Pro and Contra of Incretin therapy in Type 2 diabetes

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Abstract

Incretins are group of gastroinestinal hormones involved in glucoregulation. Two main hormones involved in glucoregulation are glucagon-like peptide-1 (GLP-1) and gastric inhibitory peptide or glucose-dependent insulinotropic polypeptide (GIP). Both are rapidly inactivated by the enzime dipeptidyl peptidase-4 (DPP-4). Incretin based therapies include GLP-1 receptor agonists and DPP-4 inhibitors. Their main mechanisms of actions are to increase insulin and inhibit glucagon secretion, reduce gastric emptying and reduce food intake. Positive effects on glycemia without hypoglycemia and weight gain are their main advantages. Direct cardiovascular effects of GLP-1 receptor agonists are also documented. Concerns have been raised that incretin based therapies were associated with an increased risk of pancreatitis and pancreatic cancer. Recent trials do not support the hypothesis. Preclinical studies in animals have suggested that incretin based therapies could be associated with thyroid C-cell cancer. However, it was not found in humans. Recent trial of one DPP-4 inhibitor suggested increased risk for hospitalization due to heart failure. Further studies are required. Several large clinical trials are in progress. In presentation *pro et contra* of incretin based therapies will be presented.

The practical issues in Type 2 diabetes management - pharmacogenomic consideration

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Type 2 diabetes (T2D) is a complex disease that has a significant potential for stratification in its management, including genetic etiology, treatment outcomes, rate of progression, and development of complications. In the light of exorbitant and still increasing costs of treating T2D and its complications, pharmacogenomics' benefit of selecting patients and adequate therapies offers a considerable potential to improve cost-effectiveness of drug therapy and avoid extra costs for side - effects treatment. Several classes of oral antidiabetic drugs (OAD) are currently available to treat T2D patients, with sulphonylureas (SU), biguanides, thiazolidinediones (TZD), and meglitnides being the most frequently used. Emerging evidence has recently demonstrated that genetic variation might be one of the key determinants of an individual's responses to OAD. A variety of approaches can be used to understand OAD's pharmacodynamic and pharmacokinetic mechanisms related to interindividual differences in drug response, with pharmacogenomics providing a unique and powerful clinically relevant tool. Furthermore, an enhanced understanding of genes and pathways that determine OAD response has also the potential to reveal new drug targets and develop novel drugs for the treatment of diabetes.

Although benefits from a personalized diabetes care are well established in patients with certain monogenic forms of diabetes, pharmacogenomics of common T2D is also anticipated and progressing rapidly. Here are summarized the results of the several recent studies, which have analyzed an association of genetic variations in drug - metabolizing enzymes (DME), drug transporters (DT),

and specific drug targets with T2D treatment outcomes in diverse population groups. The most recent and promising advances appeared to be related to therapy with the biguanide drug metformin, a first-line drug used to treat newly diagnosed T2D. The glycemic response to metformin appears to be highly variable, with about 35% of patients failing to achieve acceptable control of glucose levels on metformin monotherapy (1). Variants in *SLC47A1* (encoding the drug transporter, multidrug and toxin extrusion protein 1, MATE1) and *SLC47A2* (encoding MATE2 transporter) have also been associated with altered glucose - lowering response to metformin in humans (2). In the Diabetes Prevention Program (DPP), associations were also found for the *STK11* (encoding the drug target AMP kinase, AMPK) and *SLC22A1* gene (encoding the drug transporter organic cation transporter 1,OCT1). Although pharmacogenomics can also be a useful tool to point to a novel biological mechanism of action of metformin, studies of pharmacodynamic genetics have been limited. A recent genome-wide association study (GWAS) found an association of *ATM* (*ataxia telangiectasia mutated*) gene variation, involved in AMPK activation, with treatment success (3). Since the primary action of metformin seems to be the inhibition of hepatic glucose production through inhibition of gluconeogenesis, interactions with loci associated within this pathway (*PCK1, phosphoenolpyruvate carboxykinase 1*), *PPARA (peroxisome proliferator - activated receptor alpha),* and *PARGC1A* (*peroxisome proliferator - activated receptor gamma, coactivator 1 alpha*) were also reported (4).

Single nucleotide polymorphisms (SNPs) of the genes encoding potassium inwardly rectifier 6.2 subunit (Kir6.2) of pancreatic islet ATP- sensitive K+ (KATP) channel have been related to the efficacy of secretagogue drugs, such as sulphonylureas. This channel is essential for glucose - stimulated insulin secretion from pancreatic β-cells, modulates glucose uptake into skeletal muscle, glucose production and release from the liver. KATP channels are heterooctamers assembled from Kir6.2 and the sulphonylurea receptor 1 (SUR1), encoded by the *KCNJ11* (potassium inwardly-rectifying channel, subfamily J, member 11) and *ABCC8* gene, respectively. A common Glu23Lys polymorphism (also known as E23K) in *KCNJ11* is associated with an increased risk of SU therapeutic failure. A recent study found that *KCNJ11* variations have been associated with altered response to gliclazide (5) and glibenclamide (6). Interestingly, the most promising gene variants affecting the SU response are those involved in drug pharmacodynamics, such as the transcription factor 7-like 2 (*TCF7L2*) that encodes a transcription factor (Tcf-4), involved in the regulation of cellular proliferation and differentiation (7).

