Open Access Mini-Review

Journal of Renal Endocrinology

J Ren Endocrinol 2023;9:e25120.
https://www.jrenendo.com
doi: 10.34172/jre.2023.25120

Nickan Research Institute

Biomarkers in IgA nephropathy; an update to recent data

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Abstract
Biomarkers are molecules that can be measured in the body and can reflect disease activity or progression. They can be used to diagnose and monitor disease, predict treatment response, and identify potential therapeutic targets. Several types of biomarkers have been studied in the context of IgA nephropathy, including protein, gene expression, epigenetic, and microRNA biomarkers. Biomarkers have the potential to improve the accuracy and specificity of the diagnosis of IgA nephropathy and predict the disease progression and response to treatment. However, further studies are needed to validate their diagnostic value in larger cohorts of patients and to integrate them into clinical practice. The development of multi-omics approaches that combine different types of biomarkers may provide a more comprehensive understanding of the disease pathogenesis and potential treatments.
Keywords: IgA nephropathy, End-stage renal disease, Chronic kidney disease, Hematuria, Biomarkers, Diabetic nephropathies
Citation: Zareie R, Asadollahi Hamedani M, Sadeghian R, Khanchemehr Y, Belali Kharaji M, Zaremoghadam E, Shahkarami N, Samareh Fekri A. Biomarkers in IgA nephropathy; an update to recent data. J Ren Endocrinol. 2023;9:e25120. doi: 10.34172/jre.2023.25120.

Introduction

Immunoglobulin A (IgA) nephropathy is a common type of glomerulonephritis, which also known as Berger's disease, is a chronic kidney disease contributing to 20-40% of primary glomerular diseases, especially in Asian populations (1). IgA nephropathy is characterized by the deposition of IgA immune complexes in the mesangial region of glomeruli, leading to inflammation and progressive fibrosis. The primary clinical manifestation of IgA nephropathy is gross hematuria with or without proteinuria, but it can also produce asymptomatic microscopic hematuria and slowly progressive renal dysfunction (1,2).

The diagnosis of IgA nephropathy relies on a combination of clinical presentation, laboratory tests, histopathological examination, and exclusion of other kidney diseases (3,4). However, the accuracy and specificity of current diagnostic approaches have been limited, leading to a delay in the diagnosis and suboptimal treatment outcomes. Early diagnosis and intervention are crucial in preventing disease progression and preserving renal function. Biomarkers have emerged as a promising tool in the diagnosis and management of IgA nephropathy (5).

Several biomarkers have been investigated in the diagnosis and monitoring of IgA nephropathy. One of the most studied biomarkers is urinary protein excretion. Increased urinary protein excretion is a hallmark feature of IgA nephropathy and is used to monitor disease progression. However, proteinuria is not specific to IgA nephropathy and can also be present in other renal diseases (6).

Another promising biomarker is serum levels of galactose-deficient IgA1 (Gd-IgA1). Gd-IgA1 is a modified form of IgA1 that has been implicated in the pathogenesis of IgA nephropathy. Several studies have shown that serum Gd-IgA1 levels are elevated in patients with IgA nephropathy compared to healthy controls and other renal diseases. Furthermore, serum Gd-IgA1 levels have been shown to correlate with disease activity and histological findings on renal biopsy (7,8).

Serum levels of soluble urokinase-type plasminogen activator receptor (suPAR) have also been investigated as a potential biomarker in IgA nephropathy. suPAR is a marker of immune activation and inflammation and has been shown to predict the risk of disease progression in several renal diseases, including IgA nephropathy (9,10).

Other biomarkers that have been studied in IgA nephropathy include serum levels of complement components, such as C3 and C4, and markers of

Received: 31 March 2023, Accepted: 20 June 2023, ePublished: 26 June 2023

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Implication for health policy/practice/research/ medical education

IgA nephropathy is a common form of glomerulonephritis that can lead to chronic kidney disease and end-stage renal disease. Several biomarkers have been investigated in the diagnosis and monitoring of IgA nephropathy. While urinary protein excretion remains, the most commonly used biomarker, serum levels of Gd-IgA1, suPAR, and other markers of immune activation, inflammation, and oxidative stress show promise in improving the diagnosis and management of IgA nephropathy. Further studies are needed to validate these biomarkers and determine their clinical utility in routine practice.

oxidative stress and inflammation, such as urinary 8-hydroxydeoxyguanosine (8-OHdG) and interleukin-6 (IL-6). This review paper aims to summarize the current state of knowledge on the use of biomarkers in the diagnosis of IgA nephropathy (6,11,12).

