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MINIREVIEWS

Pharmacogenetics of type 2 diabetes mellitus: An example of success in clinical and translational medicine

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Abstract

The pharmacological interventions currently available to control type 2 diabetes mellitus (T2DM) show a wide interindividual variability in drug response, emphasizing the importance of a personalized, more effective medical treatment for each individual patient. In this context, a growing interest has emerged in recent years and has focused on pharmacogenetics, a discipline aimed at understanding the variability in patients' drug response, making it possible to predict which drug is best for each patient and at what doses. Recent pharmacological and clinical evidences indicate that genetic polymorphisms (or genetic variations) of certain genes can adversely affect drug response and therapeutic efficacy of oral hypoglycemic agents in patients with T2DM, through pharmacokinetic- and/or pharmacodynamic-based mechanisms that may reduce the therapeutic effects or increase toxicity. For example, genetic variants in genes encoding enzymes of the cytochrome P-450 superfamily, or proteins of the ATP-sensitive potassium channel on the beta-cell of the pancreas, are responsible for the interindividual variability of drug response to sulfonylureas in patients with T2DM. Instead, genetic variants in the genes that encode for the organic cation transporters of metformin have been related to changes in both pharmacodynamic and pharmacokinetic responses to metformin in metformin-treated patients. Thus, based on the individual's genotype, the possibility, in these subjects, of a personalized therapy constitutes the main goal of pharmacogenetics, directly leading to the development of the right medicine for the right patient. Undoubtedly, this represents an integral part of the translational medicine network.

Key words: Type 2 diabetes; Anti-diabetic drugs; Personalized therapy; Genetic variants; Genome-wide association study

Core tip: Type 2 diabetes mellitus (T2DM) is a heterogeneous complex disorder, in which predisposing genetic variants (polymorphisms) and precipitating environmental factors interact synergistically in the development of the disease. Besides being useful in identifying individuals at risk for T2DM, knowledge of the polymorphisms associated with T2DM is also useful in pharmacogenetics for correlating individual variants with individual responses to anti-diabetic drugs. To date, a wide variety of genes that influence pharmacogenetics of anti-diabetic drugs have been identified. However, with few exceptions, drug therapy has not taken into account the individual genetic diversity of treated patients, representing, this, a substantial limitation of pharmacogenetics. This review focuses on clinically important polymorphisms affecting a patient's response to diabetic medications.

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INTRODUCTION

The common observation that patients with type 2 diabetes mellitus (T2DM) show a great variability in the individual response to the same drug treatment suggests the importance of a personalized care approach, in which the most appropriate treatment is indicated by the genetic peculiarities of each individual[1]. The introduction, in 2007, of genome-wide association study (GWAS) has greatly enhanced the number of genes that are known to be associated with common diseases. Applied to millions of people, this method has allowed the identification of several genetic variants which are associated with T2DM[2]. However, similarly to other complex diseases, none of the individual variants identified so far is in itself sufficient to cause the disease, but most of the genetic risk for T2DM is mediated by the combined influence of more genetic variants that individually have only a small degree of risk[3,4]. This combination (haplotype) defines the genetic profile of the individual. The fact that the pathogenesis of T2DM requires the involvement of multiple genes in different combination is in line with the assumption that T2DM, far from being a disease genetically identifiable in a few specific forms, actually consists of a large number of rather different disorders[3,4], each of which is associated with a specific disease phenotype only apparently identical to one another, and in which inter-individual variability in drug response can be identified both in terms of drug efficacy and undesired drug reactions.

Therefore, clarifying the molecular mechanisms by which genetic variations may cause differences in phenotypic traits and in individual drug response is essential not only to determine the etiological role of gene variants, but also to identify new personalized medical solutions. Personalized therapy, based on the genetic diversity of each individual, is one of the most fascinating challenges of modern medicine, representing an integral part of the translational medicine effort, whose ultimate goal is to translate advances in biomedical research into new medical treatments and improvements in patient care (Figure 1). Herein, we provide an overview of this area and its relevance to clinical practice in T2DM.

