

INTISARI

Latar belakang Metformin merupakan obat antidiabetik oral terpilih pada pasien DM tipe 2 (DMT2) yang tersedia hingga di fasilitas kesehatan primer. Meskipun demikian, variabilitas respon glikemik penggunaan metformin banyak ditemukan di ranah pelayanan klinis. Telah diketahui bahwa *Organic Cation Transporter1* (OCT1) merupakan protein transporter utama metformin yang bertanggung jawab terhadap proses *influx* metformin menuju hepatosit sebagai target aksinya sebagai antidiabetik. Sementara itu, *efflux* metformin dari hepatosit maupun ekskresinya melalui renal dimediasi oleh *multidrug and toxin Extrusion 1* (MATE1). Oleh karena itu, keberadaan polimorfisme pada gen yang menyandi protein tersebut dapat berakibat variasi farmakokinetika dan farmakodinamika metformin. Penelitian ini bertujuan untuk menganalisis polimorfisme gen *SLC22A1* rs628031 A>G (Met408Val) pada OCT1 dan *SLC47A1* rs2289669 G>A pada MATE1 serta implikasinya terhadap variabilitas kadar tunak dan farmakodinamika metformin sebagai antihiperlikemik.

Metode penelitian Penelitian menggunakan rancangan kohort prospektif pada pasien DMT2 yang menggunakan metformin 500 mg setiap 12 jam di Puskesmas. Variasi genetik pada *SLC22A1* rs628031 A>G (Met408Val) dan *SLC47A1* rs2289669 G>A dianalisis menggunakan metode PCR-RFLP. Bioanalisis metformin dalam plasma dengan menggunakan metode KCKT fase terbalik dan detektor UV yang telah divalidasi sebelumnya. Pemeriksaan kadar tunak metformin dilakukan pada kadar tunak minimal dan maksimal. Nilai glukosa darah puasa dan *glycated albumin* digunakan sebagai parameter farmakodinamika penggunaan metformin. Hasil uji statistika dinyatakan signifikan bila nilai $P \leq 0,05$.

Hasil dan kesimpulan Variasi genetik pada *SLC22A1* rs628031 A>G (Met408Val) dan *SLC47A1* rs2289669 G>A tidak berkorelasi secara signifikan terhadap farmakokinetika kadar tunak dan efek terapeutik metformin ($P > 0,05$). Oleh karena C_{ss}^{max} pada kelompok alel 408Val (Met/Val dan Val/Val) 1,3-kali lebih tinggi dibanding kelompok *wild-type* serta perpanjangan $t_{1/2}$ eliminasi hingga 1,25-kali pada kelompok mutan homozigot GG pada *SLC22A1* rs628031 jika dibandingkan kelompok heterozigot AG ditemukan pada penelitian ini, mungkin diperlukan dosis maksimal metformin yang lebih rendah untuk meminimalkan akumulasi metformin dalam plasma yang melebihi batas atas kadar yang direkomendasikan.

Kata kunci: metformin, OCT1, MATE1, farmakokinetika kadar tunak, respon glikemik, Indonesia

ABSTRACT

Background Metformin is a preferred oral antidiabetic drug for patients with type 2 diabetes mellitus (T2DM) and widely available in primary healthcare centers. However, variability of glycemic response to metformin has frequently been found in the field of clinical setting. It is widely known that Organic Cation Transporter1 (OCT1) is the main transporter protein of metformin, which is responsible for the influx process of metformin towards hepatocyte as its target of antidiabetic. Meanwhile, the efflux of metformin from hepatocyte as well as its excretion through the kidneys is mediated by Multidrug and Toxin Extrusion1 (MATE1). Therefore, the existence of polymorphism in the genes encoding those proteins have various impacts on the pharmacokinetics and pharmacodynamics of metformin. This study aimed to analyze the polymorphism of *SLC22A1* rs628031 A>G (Met408Val) in OCT1 and *SLC47A1* rs2289669 in MATE1 as well as their implications for the variability of steady-state levels and pharmacodynamics of metformin as an antihyperglycemic agent.

Research Methods This study employed the prospective-cohort design on T2DM patients taking metformin 500 mg every 12 hours from several primary healthcare centers. The genetic variants of *SLC22A1* rs628031 A>G (Met408Val) in OCT1 and *SLC47A1* rs2289669 G>A in MATE1 were analyzed using the PCR- RFLP method. The bioanalysis of metformin in plasma was conducted using validated reversed-phase HPLC-UV detector. Determination of metformin steady-state concentration was performed for the trough and peak level. The values of fasting blood glucose and glycated albumin became the pharmacodynamic parameters of metformin use. P values less than 0.05 were considered statistically significant.

Results and Conclusion The genetic variants of *SLC22A1* rs628031 408M/V in OCT1 and *SLC47A1* rs2289669 G>A in MATE1 were insignificantly correlated with the steady-state pharmacokinetics and metformin therapeutic effect ($P > 0.05$). Since this study found that the C_{ss}^{max} of metformin in the allele 408Val (Met/Val and Val/Val) group was 1.3 times higher than that of the wild-type, and the prolonged half life of metformin was 1,25-fold in mutant homozygous GG compared to that in heterozygote AG, it is likely that a lower maximum dose of metformin is required to minimize the plasma metformin concentrations that exceed the upper limit of recommended level.

Keywords: metformin, OCT1, MATE1, steady-state pharmacokinetics, glycemic response, Indonesia