# Perbandingan Profil Metabolit Urin Pasien Penyakit Ginjal Diabetes Risiko Rendah dan Tinggi Menurut KDIGO2022 yang Menggunakan Terapi Metformin-Glimepirid = Urinary Metabolites Profile Comparison in Diabetic Patients with Low and High Risk Kidney Disease Based on KDIGO2022 Treated by Metformin-Glimepiride

Patricia Felia Budijarto, author



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Abstrak

Keterbatasan glomerulus filtration rate (eGFR) dan urine albumin creatinine ratio (uACR) sebagai acuan menyebabkan keterlambatan diagnosis dan prognosis penyakit ginjal diabetes. Perkembangan diabetes mengarah pada kerusakan ginjal dicerminkan oleh penanda (biomarker) yang ditemukan dalam spesimen biologis. Penelitian ini bertujuan mencari metabolit potensial sebagai biomarker pada populasi Indonesia dengan membandingkan metabolit dalam urin pasien diabetes dengan risiko ginjal rendah (n=16) dan tinggi (n=16) menurut klasifikasi KDIGO2022. Analisis metabolomik dilakukan menggunakan liquid chromatography/mass spectrometry quadrupole time-of-flight (LC/MS-QTOF) dengan analisis statistik data menggunakan software Metaboanalyst5,0. Metabolit diidentifikasi menggunakan database Human Metabolome Database (HMDB), Metlin, dan Pubchem. Diskriminasi antar 2 kelompok divisualisasikan dengan Principal Component Analysis (PCA) dan Partial Least Squares-Discriminant Analysis (PLS-DA). Signifikansi metabolit antar 2 kelompok ditentukan dengan T-test ($p<0,05$), variable importance for projection (VIP>1), dan fold change ($\log2(FC)>1,2$). Metabolit yang dipilih hanya metabolit endogen yang diketahui jalur metabolismenya. Dari berbagai parameter tersebut, metabolit yang potensial sebagai biomarker harus memenuhi nilai area under curve (AUC)>0,65. Berdasarkan karakteristik dasar dan klinis, tidak terdapat perbedaan bermakna karakteristik dasar (usia, jenis kelamin, indeks massa tubuh, durasi menderita DMT2, frekuensi olahraga, kebiasaan merokok, penyakit lain, kepatuhan minum obat, regimen terapi metformin-glimepirid) dan pemeriksaan klinis (HbA1c, tekanan darah sistol, dan diastol) antara kedua kelompok ($p>0,05$). Ditemukan 23 metabolit yang memenuhi parameter VIP, p-value, dan fold change. Disimpulkan, tiga metabolit teratas dengan AUC>0,65 merupakan biomarker potensial yang membedakan kedua kelompok, yaitu indoksil glukuronida, N-asetilserotonin glukuronida, dan gliserofosfokolin. Indoksil glukuronida dan N-asetilserotonin glukuronida terlibat dalam metabolisme triptofan dan glukuronat, sedangkan gliserofosfokolin terlibat dalam jalur metabolisme gliserofosfolipid dan eter lipid.
.....The limited utility of glomerulus filtration rate (eGFR) dan urine albumin creatinine ratio (uACR) as the gold standard lead to late diagnosing and prognosing of diabetic kidney disease. Diabetes progression contributes to kidney damage and is reflected by biomarkers in patients' biological samples. This study aims to identify potential endogenous metabolite biomarkers for improved diagnosis and prognosis by comparing metabolites in the urine of diabetic patients with low (n=16) and high (n=16) kidney disease risk in the Indonesian population according to the KDIGO2022 classification. Metabolomic analysis was conducted using liquid chromatography/mass spectrometry quadrupole time-of-flight (LC/MS-QTOF) with Metaboanalyst5.0 software. Metabolites were identified using the Human Metabolome Database, Metlin, and PubChem. Discrimination between the two groups was visualized using principal component analysis (PCA) and Partial Least squares discriminant analysis (PLS-DA). Based on patients' characteristics, no

significant differences were observed in baseline characteristics (age, gender, body mass index, duration of type 2 diabetes mellitus, exercise frequency, smoking habits, comorbidities, medication adherence, metformin-glimepiride therapy regimen) and clinical characteristics (HbA1c, systolic and diastolic blood pressure) between two groups ($p>0.05$). According to the findings of the T-test ($p<0.05$), fold change ($\log2(FC)>1.2$), and variables important for the projection ($VIP>1$), there were 23 metabolites substantially different between the two groups. In conclusion, the top 3 metabolites with the area under curve (AUC) value>0.65 demonstrated potential biomarker differentiating among two groups; these are indoxyl glucuronide, N-acetylserotonin glucuronide, and glycerophosphocholine. Indoxyl glucuronide and N-acetylserotonin glucuronide involved in tryptophan metabolism and glucuronate interconversion. Glycerophsophocholine involved in glycerophospholipid and ether lipid metabolism.