PHARMACOGENETICS AND GENE POLYMORPHISMS

Pharmacogenetics is defined as the influence of variations in DNA sequence on drug response (www.ema.europa.eu). Its relevance arises from the clinical observation that patients suffering from the same disease do not necessarily respond to the same drug treatment in terms of therapeutic efficacy as well as adverse effects. The principal aim of pharmacogenetics is to provide

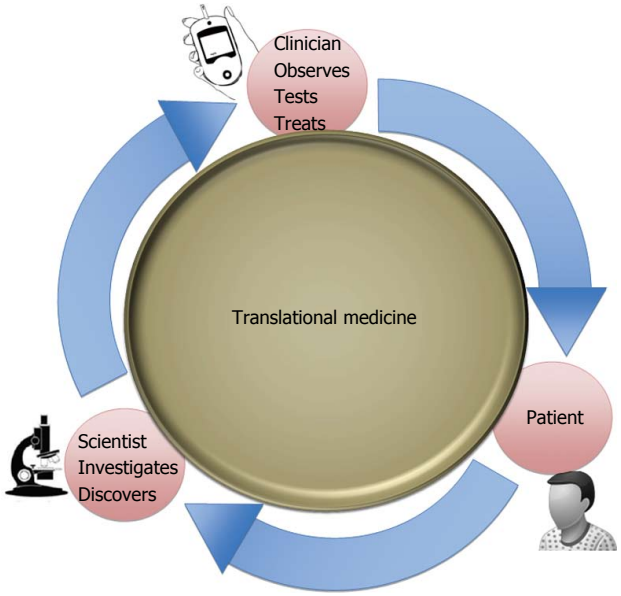

Figure 1 From bench to bedside. Translational medicine is a discipline of biomedical research that attempts to connect basic research with clinical care.

personalized medicine, tailored to an individual's genetic makeup, in order to optimize the effectiveness and safety of drug treatment. Although elements of pharmacogenetics can be traced back to ancient Greece (510 years BC), when it was already known the risk of hemolytic anemia in certain individuals in response to the ingestion of uncooked fava beans[5], the term "pharmacogenetics" was first coined by Vogel[6] in 1959 to indicate the importance of genetic polymorphisms on the disposition and action of drugs. The first evidence on the role of genetic variants in drug response back to the '70s and refers to cytochrome P-450 2D6 (CYP2D6), an enzyme of the hepatic P-450 microsomal enzyme system, which is involved in the metabolism of numerous drugs. Studies of the genetic variations within the P-450 family of enzymes provided the first direct evidence for the genetic contributions to drug therapy and efficacy, and these studies continue to be an active part of the basic and clinical research performed today. In fact, numerous other genetic variations have been identified in subsequent years, within the P-450 family of enzymes, including the biotransformation enzymes CYP3A4/5 and the CYP2C9 enzyme. It has been shown that individuals carrying genetic variants of *CYP2D6* (and other P-450 isoforms resulting in poor enzymatic activity), who are concomitantly taking medications that are influenced by these enzymes, are at risk for increased or prolonged drug effect, influencing the speed and effectiveness of drug metabolism[7]. However, there is no doubt that the greatest contribution to pharmacogenetics has come from the sequencing of the entire human genome in 2003, showing that over 99% of DNA is identical in all humans and that, therefore, phenotypic differences among individuals, as well as differences in disease susceptibility and the inter-individual variability in drug response, are the result of sequence polymorphisms that

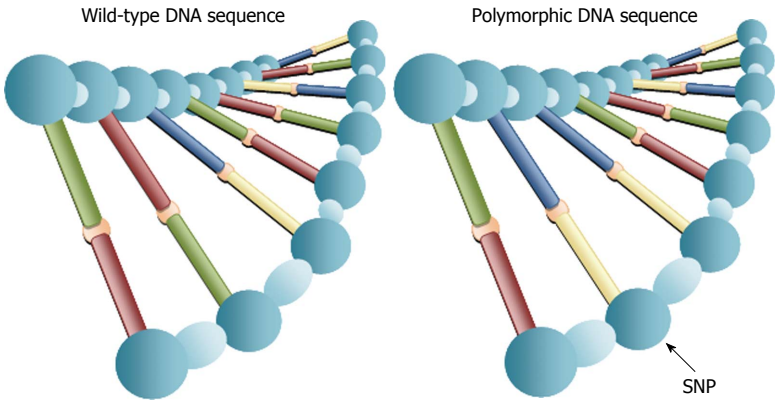

Figure 2 Single nucleotide polymorphism. As the most common type of variant, a single nucleotide polymorphism is characterized by a single DNA base pair substitution at a specific location in a gene. SNP: Single nucleotide polymorphism.

