Pharmacogenetics of Metformin

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A R T I C L E   I N F O

Keywords:
Metformin
Diabetes Mellitus
Biguanide
Heart Disease

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The author has reviewed and approved the final version of the manuscript.

https://doi.org/10.37275/OAIJMR.v1i6.573

A B S T R A C T

Hyperglycemia is a medical condition in which an increase in glucose levels in the blood exceeds normal limits. Hyperglycemia is one of the typical signs of diabetes mellitus (DM). The World Health Organization (WHO) predicts an increase in the number of people with DM which is a global health threat. Diabetes is the leading cause of kidney failure, and the leading cause of heart disease and stroke, in adults. Metformin, which is a biguanide group, is recommended by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes as the first-line oral therapy for DM and is the most widely used oral medication worldwide. Metformin can also increase peripheral glucose utilization and ultimately decrease the production of fatty acids and triglycerides. Some of the individual differences that underlie the variation in response to metformin.

Introduction

Hyperglycemia is a medical condition in which an increase in glucose levels in the blood exceeds normal limits. Hyperglycemia is one of the typical signs of diabetes mellitus (DM), although it may also be found in several other conditions. Currently, epidemiological research shows an increasing trend in the incidence and prevalence of type 2 DM in various parts of the world. The World Health Organization (WHO) predicts an increase in the number of people with DM which is a global health threat. In this manual, the hyperglycemia that is discussed is associated with type 2 diabetes. WHO predicts an increase in the number of people with diabetes in Indonesia from 8.4 million in 2000 to around 21.3 million in 2030. This report shows an increase in the number of people with diabetes mellitus by 2-3 times in 2035.1

Based on data from the Indonesia Statistics Central in 2003, it is estimated that Indonesia’s population aged over 20 years is 133 million people. By referring to the pattern of population growth, it is estimated that by 2030 there will be 194 million people over the age of 20.1

The report on the results of Basic Health Research (Riskesdas) in 2007 by the Ministry of Health, showed that the average prevalence of DM in urban areas for those over 15 years of age was 5.7%. The data above shows that the number of people with DM in Indonesia is very large. With the possibility of an increase in the number of people with DM in the future it will be a very heavy burden to be handled by specialists / subspecialists or even by all existing health workers.1

DM disease greatly affects the quality of human resources and has an impact on increasing health
costs which are quite large. Therefore all parties, both the community and the government, should participate actively in efforts to combat DM, especially in prevention efforts.\textsuperscript{1}

Diabetes is a widespread problem, with 25.8 million people in the US suffering from it and 347 million people worldwide; in adults, type 2 DM accounts for 90-95% of cases. Diabetes is the leading cause of kidney failure, and the leading cause of heart disease and stroke, in US adults.\textsuperscript{1,2} Metformin, which is a biguanide group, is recommended by the American Diabetes Association and the European Association for the Study of Diabetes as the first-line oral therapy for DM and is the most widely used oral medication worldwide. In addition, there is interest in using metformin for diabetes prevention, treatment of polycystic ovary syndrome (PCOS) and treatment of gestational diabetes. Clinically, there is considerable variation to metformin at the individual level. Genetic factors cause some of this variability, and in recent years there has been interest in exploring the influence of genetic variation on metformin pharmacokinetics. As with any medicine, understanding genomic pharmacology can help physicians personalize medical care and choose the right drug for a patient. Metformin in particular, the details underlying its molecular mechanism of action are not fully understood, thus complicating the approach to exploring its pharmacogenomics but also providing great potential for new discoveries and insights.\textsuperscript{2}

\textbf{Type 2 diabetes mellitus}

Type 2 Diabetes Mellitus (T2D) is a multifactorial, heterogeneous group of disorders characterized by a deficiency or failure in maintaining normal glucose homeostasis. Type 2 Diabetes Mellitus T2DM is a group of metabolic diseases characterized by hyperglycemia that occurs due to abnormalities in insulin secretion, insulin action or both. The diagnostic criteria for diabetes are if a plasma glucose examination is obtained at ≥200 mg / dl with classic complaints (polyuria, polydipsia, polyphagia and unexplained weight loss) or a fasting plasma glucose examination ≥126 mg / dl or a plasma glucose examination ≥200 mg / dl 2-hours after oral glucose tolerance test (TTGO) or HbA1c examination ≥6.5%. In general there are five basic principles of DM management. There are two objectives of DM management, namely the short term and the long term. Short-term goals include eliminating complaints and signs of DM, maintaining a sense of comfort and achieving targets for blood glucose control. Meanwhile, the long-term goal of this therapy is to inhibit the progression of complicating microangiopathy, macroangiopathy and neuropathy.\textsuperscript{1,3,4}

