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The Pharmacogenetics of Metformin: A Narrative Literature Review

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A B S T R A C T

Metformin is one of the used medications for the treatment of type 2 diabetes. It works by reducing glucose production in the liver and improving glucose uptake and utilization in peripheral tissues. the pharmacogenetics of metformin is a rapidly evolving field with potential implications for personalized medicine. This review aimed is to explore the pharmacogenetics of metformin, including the genetic variants that may influence its efficacy and safety, as well as the potential implications for clinical practice. Genetic testing may be useful in identifying patients who are likely to benefit from metformin and those who are at higher risk for adverse effects. However, the implementation of genetic testing for metformin response in clinical practice faces several challenges, including cost, interpretation of test results, and the need for further evidence of clinical utility. In conclusion, the pharmacogenetics of metformin is a rapidly evolving field with potential implications for personalized medicine.

1. Introduction

Metformin is a widely used medication for treating type 2 diabetes mellitus. It is considered a first-line medication for managing hyperglycemia, reducing insulin resistance, and improving glucose tolerance. However, there is substantial variability in the response of patients to metformin therapy. The field of pharmacogenetics investigates the relationship between genetic variations and the response to medications.[1-3] This review aimed to explore the pharmacogenetics of metformin, including the genetic variants that may influence its efficacy and safety, as well as the potential implications for clinical practice.

Pharmacology of metformin

Metformin belongs to the biguanide class of medications, which lower blood glucose levels by reducing hepatic glucose production and improving insulin sensitivity. Metformin achieves these effects by activating AMP-activated protein kinase (AMPK), a cellular energy sensor that regulates glucose and lipid metabolism. AMPK activation leads to inhibition of gluconeogenesis and stimulation of glucose uptake in skeletal muscles, among other effects. In addition to its glucose-lowering effects, metformin has been shown to have potential benefits in reducing the risk of cardiovascular disease, cancer, and other conditions. Metformin is absorbed in the small intestine and is primarily eliminated by the kidneys. Its pharmacokinetics is characterized by a short half-life of approximately 2-4 hours, low bioavailability of about 50%, and extensive protein binding. The dose of metformin is typically titrated based on the patient's response to therapy, with a maximum recommended dose of 2,550 mg per day.[4-8]

Pharmacogenetics of metformin

Pharmacogenetics is the study of how genetic variation affects an individual's response to medication. The genetic variants that influence the pharmacokinetics and pharmacodynamics of metformin are still being investigated. However, several studies have identified genetic markers that may contribute to inter-individual variability in metformin response.[9,10]

One of the most studied genetic variants in relation to metformin is located in the gene encoding organic cation transporter 1 (OCT1). OCT1 is responsible for the uptake of metformin into hepatocytes, where it exerts its glucose-lowering effects. The OCT1 gene is highly polymorphic, and some variants have been associated with reduced transport activity and, consequently, decreased efficacy of metformin. For example, the OCT1 variant rs622342 is associated with reduced transport activity and a decreased response to metformin in patients with type 2 diabetes. Another variant, rs628031, has been linked to a reduced reduction in hemoglobin A1c (HbA1c) levels with metformin treatment.[11-13]

Another genetic variant that may influence the response to metformin is located in the gene encoding multidrug and toxin extrusion protein 1 (MATE1). MATE1 is involved in the renal excretion of metformin. The MATE1 variant rs2289669 has been associated with a decreased renal clearance of metformin and an increased risk of metformin-induced gastrointestinal adverse effects.

Other genetic variants that may be associated with metformin response include those located in the genes encoding the ATP-binding cassette transporter ABCB1, the glucose transporter GLUT2, and the mitochondrial enzyme nicotinamide adenine dinucleotide phosphate (NADPH) oxidase 4 (NOX4).[14-16]

Clinical implications

The pharmacogenetics of metformin has the potential to impact clinical practice through personalized medicine. Personalized medicine involves tailoring medical treatment to the individual patient based on their specific genetic profile. In the case of metformin, genetic testing may identify patients who are likely to benefit from the medication and those who are at higher risk for adverse effects.[17]

Several studies have investigated the use of genetic testing to predict the response to metformin. In one study, patients with type 2 diabetes were genotyped for the OCT1 variant rs622342. The results showed that patients with the variant had a lower response to metformin than those without the variant, suggesting that genetic testing may be useful in identifying patients who may require higher doses of metformin to achieve glycemic control.[18]

