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Novel Podocyte-Targeting Biomarkers in Membranous Nephropathy: Looking beyond PLA2R & THSD7A – A Systematic Review

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We use this protocol and it's working

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Disclaimer

NA

Abstract

Membranous Nephropathy is an autoimmune glomerular disease and is the most frequent cause of nephrotic syndrome among Caucasian adults. Following Anti-Phospholipase A2 Receptor (PLA2R) and Thrombospondin Type 1 Domain Containing 7A (THSD7A), new biomarkers of Membranous Nephropathy (MN) in adults, including Neural Epidermal growth factor-Like 1 (NELL-1), Exostosin 1/ Exostosin 2 (EXT1/ EXT2), Protocadherin7 (PCDH7), Transforming Growth Factor Beta Receptor 3 (TGFBR3) and Neural Cell Adhesion Molecule 1 (NCAM1), have been discovered. PubMed, Scopus, Web of Science and CENTRAL will be systematically searched until February 2025. Two reviewers will determine study eligibility according to the title and the abstract of the articles. The full-text publications of potentially relevant articles will be retrieved and rescreened by the same investigators. ROBINS-E tool will be used to evaluate quality of evidence and risk of bias in the included studies.

Guidelines

PRISMA Guidelines
Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. J Clin Epidemiol (2021);134:178-189.

Robins-E for bias assessement of non-ramdomised trials
Higgins JPT, Morgan RL, Rooney AA, et al. A tool to assess risk of bias in non-randomized follow-up studies of exposure effects (ROBINS-E). Environ Int (2024);186:108602.

Materials

PubMed, Scopus, Web of Science and CENTRAL (Cochrane Central Register of Controlled Trials) were systematically searched from inception until 17 TH of February 2025.

Before start

The aim of the present systematic review is to evaluate all available data of patients with MN and positivity of at least one of the aforementioned biomarkers.

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1 The present systematic review will be conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.

Eligibility Criteria

2 PECOS method (P=Population, E=Exposure, C=Control, O=Outcomes, S=Studies), as per PRISMA guidelines, will be used to identify eligible studies. The population of the study will include adult patients with primary or secondary, biopsy-proven MN. The exposure of interest is positivity of either NELL-1 or EXT1/EXT2 or PCDH7 or TGFBR3 or NCAM1 in serum or tissue. Control group included patients tested showing no expression of the above-mentioned markers. The primary study outcome is to assess all available evidence regarding the importance of patients with biopsy proven MN and positivity of either NELL-1 or EXT1/EXT2 or PCDH7 or TGFBR3 or NCAM1. Secondary outcomes are recording of all their clinical, histological and prognostic characteristics, along with possible treatment interventions. Primary research papers including cohort studies, case control or case series will be included. Descriptive, animal and in vivo studies as well as review articles, editorials, opinion articles and case reports will be excluded.

Literature Search

3 PubMed, Scopus, Web of Science and CENTRAL (Cochrane Central Register of Controlled Trials) will be systematically searched from inception until 17 TH of February 2025. Full reference lists of the studies included will also be systematically searched for potential eligible articles. The following search algorithm will be applied: ("Glomerulonephritis, Membranous"[Mesh] OR “membranous nephropathy” OR “membranous glomerulonephritis” OR “membranous nephritis” OR “membranous glomerulopathy”) AND (NELL-1 OR “Neural epidermal growth factor-like 1” OR EXT1/EXT2 OR exostosin 1 / exostosin 2 OR PCDH7 OR Protocadherin7 OR TGFBR3 OR Transforming Growth Factor Beta Receptor 3 OR NCAM1 OR Neural Cell Adhesion Molecule 1), in order to assess patients with Membranous Nephropathy and positivity for either NELL-1 or EXT1/EXT2 or PCDH7 or TGFBR3 or NCAM1, among studies published in English.

4 Study selection & Quality assessment
Two reviewers (K.Z & B.I.) will determine study eligibility according to the title and the abstract of the articles. The full-text publications of potentially relevant articles will be retrieved and rescreened by the same investigators (K.Z. & B.I.). Disagreements will be

resolved by consensus following full text screening. ROBINS-E tool will be used to evaluate quality of evidence and risk of bias in the included studies in terms of confounding, selection of participants, classification of exposures, deviations from intended exposures, missing data, measurement of outcomes and selection of reported results.

Data Extraction & Synthesis

5 Data extraction will then be performed by K.Z., using an extraction form in an Excel® spreadsheet. Information extracted will include: author, country, study period, study design, number of individuals with biopsy-proven MN, demographics, assessment of one, or more, of the following NELL-1 or EXT/EXT2 or PCDH7 or TGFBR3 or NCAM1, tissue biomarker diagnostic technique used, serum biomarker testing, when available, and possible correlations including autoimmune diseases, malignancies, medication or alternative medicine exposure. Qualitative synthesis of the data will then be performed.

Protocol references

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