Currently, there are 12 drug classes available for T2D management: biguanides (metformin), thiazolidinediones (glitazones), α-glucosidase inhibitors, sulfonylureas (SU), meglitinides (glinides), DPP4 inhibitors (gliptins), incretin mimetics (aka GLP-1 receptor agonists), SGLT2 inhibitors (gliflozins), amylin mimetics, bile acid sequestrants, dopamine agonists and insulin/insulin analogs.\textsuperscript{5}

\textbf{Metformin}

Metformin is first-line therapy for type 2 diabetes, and it is also one of the most commonly prescribed drugs worldwide. Despite 50 years of clinical use, its mechanism of action remains controversial.
Metformin belongs to the biguanides antidiabetic class, which comes from the goat’s rue, French lilac or Italian fitch (Galega officinalis) plant. This plant contains galegine or isoamylene guanidine and has been used as an herbal remedy for diabetes for several centuries. Another more potent biguanide, fenformin, was withdrawn from the market in the early 1970s because of the increased risk of lactic acidosis. Metformin-related lactic acidosis is the most serious potential side effect with metformin, but it is very rare except in known high-risk groups, especially patients with severe renal impairment.6

The most common side effect of metformin is gastrointestinal symptoms limiting the maximum tolerable dose in more than 50% of patients and about 5% of subjects may not tolerate any dose of metformin. Vitamin B12 deficiency has also been associated with long-term metformin treatment in several studies. and this can lead to anemia, increased homocysteine levels and possible neurological effects.6

Hypoglycemia is very rare when metformin is used as monotherapy and metformin treatment is often associated with weight loss, especially in overweight patients, which is considered an additional benefit.6 By now metformin is the only available biguanide since other drugs in this class were shown to increase the risk for lactic acidosis (e.g., phenformin and buformin). Metformin might induce lactic acidosis in patients with renal insufficiency, therefore it is not prescribed in this subgroup of patients with T2D.5

To date, many pharmacogenetic studies have focused on the relationship between genetic variants in transporters and metformin pharmacokinetic parameters, and there has been one genome-wide association study for metformin response. Although genetic studies have demonstrated associations between single-nucleotide polymorphisms (SNPs) in transporters and metformin PK and pharmacodynamics (PD), each individual SNP accounts only for a small fraction of the variation in HbA1c among type 2 diabetes patients.7

**Pharmacokinetics**

Metformin is a hydrophilic compound with a pKa of 11.5 and a log P value of −1.43 so that it is mostly ionized at physiological pH values and recorded as hydrochloride salt. The main pharmacokinetic parameters are shown in Table 1.6

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bioavailability (F)</td>
<td>55%</td>
</tr>
<tr>
<td>Time for maximum plasma concentration (t max)</td>
<td>3 hours</td>
</tr>
<tr>
<td>Apparent volume of distribution (Vd/F)</td>
<td>~ 600 L</td>
</tr>
<tr>
<td>Clearance (CL/F)</td>
<td>~ 1140 ml/min</td>
</tr>
<tr>
<td>Protein binding (%)</td>
<td>Negligible</td>
</tr>
<tr>
<td>Elimination half-life (t1/2)</td>
<td>5-6 hours</td>
</tr>
</tbody>
</table>

The absorption of metformin in the small intestine is dose-dependent and involves an active, saturable uptake process. Metformin has a large volume of distribution (Vd) of about 63–276 L after intravenous administration and the apparent Vd after oral administration (Vd/F) is about 600 L. The trough steady-state metformin plasma concentrations show an enormous (80-fold) variability between individuals after repeated doses. It is not metabolized and is excreted unchanged in the urine and the renal clearance exceeds the glomerular filtration rate indicating active tubular secretion. About 20 to 30% of an oral dose of metformin appears in the feces representing the proportion of the dose that was not absorbed, whereas there is no metformin in the feces after intravenous dosing. The elimination half-life
(t1/2) from whole blood is prolonged compared to that from plasma because metformin is concentrated in the erythrocytes and the t1/2 from erythrocytes was about 23 hours. These pharmacokinetic properties all indicate that the adsorption, distribution and excretion of metformin must be dependent on drug transporters and metformin is considered class 3 in the Biopharmaceutics Drug Disposition Classification System (BDDCS). Metformin is a substrate for various polyclastic solute carrier organic cation transporters, which are important determinants of the pharmacokinetics and tissue Table 2.

