects of repaglinide treatment on fasting plasma glucose ($p < 0.05$) and postprandial plasma glucose ($p < 0.05$) were reduced in patients with the rs1470579 AC+CC genotypes compared to AA genotype carriers. Patients with the rs4402960 GT+TT genotypes exhibited an enhanced effect of repaglinide.

Table I shows summarized mutations of genes that can affect treatment for each pharmacologic group of antidiabetic drugs.

CONCLUSIONS

Numerous genes that influence pharmacogenetics of oral antidiabetics have been discovered to date. The number of new conclusions regarding individual therapy of diabetes is growing every day. Particularly interesting area of oral antidiabetics is the importance of accurate dosage to prevent hypoglycemia and use of wrong medicines. With the development of pharmacogenetics it is easier for patients to cope with this disease and new opportunities for therapeutic improvement are provided. However, further research is needed in the field.

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SAŽETAK

Genetički polimorfizmi u dijabetesu: Utjecaj na terapiju oralnim antidijabeticima

UNA GLAMOČLIJA i ADLIJA JEVRIĆ-ČAUŠEVIĆ

Dijabetes tipa 2 dosegao je proporcije epidemije u SAD (> 18 milijuna) i cijelom svijetu (170 milijuna oboljelih osoba) te ima tendenciju daljnjeg dramatičnog rasta. Stoga se u posljednje vrijeme ulažu napori da se otkriju i razviju novi farmakološki agensi za liječenje ove bolesti. Klasifikacija šećerne bolesti proširena je uspjesima istraživača na području genetike. Da bismo razumjeli farmakogenetiku antidijabetika neophodno je razumjeti genetiku samog dijabetesa. Kao što će biti prikazano u ovom radu veliki broj gena koji su povezani s razvojem dijabetesa također utječe i na odgovor na terapiju antidijabeticima. S druge strane, mutacije gena koji utječu na ADME (apsorpcija, distribucija, metabolizam i ekskrecija) lijeka imaju značajan utjecaj na farmakogenetiku oralnih antidijabetika.

Utvrđeno je da je dijabetes genetički heterogena bolest. Uobičajeni oblici dijabetesa su gotovo uvijek poligenski i za razvoj same bolesti vrlo su značajne snažne interakcije među različitim genima kao i između gena i okoliša. Zbog toga mutacije ili polimorfizmi koji u manjoj mjeri utječu na funkciju gena mogu postati klinički značajni samo u slučaju kada se kombiniraju s drugim faktorima odnosno genima. Smatra se da u razvoju dijabetesa mogu sudjelovati stotine pa čak i tisuće gena. Do 2006. identificirano je nekoliko

uobičajenih alela koji povećavaju rizik za razvoj dijabetesa, od kojih su najznačajniji *PPARG* (Pro12), *KCNJ11* (Lys23) i *TCF7L2* (T na rs7903146). Do danas je najveći uspjeh postignut u identifikaciji gena odgovornih za razmjerno rijetke oblike ove bolesti poput »Maturity-onset diabetes of the young« (MODY) i neonatalnog dijabetesa. Monogenske oblike dijabetesa odlikuju jedinstvene kliničke karakteristike i mogućnost primjene individualnog tretmana.

Genetički polimorfizmi enzima koji utječu na metabolizam lijekova, transportera, receptora i drugih ciljeva djelovanja lijekova povezani su s interindividualnim razlikama u efikasnosti i toksičnosti mnogih lijekova. Vrlo je važno da se na temelju farmakogenetičkih istraživanja mogu predvidjeti neki neželjeni efekti lijekova.

Trenutačno postoji pet glavnih klasa oralnih antidijabetika: sulfoniluree, meglitinidi, metformin (bigvanid), tiazolidindioni i inhibitori α-glukozidaze. U literaturi se također spominju inhibitori dipeptidil peptidaze IV (DPP-IV), selektivni antagonisti kanabinoidnog receptora 1 (CB-1), mimetici glukagonu sličnog peptida 1 i mimetici amilina.

Razumijevanje mehanizama koji rezultiraju disfunkcijom β stanica na fiziološkom i molekularnom nivou neophodno je za napredak u razumijevanju tretmana dijabetesa. U ovom radu dat je pregled različitih genetičkih mutacija (mutacije gena za glukokinazu, HNF 1α, HNF1β, Kir6.2 i SUR 1 podjedinicu K_{ATP} kanala β stanica, *PPAR-*γ, *OCT1* i *OCT2*, citohrome, *KCNJ11*, faktore koji utječu na razvoj bolesti (*TCF7L2*) i varijante gena koji dovode do hepatosteatoze uzrokovane tiazolidindionima) te njihov utjecaj na odgovor na terapiju oralnim antidijabeticima.

Ključne riječi: farmakogenetika, oralni antidijabetici

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