Association between Genetic Polymorphisms of the Organic Cation Transporter-1 and Response to Metformin Therapy in Patients with Type 2 Diabetes

Y.A Illangasekera[1]*, C.F Dalton[2], G.D.D.J Bandara[1], D.M.S.N.B Dassanayake, O.R Gamage[3]

[1]*Dept. of Pharmacology, Faculty of Medicine, University of Peradeniya, Peradeniya, P20400, Sri Lanka*
[2]*Biomoleculr Sciences Research Centre, Sheffield Hallam University, Sheffield, S1 1WB, United Kingdom*
[3]*Divisional Hospital Katugastota, Kandy, P20800, Sri Lanka*

The Organic Cation Transporter-1 (OCT1) plays a key role in the pharmacokinetics of metformin, a widely used antidiabetic drug. OCT1 protein is involved in transporting the drug from the gastrointestinal tract into the portal vein and subsequent uptake into the hepatocyte. The *SLC22A1* gene encodes OCT1 and its genetic variation affects the protein's function. Thus, two recognized variants of *SLC22A1*, the rs628031 and rs12208357 single nucleotide polymorphisms (SNPs) have the potential to affect the therapeutic outcomes of metformin. The objective of the study was to investigate the association of the rs628031 and rs12208357 SNPs with the efficacy and adverse effects of metformin therapy in 180 Sri Lankan type 2 diabetic patients. The associations of the 2 SNPs with diabetic control outcomes of HbA1c, Fasting Blood Sugar (FBS), and Postprandial blood Sugar (PPBS) levels, and common adverse effects of metformin were tested. The average of glycaemic control measures over 3 months when patients were on metformin monotherapy was used in the analysis. DNA extracted from whole blood was genotyped using real-time PCR to determine genotypes. The results revealed that the minor allele frequencies of rs628031 and rs12208357 SNPs were 0.41 and 0.04 respectively. The rs628031 SNP was associated with metformin adverse drug effects symptoms of nausea and/or vomiting and abdominal discomfort. Here the `A allele' carrying genotypes (AA+AG) were more prevalent in patients reporting the said adverse effects compared to those who did not. Neither of the SNPs tested was associated with the glycaemic control measures tested following adjustment for metformin dosage. The moderate sample size and other pharmacokinetic factors may have contributed to the results. The present study is the first to report on the pharmacogenomics of metformin therapy in Sri Lankans. In conclusion, the *SLC22A1* rs628031 SNP is associated with metformin adverse effects in Sri Lankans.

Keywords: Pharmacogenomics, Metformin, Diabetes, SLC22A1 Gene, Adverse Effect