### Table 2. Transporters involved in the absorption, distribution and elimination of metformin.

<table>
<thead>
<tr>
<th>Transporter (gene)</th>
<th>Affinity apparent Km (mM)</th>
<th>Main network</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>OCT1 (SLC22A1)</td>
<td>1.47</td>
<td>Intestine (basolateral) and liver (sinusoidal)</td>
<td>Wang et al. 200224</td>
</tr>
<tr>
<td>OCT2 (SLC22A2)</td>
<td>1.07</td>
<td>Kidney (basolateral)</td>
<td>Kimura et al. 200525</td>
</tr>
<tr>
<td>OCT3 (SLC22A3)</td>
<td>1.10</td>
<td>Intestine (apical), liver (sinusoidal) and other tissues</td>
<td>Chen et al. 201026</td>
</tr>
<tr>
<td>MATE1 (LC47A1)</td>
<td>0.23</td>
<td>Kidneys and liver</td>
<td>Chen et al. 200927</td>
</tr>
<tr>
<td>MATE2-K (SLC47A2)</td>
<td>1.05</td>
<td>Kidney (brush limit)</td>
<td>Masuda et al. 200628</td>
</tr>
<tr>
<td>PMAT (SLC29A4)</td>
<td>1.32</td>
<td>Intestine (apical)</td>
<td>Zhou et al. 2007</td>
</tr>
<tr>
<td>OCTN1 (SLC22A4)</td>
<td>NA</td>
<td>Intestine (apical)</td>
<td>Nakamichi et al. 201322</td>
</tr>
<tr>
<td>THTR-2 (SLC19A3)</td>
<td>1.15</td>
<td>Intestine (apical) and liver</td>
<td>Liang et al. 201515</td>
</tr>
<tr>
<td>SERT (SLC6A4)</td>
<td>4</td>
<td>Intestine (apical)</td>
<td>Han et al. 201523</td>
</tr>
</tbody>
</table>

Metformin include the organic cation transporters (OCT), OCT1 (encoded by gene SLC22A1), OCT2 (encoded by SLC22A2) and OCT3 (encoded by SLC22A3), and the human multidrug and toxin extrusion (MATE) transporters MATE1 (encoded by SLC47A1), and MATE2-K (encoded by SLC47A2). In 2007, it was shown that metformin is a substrate of the plasma membrane monoamine transporter (PMAT, encoded by SLC29A4) expressed on the luminal side of the enterocytes in human intestine and in 2013, Nakamichi et al. showed that the carnitine/organic cation transporter (OCTN1, encoded by SLC22A4), and also localized on apical membranes in the small intestine, is a transporter for metformin. Han et al. in 2015 demonstrated that the serotonin reuptake transporter (SERT; SLC6A4) transports metformin with a Km of 4mM in vitro, although these results were not reproduced in another study from Liang et al., which found that metformin was both a substrate and inhibitor of the human thiamine transporter 2, THTR-2 (encoded by SLC19A3).

### Pharmacodynamics
Metformin decreases both fasting and postprandial glucose levels primarily by reducing excessive hepatic glucose production through suppression of gluconeogenesis. Metformin can also increase peripheral glucose utilization and ultimately decrease the production of fatty acids and triglycerides. Because metformin is non-stimulating endogenous insulin production, so metformin is not causes hypoglycemia, which is a common side effect of some anti-diabetics. The molecular mechanism of action of metformin was previously described. Below we will describe candidate gene studies that have provided information about the genes, proteins and pathways involved in uptake, disposition and response to metformin.

Zhou et al. demonstrated that metformin activates the serine / threonine kinase AMP-activated protein kinase (AMPK) in hepatocytes. This results in several effects including suppression of the expression of key lipogenic transcription factors sterol regulatory
element-binding protein 1 (SREBP-1). It also suggests that the protein-threonine kinase, LKB1, is required for the action of metformin via AMPK. AMPK activation occurs because metformin induces energy stress via inhibition of respiratory chain complex I in the mitochondria which causes changes in the ATP-to-AMP ratio resulting in AMPK activation, which affects many substrates including acetyl-CoA carboxylases (ACCs) and through other pathways increase plasma membrane localization GLUT1 and GLUT4. Metformin has also been shown to inhibit hepatic gluconeogenesis via a pathway that is independent of the LKB1 / AMPK pathway. Single nucleotide polymorphisms (SNP) in the AMPK gene (STK11) and in various AMPK subunit genes have been analyzed in several studies that predicted to be associated with the effects of metformin, such as the Diabetes Prevention Program (DPP), where there was a small effect seen.6

Other mechanisms of the hypoglycemic effect of metformin include glucoagon-dependent antagonism of glucose output from hepatocytes by reducing cyclic AMP production, and inhibition of glucose hepatic mitochondrial glycerophosphate dehydrogenase. Metformin has also been shown to inhibit transit through Nuclear Pore Complex (NPC) and Raise Acyl-Coa Dehydrogenase Family Member-10 (ACAD10) which reduces viability in some cancer cells and may explain its anti-cancer effects.6