Meglitinides (glinides) represent a class of short - acting insulin secretagogues that act by binding to pancreatic - cells and inhibiting KATP channel to stimulate insulin release. This is similar to the mechanism of action of the sulphonylureas and both, meglitinides and SU, bind to the SUR1 subunit to inhibit channel activity. Due to their short action, repaglinide and nateglinide have a lower risk to induce hypoglycemia than SU. Furthermore, meglitinides offer an alternative OAD agent of similar potency to metformin, and may be indicated where side effects of metformin are intolerable or where metformin is contraindicated. A recent study showed that *SLCO1B1* gene, which encodes the organic anion-transporting polypeptide 1B1 (OATP1B1) that transports repaglinide into hepatocytes, is a major factor that significantly affects the repaglinide pharmacokinetics (8), consistent with an enhanced hepatic uptake by OATP1B1.

The thiazolidinediones activate their molecular target PPARs (peroxisome proliferator - activated receptors). TZD bind with greatest specificity for PPARYγ to promote adipogenesis and fatty acid uptake. By reducing circulating fatty acid levels and lipid availability in liver and muscle, these drugs improve the patients' sensitivity to insulin and reduce hyperglycemia. Thus, variation in PPARg would likely affect response to TZD and this was suggested in a recent study that analyzed pioglitazone response (9). Recently, several additional gene variants have been also associated with the TZD therapy outcomes (10), including adiponectin, leptin, resistin, and tumor necrosis fac-

tor (TNF)-a that are of a particular interest due to their important role in insulin resistance.

Variation in the cytochrome P450 (CYP) enzymes, which metabolize oral antidiabetic drugs, appear also to impact their effects, including variation in *CYP2C9* and *CYP2C19* for SU metabolism, *CYP3A4* and *CYP2C8* for repaglinide, *CYP2C9* for nateglinide, and *CYP2C8* and *CYP3A4* for pioglitazone.

Interestingly, a very recent systemic review reported by Maruthur et al. (11), summarized the major genetic variants that could predict response to oral antidiabetic drugs. They performed a qualitative synthesis of results from twenty one studies, comprised from more than ten thousand subjects, to determine if the effect of OAD treatment on diabetes incidence, levels of glycosylated hemoglobin (HbA1c), and fasting and postprandial glucose is associated with genetic variations in patients with impaired glucose tolerance or Type 2 diabetes. Based on this rigorous analysis, the authors recommended as a priority further confirmation if variations of following selected genes could be used to individualize the choice of diabetes management: *SLC22A1, SLC22A2, SLC47A1,* AMPK subunits *(PRKAB2, PRKAA2, PRKAA1),* and *STK11* for metformin; *CYP2C9* and *TCF7L2* for sulphonylureas; *KCNJ11, SLC30A8* (*solute carrier family 30 (zinc transporter), member 8*), *NEUROD1/BETA2* (*neurogenic differentiation 1 transcription factor*), *UCP2* (*mitochondrial uncoupling protein 2*), and PAX4 (*paired box gene 4*) for repaglinide; and PPARG2 and PTPRD (*protein tyrosine phosphatase, receptor type, D*) for pioglitazone. Importantly, this study (11) also indicated that although diabetes research is extensively funded, the major limitation of the pharmacogenomic research of Type 2 diabetes is the lack of high - quality studies to identify and confirm findings for specific interactions between drug, genetic variation, and treatment outcome. The most of pharmacogenomic studies on diabetes treatment performed to date are small and inadequately replicated. The small size of many of the studies does not exclude the possibility that interactions exist, although they could not be identified because of the lack of power. Thus, since the pharmacogenomic associations in diabetes that have been reported to date have had limited impact on the individual treatments choice, the value of genetic information in guiding therapeutic decisions in T2D treatment must be further tested in adequately designed and carefully conducted clinical trials, controlling for population stratification and relatedness. This important goal could only be achieved by a broad transnational collaboration between numerous research groups with large patient cohorts. Particularly, it would be pertinent to explore genotype - phenotype associations by using standardized therapy outcomes (e.g., HbA1c at three months) in order to reveal a number of genetic variants that stand out as statistically significant with high positive predictive value and may be used as pharmacogenomic markers for an optimal T2D treatment. With recent scientific and technological advances, as well as decreasing sequencing costs, pharmacogenomics has a great potential to yield therapeutic advances leading the way towards personalized diabetes care. This stratified approach to diabetes therapy should be also more cost-effective than a classical 'trial and error' approach. Furthermore, analysis of the underlying genetic factors related to OAD response may also lead to the identification of novel targets and development of improved, more effective antidiabetic drugs.

In conclusion, the evidence has been accumulating to show that pharmacogenomics offers the considerable potential to improve the management of T2D and the effective prescribing of oral antidiabetic drugs. As summarized here, significant pharmacogenomic evidence has demonstrated an association between specific gene polymorphisms and interindividual variability in OAD therapeutic and side effects. Thus, several variants related to drug-metabolizing enzymes, drug transporters, drug targets, and diabetes risk genes that were recently identified, could be employed to predict treatment outcomes and treat Type 2 diabetes more efficiently. Further identification and confirmation of drug - genotype interactions would encourage a promotion of personalized medicine in clinical settings, where genotype would be used to guide diabetes therapy.

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