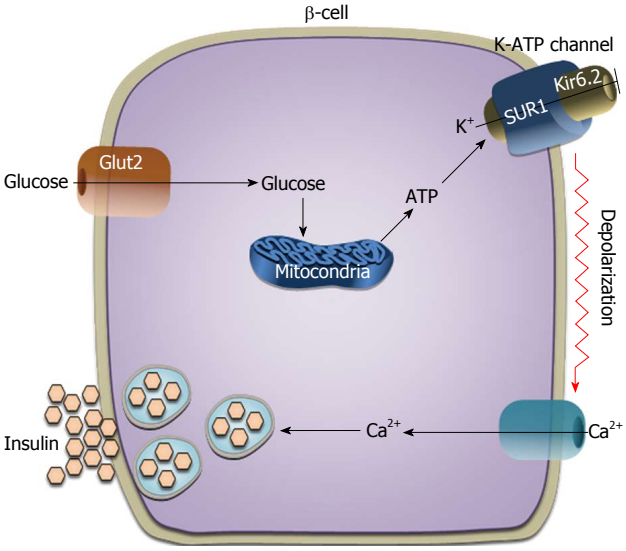

Figure 3 The ATP-sensitive K^+ channels regulate insulin release in beta-cells. Single nucleotide polymorphism in *SUR1* and/or *Kir6.2* genes may cause functional abnormalities of the ATP-sensitive K^+ channel on the pancreatic β-cell membrane, leading to abnormalities in insulin secretion.

affect less than 1% of 3 billion bases of human DNA. In most cases, these variants consist of the exchange of single nucleotides in both coding and noncoding DNA regions and are defined as single nucleotide polymorphisms (SNPs) (Figure 2). The ability of the SNP to influence drug response and therapeutic efficacy may rely on the capacity of the variant to induce changes in the expression of proteins that may influence either the pharmacokinetic and/or pharmacodynamic profile and hence the clinical efficacy of the drug. On the basis of these acquisitions, recent GWAS have identified several SNPs that can affect both the therapeutic efficacy and the occurrence of adverse reactions after drug intake[8-10].

PHARMACOGENETICS IN T2DM TREATMENT

Pharmacogenetics of sulfonylureas

In Caucasians, sulfonylureas are metabolized primarily in the liver by CYP2C9 to active metabolites, which are ultimately excreted by the kidney[11]. In previous work, it was demonstrated that polymorphisms of the *CYP2C9* gene significantly affect the pharmacological response of diabetic patients to sulfonylureas[12], due to the reduction of the catalytic activity in the metabolism of these drugs[13-16], with a consequent increase in drug bioavailability. In particular, in certain diabetic patients with the variants Ile359Leu (isoleucine changes to leucine in exon 7 position 359) and Arg144Cys (arginine changes to cysteine in exon 3 position 144) in the *CYP2C9* gene, the clearance of glibenclamide was reduced by 30%-80%, allowing the use of lower doses of this drug to limit the risk of hypoglycemia[12,17-20]. The risk of hypoglycemia in sulphonylurea treated patients was confirmed in a study with a larger population, in which the simultaneous presence (or the presence in homozygosity) of the variants Ile359Leu and Arg144Cys in the *CYP2C9* gene was associated with the improvement in markers of glycemic control, including glycated hemoglobin A1c (HbA1c)[21]. Therefore, genotyping of the *CYP2C9* gene may provide important additional information in predicting the adverse effects of these drugs and to assist physicians in prescribing oral hypoglycemic agents.