The genetic approach as a potential solution

There are differences in each individual in response to metformin, most likely this variation is due to genetic variation. For example, epidemiological studies suggest that there are differences between ethnicities in the response to metformin, and a genetic component may underlie some of these differences. However, environmental factors may also play a role, either directly or by interacting with genetic backgrounds; to guide further exploration, it will be important to measure the relative contribution of each. Typically, this is done through classic heritability studies but it presents clear challenges in finding a sufficient number of close relatives who are treated with metformin and phenotypes for a therapeutic response. Recently, the availability of genotypically dense genotypes in cohorts in which the metformin response has been quantified allows researchers to measure the degree of genetic association with sufficient precision and estimate its contribution to variance in traits of interest.9

The Genetics of Diabetes and Audit Research Tayside Study (GoDARTS) research group has pioneered a genome-wide association (GWAS) study for metformin response in participants with type 2 diabetes. GoDARTS enrolled more than 17,000 patients with type 2 diabetes, followed their clinical system, and matched non-diabetic control participants for genetic studies, utilizing clinical information available in electronic medical records. Most of these participants had undergone a whole-genome genotype and researchers have determined how to measure metformin’s glycemic response based on HbA1c levels at the time of initial metformin prescription as well as changes during treatment. They can also control compliance to access pharmacy records. Using the complex trait analysis method of the whole geno, Zhou et al analyzed 2085 participants with available data and concluded that the heritability of response to metformin responses based on the common variant captured by commercial genotypes ranges from 20-34%, depending on the specifications of the measuring instrument used, providing a quantitative limit for genetic effects, at least to the extent that co-variants across the population concerned. Heritability could have been higher if the less common variants were also considered. at least as far as co-variance across the population is concerned. Heritability could have been higher if the less common variants were also considered. at least as far as co-variance across the population is concerned (Table 3). Heritability could have been higher if the less common variants were also considered.9
Tabel. 3 Heritability estimates of various measures of glycaemic response to metformin obtained from a genome-wide association study in GoDARTS

<table>
<thead>
<tr>
<th>Glycaemic measure</th>
<th>Heritability (h²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolute reduction in HbA1ca</td>
<td>23%</td>
</tr>
<tr>
<td>Proportional reduction in HbA1cb</td>
<td>20%</td>
</tr>
<tr>
<td>Adjusted reduction in HbA1cc</td>
<td>34%</td>
</tr>
<tr>
<td>Achieved target HbA1c</td>
<td>32%</td>
</tr>
</tbody>
</table>

Having established that searching for genetic determinants of metformin response is plausible, it is useful to articulate the main aims of pharmacogenetic investigations. One of the goals is to use genetic variation to classify patients into responders and non-responders, so as to adapt the most appropriate therapy. A related but distinct aim is to identify genes that are thought to encode drug targets, especially for pharmacological agents whose mechanisms of action are unclear. A third objective involves using known pharmacological disorders to explain the role of genes with unknown functions that code for variations responsible for different responses. However in order for the subsequent exercise to be fully informative, the exact mechanism of action of the drug must be understood in order for the gene product to be placed on the relevant pathway, which is not yet applicable to metformin. Thus, genetic investigations surrounding the action of metformin initially focused on the dual purpose of segmenting patients based on response rates and identifying molecular targets.9

Prior to the development of the GWAS approach to interrogating the entire genome, researchers were limited by pre-existing biological knowledge; for metformin, research has centered on the cellular transporters that control metabolism, which can now be questioned through studies of candidate related genes. If a strong association is found, they will probably divide the patient classification into responders and non-responders, but no new insights about the metformin target will be obtained; the panorama will change radically with the emergence of GWAS.9

Conclusion

Diabetes mellitus is a metabolic disease that can cause various complications. This situation greatly affects the quality of life of people with DM so it needs serious attention from all parties. The World Health Organization (WHO) predicts an increase in the number of people with DM which is one of the global health threats. DM treatment is very specific and individual for each patient. Metformin is the most commonly used and easily available first-line treatment for diabetes mellitus.

Metformin decreases both fasting and postprandial glucose levels primarily by reducing excessive hepatic glucose production through suppression of gluconeogenesis. Metformin can also increase peripheral glucose utilization and ultimately decrease the production of fatty acids and triglycerides. Some of the individual differences that underlie the variation in response to metformin are likely genetic in nature. For example, epidemiological studies suggest that ethnic disparities exist in metformin response and a genetic component is likely to underlie some of these disparities.

References


