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Urinary Metabolomics Identifies Novel Metabolites for Distinguishing Membranous Nephropathy And Its Subtype

Ji Hye Kim[1], Yufei Li[3], Donghwan Yun[2], Jihyun Kang[4], Sohyun Bae[2], Chaelin Kang[4], Joo-Youn Cho[3], Seung Seok Han[2]
[1]Department of Internal Medicine-Nephrology, Chungbuk National University Hospital, Korea, Republic of
[2]Department of Internal Medicine-Nephrology, Seoul National University Hospital, Korea, Republic of
[3]Department of Clinical Pharmacology and Therapeutics, Seoul National University College of Medicine, Korea, Republic of
[4]Department of Biomedical Sciences, Seoul National University College of Medicine, Korea, Republic of

Objectives : Membranous nephropathy (MN) stands as the most prevalent cause of nephrotic syndrome in adults. Currently, MN diagnosis relies on either the presence of anti-phospholipase A2 receptor (PLA2R) antibodies in the serum or a kidney biopsy. However, approximately 30% of MN patients exhibit negative anti-PLA2R antibodies, and the applicability of kidney biopsy is hindered for some patients due to its invasive nature. Herein, the study aimed to identify diagnostic metabolites associated with MN and its subtype using untargeted urinary metabolomics.
Methods : A total of 73 biopsy-confirmed MN patients between April 2021 and December 2022 were included in the study. Untargeted metabolomic analysis of collected urine samples was performed using a high-resolution liquid chromatography-tandem mass spectrometry system. The results were compared to healthy individuals and patients with immunoglobulin A nephropathy as control groups. Processed feature data were normalized for variations in urinary dilution using the probability quotient normalization method.
Results : Among the total of 73 patients (mean age; 57 ± 11, male; 65.8%), 37 tested positive for anti-PLA2R antibodies, while 36 tested negative. A total of 156 endogenous metabolites were identified through matching with an open-source database. After adjusting for age and sex, seven urinary metabolites showed significant associations with MN, namely pregnanolone sulfate, indole-3-acetic acid, phenylalanine, tetradecanoylcarnitine, norleucine, 7-ketodeoxycholic acid, and 3a, 7b, 12b-trihydroxy-5a-cholan-24-oic acid. Additionally, twelve metabolites were associated with anti-PLA2R antibody positivity, with two up-regulated (threonylphenylalanine and 1-methylhistidine) and ten down-regulated (S-lactoylglutathione, deoxycholic acid 3-glucuronide, undecanedioic acid, 3-carboxy-4-methyl-5-propyl-2-furanpropionic acid, 1-methylxanthine, allocholic acid, prostaglandin K2, thromboxane B3, 3-(3-hydroxyphenyl)propionic acid and 5'-deoxy-5'-(methylthio)adenosine).
Conclusions : These novel urinary metabolites related to MN hold potential utility in clinically diagnosing MN and distinguishing between anti-PLA2R antibody-positive and -negative cases.