Pharmacogenomics of Metformin- A Way to Personalised medicine

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ABSTRACT

Diabetes is fast gaining the status of a potential epidemic in India with more than 62 million diabetic individuals currently diagnosed with the disease. There are at least 10 different drug classes for the treatment of Type 2 diabetes mellitus (T2DM) but metformin is recommended as the initial medication for treatment of T2DM. Inter-individual variability in response and few clinical or biomarker predictors of response reduces its optimal use. Personalized medicine promises a path for individually optimized treatment, but realizing this promise will require a more comprehensive characterization of disease and drug response. As per American Medical Association, pharmacogenomics is the study of genetic variations that influence individual response to drugs. Knowing whether a patient carries any of these genetic variations can help prescribers individualize drug therapy, decrease the chance for adverse drug events, and increase the effectiveness of drugs. There are a variety of genes controlling metformin transport in the body, for example, SLC22A1, SLC22A2, SLC22A3, SLC22A4 etc. The purpose of this review article is to explain in brief pharmacogenomics of metformin and its application and practical hurdles in its translation.

Key words: Metformin, Pharmacogenomics, Personalised medicine, Diabetes mellitus, SLC2A4.

INTRODUCTION

Diabetes is fast gaining the status of a potential epidemic in India with more than 62 million diabetic individuals currently diagnosed with the disease. The prevalence of diabetes is predicted to double globally from 171 million in 2000 to 366 million in 2030 with a maximum increase in India. There are at least 10 different drug classes for the treatment of Type 2 diabetes mellitus (T2DM) but metformin is recommended as the initial medication for treatment of T2DM. The incidence of T2DM and its costs to the healthcare system continues to rise. Despite its widespread use, there is considerable variation in response to metformin, with about 35% of patients failing to achieve initial glycemic control on metformin monotherapy. Inter-individual variability in response and few clinical or biomarker predictors of response reduce its optimal use. Personalized medicine promises a path for individually optimized treatment, but realizing this promise will require a more comprehensive characterization of disease and drug response. Understanding of the genetic determinants of metformin response may lead to the identification and development of effective drug targets for diabetes treatment. Pharmacogenomics as the most widely applied discovery-based approach to date has opened up the opportunity to understand the genetics underlying the interindividual variation in metformin responses so that...
the clinicians can prescribe treatment to the individuals for better efficacy and safety, metformin for those predicted to respond and alternative therapies for those predicted to be non-responders or who are at increased risk for adverse side effects.[4]

**OBJECTIVE**

To review the research on metformin pharmacogenomics and its application in improving patient outcomes.

**METHODS**

Relevant articles were identified in MEDLINE, PUBMED using MeSH terms Metformin, Pharmacogenomics and Personalized medicine.

Why to study pharmacogenomics of metformin?

As per American Medical Association, pharmacogenomics is the study of genetic variations that influence individual response to drugs. Knowing whether a patient carries any of these genetic variations can help prescribers individualize drug therapy, decrease the chance for adverse drug events, and increase the effectiveness of drugs. Currently, much of the research in the field of pharmacogenomics is focused on genes encoding either metabolic enzymes that can alter a drug’s activity or defective structural proteins that result in increased susceptibility to disease. Variability in drug response, with respect to efficacy, tolerability, and safety, is a major issue for most drugs. Diabetes, like other complex diseases, is the product of many genes interacting with environmental factors. These interactions affect many pathways and even whole signaling networks in ways that cause disease. The promise of personalized medicine is that this complexity can be teased apart to refine the definition of disease, identify disease subtypes, and ultimately define biomarkers capable of discriminating between the patients most likely to benefit from a specific treatment and those unlikely to respond or likely to experience adverse events.[9]

**Anticipated benefits of pharmacogenomics**

**More powerful medicines:** Pharmaceutical companies will be able to produce therapies more targeted to specific diseases, maximizing therapeutic effects while decreasing damage to nearby healthy cells.

**Better, safer drugs the first time:** Recovery time will go down and safety will go up as the likelihood of adverse reactions goes down or is eliminated altogether.

**More accurate methods of determining appropriate drug dosages:** Current methods of basing dosages on weight and age will be replaced with dosages based on a person’s genetics- how well the body processes the medicine and the time it takes to metabolize it.

**Economic issues from molecule to marketplace**

Pharmacogenomics eventually can lead to an overall decrease in the cost of health care because of decreases in:

- the number of adverse drug reactions,
- the number of failed drug trials,
- the time it takes to get a drug approved,
- the length of time patients are on medication,
- the number of medications patients must take to find an effective therapy, and
- the effects of a disease on the body (through early detection).

**Metformin**

Metformin and phenformin were discovered in the 1920s in a search for guanidine containing compounds with antidiabetic activities. Phenformin was withdrawn in the 1970s due to its potential to induce lactic acidosis. Metformin was approved for use in the United States in 1995.[6] A major action of metformin is suppression of hepatic glucose production. In addition to its efficacy in lowering glucose levels, metformin has the clinical advantages of inducing mild weight reduction and only a minimal risk of hypoglycemia, but it has some gastrointestinal side effects and, very rarely, causes lactic acidosis.

**Metformin Pharmacokinetics**

Metformin is not metabolized in the liver or kidney but rather excreted intact in the urine. Briefly, metformin appears to be taken up from the intestine by plasma monoamine transporter (PMAT; SLC29A4) and organic cation transporter 3 (OCT3; SLC22A3), transported into the bloodstream by OCT1 (SLC22A1), and then passed from proximal tubule cells into the urine via MATE1 and MATE2 (SLC47A2). About 50% of an orally administered dose is absorbed into the systemic circulation. The half-life of the drug measured in plasma is between 4 and 8 h in individuals without renal dysfunction, and the clearance exceeds glomerular filtration rate, consistent with tubular secretion (Figure 2).
Figure 1: Various transporters with corresponding genes involved in metformin absorption, hepatic uptake and excretion.

