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IMPACT OF OCT-1 GENETIC VARIATION ON METFORMIN RESPONSE AND ITS GASTROINTESTINAL SIDE EFFECTS

A. Mercy Jenifa [*1] and B. Jayanthi [2]

Department of Pharmacy Practice [1], Department of Pharmacology [2], Karapaga Vinayaga Institute for Pharmaceutical Sciences, Maduranthakam - 603308, Tamil Nadu, India.

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Correspondence to Author:
A. Mercy Jenifa

Assistant Professor,
Department of Pharmacy Practice,
Karapaga Vinayaga Institute for Pharmaceutical Sciences,
Maduranthakam - 603308, Tamil Nadu, India.

E-mail: mercyjenifa111@gmail.com

ABSTRACT: Metformin used successfully by clinicians over the decades as a first-line treatment for hyperglycemia also it was a popular treatment for type-2 diabetes in those who are overweight, when diabetes is not controlled by a healthy diet and lifestyle changes. Genetic factors place an important role in modulating metformin efficacy and toxicity in which OCT- 1 was a major transporter of metformin so genetic polymorphism of OCT-1 largely influences the metformin response and toxicity. This review outlines the relation between OCT-1 variants and metformin induced gastrointestinal side effects with similar and varied results among studies and portrays the need for studies to prove the relation between metformin efficacy, gastrointestinal side effects, and genetic variation of OCT-1 so that future studies may contribute to personalized and safer metformin treatment.

INTRODUCTION: Most of the drug response and disposition depends upon the membrane transporter which regulates drug intake into the cells. Organic cation transporter (OCT-1) is largely expressed in the liver which helps many endogenous compounds and cationic drugs to transport across biological membranes [1]. Metformin (dimethyl biguanide) is one of the cationic drugs used successfully by clinicians over the decades as first-line treatment for hyperglycemia which requires membrane transporters. OCT-1 majorly helps metformin uptake into the liver. OCT 1 has many variants rs594709, rs36056065, rs628031, rs12208357, rs622342, rs72552763, rs2282143 [2, 3].

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Some of the variants have reduced functionality which might influence metformin pharmacokinetics and pharmacodynamics and induce gastrointestinal adverse effects such as nausea, vomiting, diarrhea, and constipation [4]. There are differences in results between many studies regarding whether the reduced function influences the metformin efficacy and side effects. This review outlines the similar and varied results among studies and portrays the need for studies to prove the relation between metformin efficacy, gastrointestinal side effects, and genetic variation of OCT-1.

Metformin Response: Many studies showed the relation between the OCT-1 variants and the metformin response among them the study analyzed the changes in the HbA1c level in relation to 11 tagging single nucleotide polymorphisms in the SLC22A1 gene. There were no discernible variations in metformin response but only one variant rs622342 showed a 0.28% reduction in

HbA1C in patients who were incident users of metformin [6]. The study performed in the south Indian population showed carriers of allele of variant rs622342 has greater response for metformin treatment [7]. On the contrary the study examined the variants of OCT-1 gene rs72552763, rs12208357 there is no substantial changes in glycemic index [8]. In a GODARTS study showed the loss of function variant of SLC22A1 does not influence the initial period of metformin treatment so they stated that further investigation into the variants of SLC22A1 is needed to fully gauge the gene's effect on metformin response [9]. In the study patients with reduced function alleles showed varied steady state plasma concentration in both initial and long-term metformin treatment [10].

In Chinese population the study investigated Type-2 Diabetes patients with the SLC22A1 rs594709 GG genotype which exhibited a greater increase in Fasting insulin level and patients with the SLC22A1 rs594709 AA genotype, experienced a greater decrease in both Fasting blood glucose and Postprandial insulin [11]. The study Shikata *et al.* 2007 showed there is no difference between the responders and non-responders in the level of HbA1c but rs628031 showed an association between the presence of allele A with metformin response. They also relate BMI and lipid-lowering agents with metformin response by finding that obese patients have increased metformin efficacy [12]. However, in the study showed is no relation between mutant allele rs628031 (M408V) and the metformin response [13]. The study by Kawoosa *et al* 2022 showed that variations in OCT-1 affect the transportation of metformin it may result in decreased metformin response and Variations in non-responders disrupt the protein's structure, which can affect OCT-1 function and reduce metformin uptake. In Brazilian population the study showed the Variations in the OCT1 gene SLC22A1 rs12208357, along with factors such as age, body surface area, African genetic background, and food intake, accounted for 29.7% of the differences in metformin Plasma concentration curve [14].

Metformin-Induced Gastrointestinal Side Effects: Many studies showed the relationship between OCT-1 variants and the metformin-induced gastrointestinal side effects, while various theories have been suggested, the underlying cause of metformin-induced gastrointestinal side effects remains unknown, and there are insufficient data to account for the significant differences between individuals [15, 16, 17]. The study assessed the five single nucleotide polymorphisms of OCT-1 gene which were associated with gastrointestinal side effects of metformin and showed a allele of the rs628031 and 8 bp insertion (rs36056065) of OCT-1 gene have increased prevalence of gastrointestinal side effects among type-2 diabetes mellitus patients [18]. Dawed *et al.* 2019 investigated the OCT-1 and other transporters of metformin with its gastrointestinal side effects and concluded that the presence of two or more reduced function allele increase the probability of metformin-induced gastrointestinal side effects [19]. Another study Dujic *et al.* 2015 showed the relationship between common OCT-1 genetic polymorphism (M408V and 8 bp insertion) and the metformin induced gastrointestinal side effects and identified that the concomitant use of other drugs which inhibit OCT-1 action, also influences the side effects of metformin [20, 21]. Dujic *et al.* 2016 genotyped two reduced function variants such as R61C (rs12208357) and M420del (rs72552763) showed there is no significant association with metformin-induced gastrointestinal side effects and identified female sex has more probability for metformin intolerance [22].

CONCLUSION: Although there are many findings stating that the relationship between OCT-1 variants and the metformin response, side effects. The mechanism behind the association between them was unclear. The genetic polymorphism of OCT -1 may increase the prevalence of the gastrointestinal side effects induced by metformin and to our knowledge, there are very few studies done in the Indian population. This review portrays the need for future studies to prove the relation between metformin efficacy, gastrointestinal side effects, genetic variation of OCT-1, the mechanism behind them in a large population so the results may contribute to personalized and safer metformin treatment.

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Chinna Kolambakkam (PO), Madurantham (TK), Chengalpattu- 603 308, Tamil Nadu, India.

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