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Genetic polymorphisms of Organic Cation Transporter 1 (OCT1) and metformin effects in individuals with type 2 diabetes: A systematic review

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Background: Metformin is one of the most commonly used drugs for the treatment of type 2 diabetes mellitus (T2DM). Despite its widespread use, there are considerable inter-individual variations in metformin response, with about 35% of patients failing to achieve initial glycemic control. These variabilities that reflect phenotypic differences in drug distribution and action may indeed due to polymorphisms in genes related to the pharmacokinetics and pharmacodynamics of metformin. Moreover, interethnic differences in drug responses in some cases correspond to substantial differences in the frequencies of the associated pharmacogenomics risk allele.

Aim: This review aims to highlight and summarize the overall effects of OCT1 polymorphisms on therapeutic responses to metformin and to evaluate the potential role of such polymorphisms in interethnic differences in metformin therapy.

Methods: We conducted a systematic review according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines. We searched for PUBMED/MEDLINE, EMBASE and CINAHL, relevant studies reporting the effects of OCT1 polymorphisms on metformin therapy in T2DM individuals. Data were extracted on study design, population characteristics, relevant polymorphisms, measure of genetic association and outcome. Presence of gastrointestinal side-effects, glycated hemoglobin A1 (HbA1c) levels, fasting plasma glucose (FPG) and post-prandial plasma glucose (PPG) concentrations after the treatment with metformin were chosen as measures of the metformin responses. This systematic review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO).

Results: According to the data extracted, a total of 34 OCT1 polymorphisms were identified in 10 ethnic groups. Significant differences in the frequencies of common alleles were observed among these groups. *Met408Val (rs628031)* variant was the most extensively explored with metformin responses. Although some genotypes and alleles have been

associated with deleterious effects on metformin response, others indeed, exhibited positive effects.

Conclusion: The genetic effects of OCT1 polymorphisms on metformin responses were population specific. Further investigations in other populations are required to set ethnicity-specific reference for metformin responses and to obtain a solid basis to design personalized therapeutic approaches for T2DM treatment.

Keywords: Genetic polymorphisms; glycemic response; metformin; OCT1; type 2 diabetes mellitus.