The ATP-sensitive potassium [ATP-sensitive K^+ (K-ATP)] channel plays a central role in mediating glucose-stimulated insulin release from pancreatic beta-cells (Figure 3). In physiological conditions, the rapid entry of glucose into the beta-cell results in an increase in the intracellular concentration of ATP, which promotes the closure of the K-ATP channel with consequent opening of the voltage-dependent calcium channel, elevation of intracellular calcium ion concentration and insulin secretion. The K-ATP channel is composed of two subunits: the sulphonylurea receptor (SUR1) and the pore-forming inward rectifier K^+ channel Kir6.2[22,23]. Genetic variants inactivating the *KCNJ11* (potassium inwardly-rectifying channel, subfamily J, member 11) gene, which encodes for the protein Kir6.2, and the ATP-binding cassette, subfamily C (CFTR/MRP), member 8 (*ABCC8*) gene, which encodes the SUR1 protein, are responsible for neonatal diabetes mellitus; conversely, activating mutations of

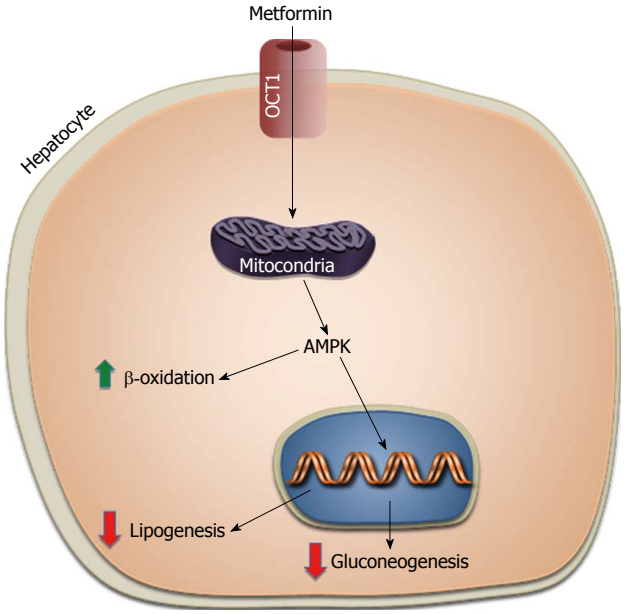

Figure 4 Organic cation transporter 1 plays a major role in drug uptake across the liver cell membrane. Single nucleotide polymorphism associated with organic cation transporter 1 may contribute to variation in response to metformin. AMPK: Adenosine 5'-monophosphate (AMP)-activated protein kinase; OCT1: Organic cation transporters 1.

these two genes lead to hyperinsulinism and neonatal hypoglycemia[24]. As an example of pharmacogenetics with important clinical implications, recent studies have found that diabetic patients carrying mutations in the *KCNJ11* gene respond better to treatment with sulfonylureas than to treatment with insulin[25-27].

Association of the polymorphism Ser1369Ala (serine 1369 to alanine substitution) in *ABCC8* with the antidiabetic efficacy of gliclazide was found in patients with T2DM, after two months of treatment[28]. In particular, patients with the genotype alanine/alanine had a greater reduction in either fasting plasma glucose or 2 h postload plasma glucose during oral glucose tolerance test, and a greater decrease in HbA1c levels compared to patients with the Serine/Serine genotype[28]. The variant Ser1369Ala in *ABCC8* is often associated in linkage disequilibrium with a variant, Glu23Lys (glutamine to lysine variant at position 23), in the *KCNJ11* gene, forming a haplotype that increases the risk of developing T2DM[29]. It has been observed that this haplotype displays large differences to the therapeutic effects of various sulfonylureas: greater to gliclazide, less apparent to tolbutamide, chlorpropamide and glimepiride, invariable in the glipizide and glibenclamide treatment group[30].

Interesting results, in this context, have been obtained from the study of the transcription factor 7-like 2 (*TCF7L2*) gene, which encodes a nuclear transcription factor that appears to play a role in beta-cell function. Genetic variants of *TCF7L2* are associated with increased risk of T2DM[3]. Recently, two variants of the *TCF7L2* gene, rs7903146 (G > T), and rs7903146 (C > T), have been shown to influence the therapeutic efficacy of sulfonylureas[31-33]. In particular, the reduction in both HbA1c and fasting plasma glucose was higher in diabetic patients carrying either GG or CC genotypes[31-33]. In contrast, diabetic patients with the TT genotype in both the rs7903146 (G > T) and the rs7903146 (C > T) variants showed a lower response to sulfonylureas and appeared to be more prone to therapeutic failure[31-33].