Figure 2: Illustration showing transport of metformin from the gastrointestinal tract into the bloodstream, disposition into the liver, and secretion intact by the kidneys.
Variable response of metformin observed in various studies

Treatment Options for T2D in Adolescents and Youth[15]

In this study, adolescents appear to have high metformin failure rates when compared with similar intervention studies in adults. In addition, metformin monotherapy was more effective in Hispanics and non-Hispanic whites compared with non-Hispanic blacks. Taken together, these observations suggest there are significant gaps in our ability to select the most efficacious medication for individuals in some of the populations at the highest risk for T2D and its complications.

U.K. Diabetes Audit and Research in Tayside Scotland Study[16]

This study utilized the extensive electronic health record (EHR) system in Scotland, allowing the inclusion of 10,000 patients with diabetes and 8,000 control patients who had electronic health information. Of these, 3,200 metformin-treated patients underwent genotyping on a genome-wide single nucleotide polymorphism (SNP) chip or other arrays. Of note in this study was a considerable interindividual variation in metformin response, with some patients experiencing lowering of their percent A1C by close to 4%, while other patients exhibited no change or substantial increases in A1C after treatment. The strongest association with metformin response was found in a variant lying in a region on chromosome 11 containing seven genes, and has been replicated in additional meta-analyses (30,31). One potential candidate gene is the ataxia telangiectasia mutated gene (ATM), which encodes a serine/threonine kinase and may regulate enzymes involved in response to metformin. Although the investigators presented in vitro data showing ATM was involved in metformin’s activation of AMPK in cell cultures, it has since been shown that the small molecule used to inhibit ATM in the in vitro cellular studies is actually an inhibitor of OCT1. As OCT1 is the major metformin transporter in the liver and in hepatic cell lines, the ATM inhibitor reduced metformin’s activation of ATM by preventing the drug from getting into the cells, greatly complicating the interpretation of the experiments.
Future work will be necessary to fully explore the genic and intergenic regions around this locus and to understand differences between cohorts where this pharmacogenomic association with metformin response has not been replicated.

**DPP and DPP Outcomes Study**[17]

Variability in the ability of metformin to prevent diabetes was seen, with it being less effective in the older participants but more effective in the more obese participants. An intriguing mechanistic insight comes from the observation that metformin-associated weight loss can account for a substantial fraction of the benefit in obese subjects. The reduction in diabetes incidence persisted for at least 10 years of follow-up, even after metformin washout, and may be partly due to some persistent weight loss. Metformin was effective in decreasing diabetes incidence in women with a history of gestational diabetes mellitus. Metformin also improved HDL levels and LDL particle size, but had insignificant effects on blood pressure or triglyceride levels.

A candidate gene analysis has been reported with several variants in genes showing a nominally significant effect on the response of metformin. Of particular note were variants in genes in the AMPK pathway, supporting the relevance of that pathway in metformin’s clinical action. Variants in the genes encoding the transporters OCT1 and MATE1 were also nominally associated with metformin response. Shu et al.[18] showed reduced metformin uptake into transfected cells expressing naturally occurring amino acid altering variants of OCT1. Translating these *in vitro* studies to the clinic, the investigators also showed that healthy volunteers heterozygous for these OCT1 variants had reduced response to the drug and altered pharmacokinetics (Table 1).

**Metformin Pharmacodynamics**

Its primary action is through its insulin-sensitizing effect in the liver resulting in a decrease of hepatic glucose output, mainly through inhibition of gluconeogenesis.[9] In isolated hepatocytes, metformin action requires the enzyme AMP-activated protein kinase (AMPK), a master sensor, integrator, and regulator of cell and body energy homeostasis. AMPKs are activated by an increased AMP/ATP ratio and by upstream kinases (e.g., LKB1). AMPK activation affects many pathways, generally causing...
conservation and generation of ATP. How metformin activates AMPK, such as through an upstream kinase or by altering the cell’s energy status and thus AMP/ATP ratio, is not yet clear (Figure 3).[19]

Metformin can be taken up by the muscle via OCT3 where it results in increased translocation of the facilitated glucose transporter 4 (SLC2A4) and a concomitant increase in glucose uptake by the muscle. Additionally, metformin inhibits lipogenesis and promotes free fatty acid oxidation.

Table 1 shows list of known metformin pharmacokinetic genes and select pharmacodynamic genes for which there are associations with clinical response of metformin.

### Practical hurdles of pharmacogenomics today

There appears to be a strong desire among patients and physicians to use pharmacogenomic guidance to help select medications and dose. However, uptake in the real world is slow. In a recent survey of U.S. physicians, only 13% of physicians reported having ordered or recommended a pharmacogenetic test in the previous 6 months, and only 29% of physicians reported that they received graduate or postgraduate training in pharmacogenomics.[19] There is a lack of prospective randomized clinical trials to address whether pharmacogenomic testing improves patient outcomes, what the optimal clinical algorithm for its application is, and whether it is cost-effective. We do hope the use of individual genetic information can help guide intelligent medication choices in the future: public and private funding bodies should support clinical trials with large sample sizes in an effort to show improved outcomes and cost effectiveness before this promise can be delivered to clinical practice.

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NIL.

### REFERENCES