In another study, patients were genotyped for the MATE1 variant rs2289669. The results showed that patients with the variant had a higher risk of gastrointestinal adverse effects with metformin treatment (2). This suggests that genetic testing may be useful in identifying patients who are at higher risk for adverse effects and may require closer monitoring or alternative treatments.[19]

Despite these promising findings, there are several challenges to implementing genetic testing for metformin response in clinical practice. First, the cost of genetic testing may be prohibitive for some patients and healthcare systems. Second, the interpretation of genetic test results is complex and requires expertise in pharmacogenetics. Third, the evidence for the clinical utility of genetic testing for metformin response is still evolving, and more studies are needed to establish its efficacy and cost-effectiveness.[20]

2. Conclusion

The pharmacogenetics of metformin is a rapidly evolving field with potential implications for personalized medicine. Several genetic variants have been identified that may influence the response to metformin, including variants in the genes encoding OCT1 and MATE1. Genetic testing may be useful in identifying patients who may require higher doses of metformin to achieve glycemic control or who are at higher risk for adverse effects.

3. References

1. Nathan DM, Buse JB, Davidson MB. Medical management of hyperglycaemia in type 2 diabetes mellitus: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. Diabetologia. 2009; 52: 17–30.
2. Rodbard HW, Jellinger PS, Davidson JA. Statement by an American Association of Clinical Endocrinologists/American College of Endocrinology consensus panel on type 2 diabetes mellitus: an algorithm for glycemic control. Endocr Pract. 2009; 15: 540–559.
3. Inzucchi SE, Bergenstal RM, Buse JB. Management of hyperglycaemia in type 2 diabetes, 2015: a patient-centred approach. Update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetologia. 2015; 58: 429–42.
4. Bailey CJ, Turner RC. Metformin. N Engl J Med. 1996; 334: 574–9.
5. Nathan DM. Finding new treatments for diabetes--how many, how fast... how good? N Engl J Med. 2007; 356: 437–40.
6. The Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med. 2002; 346: 393–403.
7. Kirpichnikov D, McFarlane SI, Sowers JR. Metformin: an update. Ann Intern Med. 2002; 137: 25–33
8. The United Kingdom Prospective Diabetes Study. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34) Lancet. 1998; 352: 854–65.
9. Knowler WC, Fowler SE, Hamman RF. 10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. Lancet. 2009; 374: 1677–86.
10. Stumvoll M, Nurjhan N, Perriello G, Dailey G, Gerich JE. Metabolic effects of metformin in non-insulin-dependent diabetes mellitus. N Engl J Med. 1995; 333: 550–4.
11. The Diabetes Prevention Program Research Group. Long-term safety, tolerability, and weight loss associated with metformin in the Diabetes Prevention Program Outcomes Study. Diabetes Care. 2012; 35: 731–7.
12. Aroda VR, Knowler WC, Crandall JP Group DPPR. Metformin for diabetes prevention: insights gained from the Diabetes Prevention Program/Diabetes Prevention Program Outcomes Study. Diabetologia. 2017.
13. Sam S, Ehrmann DA. Metformin therapy for the reproductive and metabolic consequences of polycystic ovary syndrome. Diabetologia. 2017.
14. Heckman-Stoddard B. Metformin and cancer. Diabetologia. 2017.
15. Turner RC, Cull CA, Frighi V, Holman RR. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). UK Prospective Diabetes Study (UKPDS) Group. JAMA. 1999; 281: 2005–12.
16. Kahn SE, Haffner SM, Heise MA. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. N Engl J Med. 2006; 355: 2427–43.
17. Zeitler P, Hirst K, Pyle L. A clinical trial to maintain glycemic control in youth with type 2 diabetes. N Engl J Med. 2012; 366: 2247–56.
18. Rena G, Hardie DG, Pearson ER. The mechanisms of metformin action. Diabetologia. 2017.
19. Williams LK, Padhukasahasram B, Ahmedani BK. Differing effects of metformin on glycemic control by race-ethnicity. J Clin Endocrinol Metab. 2014; 99: 3160–8.

20. Lee SH, Wray NR, Goddard ME, Visscher PM. Estimating missing heritability for disease from genome-wide association studies. Am J Hum Genet. 2011; 88: 294–305.