Pharmacogenetics of metformin

Metformin, in use for control of diabetes since 1950s, is the first-line pharmacological therapy for T2DM. After oral administration, the drug is absorbed into the blood *via* the gastrointestinal tract, rapidly distributed in body tissues by travelling through specific transport proteins [including the organic cation transporters 1 (OCT1) and OCT2, the multidrug and toxin extrusion 1 (MATE1) transporters and MATE2-K, and the plasma membrane monoamine transporter (PMAT)] located on the cytoplasmic membrane of many cells, especially intestinal cells, liver cells and kidney cells[34], and excreted in the urine almost unchanged from the original drug. The individual's response to metformin is highly variable with less than 2/3 of treated patients achieving glycemic control[35]. Thus, identification of genetic variants that may influence the interindividual variability to metformin would be of major importance for the effective treatment of these patients. However, studies on the pharmacogenetics of metformin are relatively limited, mainly because its mechanism of action is still poorly defined. So far, most of the studies on this topic have involved the solute carrier family 22A1 (*SLC22A1*) gene, which by coding for the OCT1 transport protein, plays a key role in the cell absorption of the drug[36], and is essential for the anti-gluconeogenic effect of metformin into the liver[37] (Figure 4). It has been shown that polymorphisms of this gene (rs12208357; rs34130495; rs72552763; rs34059508), by reducing the functional capacity of OCT1, can alter the bioavailability of metformin and mitigate its hypoglycemic response in healthy people carrying these gene variants[37-39]. Recently, two polymorphisms of *SLC22A1* (rs628031 and rs36056065) have been associated with gastrointestinal side effects in diabetic patients treated with metformin[40]. At the same time, other authors[41,42] have also reported that the bioavailability of metformin was increased in healthy individuals carrying mutations of the *SLC22A2* gene, which encodes for the OCT2 transport protein. Variants of this gene, by adversely affecting OCT2 function, may decrease the renal clearance of metformin, and may contribute to increased plasma metformin levels with increased risk of hypoglycemic events.

Interindividual variation in metformin response has been recently reported in subjects with genetic variations in *SLC47A1* and *SLC47A2* genes coding for MATE1 and MATE2-K, respectively, which play important roles in the urine excretion of metformin. A better glycemic response to metformin, with lower HbA1c levels, has been reported in association with the *SLC47A1* gene variant rs2252281[43-46]. In contrast, the therapeutic response to metformin was reduced in diabetic patients

carriers of the variant rs12943590 in the *SLC47A2* gene[45,46]. Therefore, these observations imply that genetic variants of MATE1 and MATE2-K are important determinants of the therapeutic efficacy of metformin in patients treated with this drug. The first GWAS on the efficacy of metformin on glycemic control in diabetic patients resulted in the demonstration that a gene variant near ataxia telangiectasia mutated (*ATM*), rs11212617, is significantly associated with metformin treatment response in T2DM, more frequently with HbA1c levels < 7%[47]. The explanation of this phenomenon lies in the role ATM, the protein product of the *ATM* gene, plays in the context of insulin signaling and insulin action[48].

Thus, genetic variants of *SLC22A1* and *SLC22A2* may be determinant in the therapeutic efficacy of metformin. Furthermore, genotyping of *SLC22A1* and *SLC22A2* is useful in the management of diabetic patients under metformin theraphy.

