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Identification of a urinary diagnostic biomarker panel for membranous glomerulonephitis and pathogenic metabolic pathways using metabolomics techniques

Shiva Kalantari[1], **Mohsen Nafar**[1], **Amir Taherkhani**[2] and **Afsaneh Arefie-Oskouee**[2]
[1]Shahid Beheshti University of Medical Sciences, Iran

Background: Biopsy is an invasive diagnostic method for primary form of membranous glomerulosclerosis (MGN) and traditional serum or urinary current biomarkers are also not enough sensitive or specific. Our purpose is to identify a sensitive and specific noninvasive panel of biomarkers for diagnosis of primary MGN using metabolomics techniques and explore the pathogenic pathways that are involved in the disease development.

Study Design: Diagnostic test study.

Setting & Participants: The training set (discovery set) for nuclear magnetic resonance (NMR) analysis included 31 patients with primary MGN, 14 normal control and 26 disease control. The test set (validation set) included 16 patients with MGN, seven normal control and 30 disease control. Thirty two patients with MGN, 30 normal control and 27 disease control were used for gas chromatography coupled with mass spectrometry (GC-MS) analysis.

Index Tests: Panel of biomarkers identified using metabolomics techniques: alpha-hydroxybutyric acid, 3,4-Dihydroxymandelic acid, 5alpha-cholestanone, 2-Hydroxyglutaric acid lactone, nicotinamide, Epi-coprostanol and palmitic acid.

Reference Test: MGN diagnosed by biopsy.

Results: NMR-based diagnostic model showed allantoic acid (area under the curve (AUC) = 0.78) as the most overrepresented and Deoxyuridine (AUC = 0.85) as the most underrepresented biomarkers. GC-MS based diagnostic model showed oxalic acid (AUC = 0.79) as the most overrepresented biomarker and 2-Hydroxyglutaric acid lactone (AUC = 0.88) as the only underrepresented specific biomarkers. A panel of a combination of most accurate predictors of NMR and GC-MS results with sensitivity and specificity of 100% was acquired by ROC analysis. This panel was composed of alpha-hydroxybutyric acid, 3,4-Dihydroxymandelic acid, 5alpha-cholestanone, 2-Hydroxyglutaric acid lactone, nicotinamide, Epi-coprostanol and palmitic acid. Nine impaired pathways were identified in MGN such as pyrimidine metabolism and NAD salvage. Some of the biomarkers showed correlation with clinical factors.

Limitations: lack of information of anti- phospholipase A2 receptor to compare with the results.

Conclusion: We represented a noninvasive sensitive and specific panel of biomarkers for diagnosis of primary MGN as well as pathogenic mechanisms using metabolomics techniques.

shiva.kalantari@sbmu.ac.ir