Pharmacogenetics of thiazolidinediones

Genetic variants that can influence the pharmacogenetics of oral antidiabetic medications were also assessed in diabetic patients treated with pharmacogenetics of thiazolidinediones (TZDs) (pioglitazone and rosiglitazone). As agonists of peroxisome proliferator-activated receptor gamma (PPAR-γ), TZDs act as insulin-sensitizing, thus reducing the release of glucose from the liver and increasing glucose uptake in muscle[49]. The *PPAR-γ* gene has been extensively investigated in pharmacogenetic studies of TZDs, especially because genetic variants of this gene have been associated with an increased risk of T2DM[3]. However, pharmacogenetic studies with TZDs have shown conflicting results, probably due to insufficient sample size and low levels of statistical power[50]. Furthermore, it is worthy noting that the retrospective study design used in the majority of studies on pharmacogenetics has its own drawbacks, being able to expose to a variety of confounding and bias, including age, gender, ethnicity, lifestyle, concomitant use of other medications, *etc*. A similar discrepancy has emerged from studies on the genetic variants of the *CYP2C8* gene, which is responsible for metabolizing pioglitazone[50]. A reduction in the blood glucose-lowering effect of pioglitazone was recently observed in diabetic patients carriers of the truncation variant, Ser447X, of the lipoprotein lipase gene[51]. Another study has reported that the -420 C/G variant of the *resistin* gene promoter can also be used as an independent predictor of the reduction of fasting plasma glucose and insulin resistance by pioglitazone in T2DM[52]. As it is known, side effects of TZDs therapy include fluid retention and peripheral edema, worsening heart failure[53]. In this context, various genetic variations have been discovered in genes known to be involved in sodium and water reabsorption. Among these, the aquaporin 2 (*AQP2*) rs296766 variant and the *SLC12A1* rs12904216 variant, both of which have been associated with edema in T2DM patients treated with a TZD[54]. *AQP2* gene codes aquaporin-2, which function as a water channel in the collecting duct of the kidney[55]. *SLC12A1* encodes the kidney-specific sodium-potassium-chloride cotransporter (NKCC2), which plays an important role in both urine concentration and NaCl reabsorption[54,56]. Therefore, it is quite evident that these variants may represent both a risk factor for the development of edema in diabetic patients during treatment with TZDs.

Pharmacogenetics of metiglinides

Metiglinides (repaglinide and nateglinide) are a class of rapid-acting, short duration insulin secretagogues that act in a manner similar to that of the sulfonylureas[57]. Nateglinide is also metabolized by the CYP2C9 enzyme of the cytochrome P-450 system, and gene variants of *CYP2C9* are associated with variability in glucose-lowering effect of nateglinide[58]. Repaglinide is metabolized by CYP2C8 and to a lesser degree by CYP3A4[59]. Also in this case, gene variants of *CYP2C8* have been associated with increased clearance of repaglinide, although with contradictory results[60]. The solute carrier organic anion transporter family member 1B1 (*SLCO1B1*) gene encodes for the organic anion transporting polypeptide, OATP1B1, which regulates cellular uptake of various drugs, including statins by the liver. Recent studies have reported the role of some variants of *SLCO1B1* in the pharmacokinetics of metiglinides[61-64]. For example, a more effective hypoglycemic effect of repaglinide was observed in diabetic patients carrying the Glu23Lys (E23K) polymorphism in the *KCNJ11* gene[65], and the rs13266634 variant in the *SLC30A8* gene[66]. Similarly, polymorphisms of neurogenic differentiation 1 (*NEUROD1*), also called beta2 (*NEUROD1/BETA2*), paired box gene 4[67] and uptake control 2[68] genes were also found to be associated with the hypoglycemic efficacy of repaglinide. An association of the variant G2677 T/A in the multidrug resistance gene, which encodes a multidrug efflux pump, with the variability in the pharmacokinetics of repaglinide was found recently in a Chinese study in healthy volunteers[69].

Pharmacogenetics of incretins

Glucagon-like peptide-1 (GLP-1) is part of the group of incretin hormones that are secreted from endocrine cells in the intestinal mucosa in response to meals. It mediates insulin secretion in a glucose-dependent manner and is easily inactivated after being secreted by the enzyme dipeptidyl peptidase-Ⅳ (DPP-Ⅳ). Recent pharmacological research has led to the development and synthesis of medications that are capable of acting at this level as both GLP-1 agonists (exenatide and liraglutide) and DPP-IV inhibitors (gliptins)[70]. Variants of the GLP-1 receptor gene have been shown to be associated with altered sensitivity to GLP-1[71]. Furthermore, whereas variants in the *TCF7L2* (rs7903146) and wolfram syndrome 1 (rs10010131) genes have been associated with a reduced response to exogenous GLP-1, variations in the *KCNQ1* (rs151290, rs2237892, and rs2237895) gene appear to alter the secretion of endogenous GLP-1[72]. The only significant study on the pharmacogenetics of gliptins

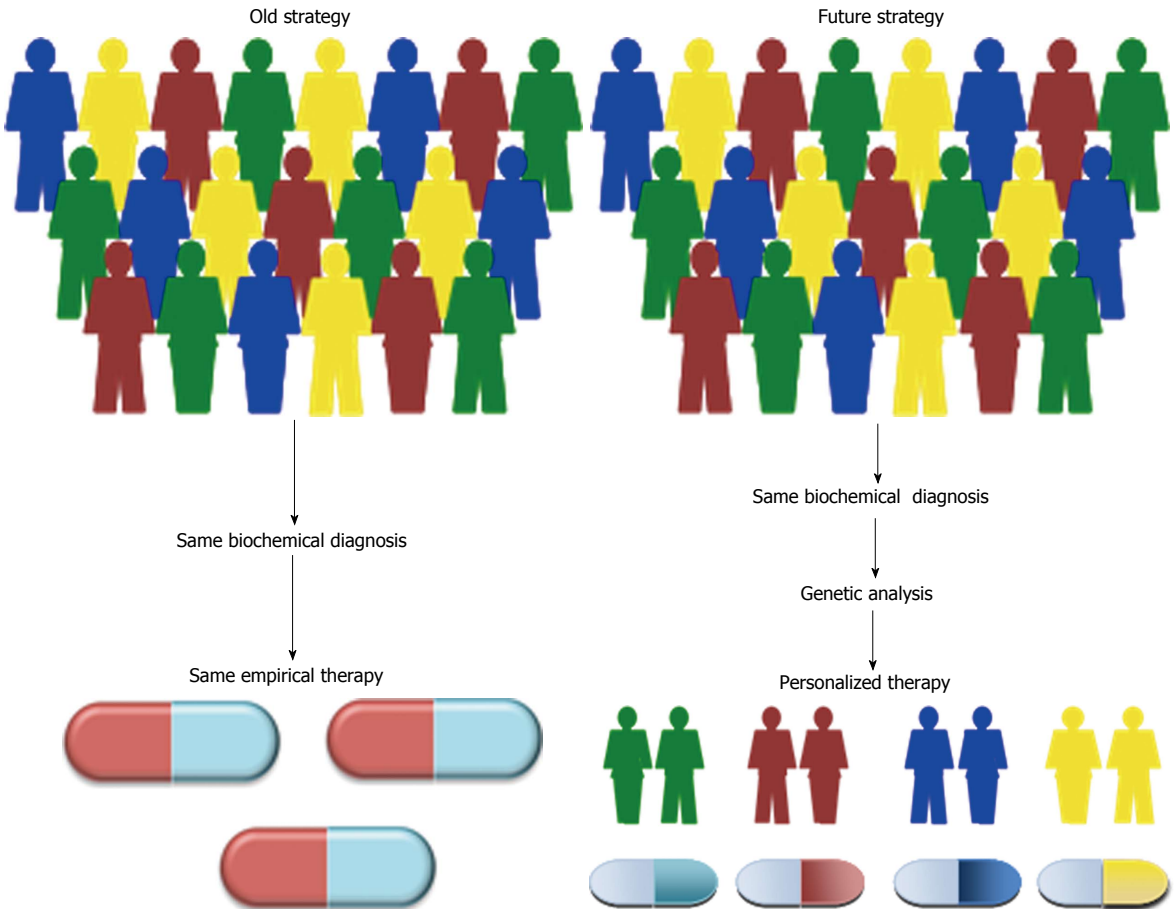

Figure 5 Pharmacogenetic testing. The pharmacogenetic test has the potential to provide personalized therapy based on individual genetic variability.

showed that three novel genetic loci (transmembrane protein 114, carbohydrate sulfotransferase 3 and Chymotrypsinogen B1/2) were identified, which affect GLP-1-induced insulin release during hyperglycemic clamp in nondiabetic Caucasian subjects[73].

CONCLUSION

Pharmacogenetics is an expanding area of research which seeks to understand how variations in the genome influence medication response. Pharmacogenetics has gained increasing attention in the context of translational medicine, providing an opportunity for personalized treatment strategies based on an individual's genetic makeup. The results obtained so far with the study of genetic variants in patients with T2DM (and other common diseases) may be used for the realization of a pharmacogenetic test, which can assist in making treatment decisions on the basis of each patient's genetic profile, thus improving the overall management of the disease and ensuring better results in terms of safety and therapeutic efficacy. The clinical use of pharmacogenetics, through the identification of individual genetic variants (genetic polymorphisms), can contribute to move to a more evidence-based and less empiric clinical management of patients, thereby avoiding treatment failures, while reducing the incidence of adverse drug reactions (Figure 5).

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