Search strategy

For this review, we searched PubMed, Web of Science, EBSCO, Scopus, Google Scholar, Directory of Open Access Journals (DOAJ) and Embase, using different keywords including; IgA nephropathy, biomarkers, hematuria, mesangial area, prognosis, end-stage renal disease and chronic kidney disease.

Diagnosis of IgA nephropathy

IgA nephropathy is a relatively common chronic kidney disease, with an estimated prevalence of one in 1000 individuals. It typically affects young adults and can progress slowly over many years, leading to end-stage kidney disease in up to 30% of patients (13). Current treatment options for IgA nephropathy are limited and aimed at slowing disease progression and managing symptoms. IgA nephropathy occurs when an antibody called IgA forms immune complexes in the glomerular mesangial area. This can lead to inflammation and damage to the glomeruli, finally leading to reduced kidney function (3,14). The current diagnostic approach for IgA nephropathy involves a combination of clinical presentation, laboratory tests, and histopathological examination. However, the accuracy and specificity of these methods can be limited, leading to delays in diagnosis and suboptimal treatment outcomes (15,16).

Biomarkers in the IgA nephropathy

Protein biomarkers and several candidate biomarkers in IgA nephropathy have been extensively studied and identified, including serum creatinine, albuminuria, serum IgA, complement C3, C4, and activation products, and urinary levels of cytokines, chemokines, and growth factors (6,17). However, the specificity and sensitivity of these biomarkers have been variable, and their diagnostic value needs to be further validated in large-scale multicenter studies.

Gene expression biomarkers

Gene expression profiling has emerged as a promising tool for the diagnosis and monitoring of Immunoglobulin A nephropathy. Several studies have identified gene signatures that are associated with the disease progression and treatment response (18). For example, the upregulation of genes involved in the innate and adaptive immune response, such as IL-8, LCN2, and TLRs, has been associated with more severe disease. In contrast, the downregulation of genes involved in kidney function, such as nephrin and podocin, has been associated with kidney damage and poor prognosis (18,19).

Epigenetic biomarkers

Epigenetic modifications, such as DNA methylation and histone modifications, have been implicated in the pathogenesis of IgA nephropathy. Several studies have identified differential DNA methylation patterns in genes involved in immune regulation, mesangial cell proliferation, and fibrosis, suggesting their potential utility as diagnostic and prognostic biomarkers (20, 21).

MicroRNA biomarkers

MicroRNAs are small non-coding RNAs that regulate gene expression by targeting mRNA transcripts. Several studies have identified dysregulated microRNAs in IgA nephropathy, which are involved in the regulation of key pathways related to inflammation, fibrosis, and immune regulation. The identification of specific microRNAs as diagnostic and prognostic biomarkers may provide insights into the underlying pathogenesis and potential therapeutic targets (22).

Conclusion

In summary, biomarkers have the potential to improve the accuracy and specificity of the diagnosis of IgA nephropathy and predict the disease progression and response to treatment. However, their diagnostic value needs to be further validated in large-scale studies and integrated into clinical practice. The development of multi-omics approaches that combine different types of biomarkers, such as protein, gene expression, epigenetic, and microRNA biomarkers, may provide a more comprehensive and accurate picture of the disease pathogenesis and treatment response.

Authors' contribution

Conceptualization: RZ and AS.
Validation: RS.
Investigation: YKh and MB.
Resources: MA.
Data curation: EZ and RZ.
Writing-original draft: MA, RS, RZ, and MB.
Writing-review and editing: YKh, EZ, NSh, and AS.
Visualization: RS.
Supervision: AS.
Funding acquisition: All Authors.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

Funding/Support

None.

References

1. Rajasekaran A, Julian BA, Rizk DV. IgA Nephropathy: An Interesting Autoimmune Kidney Disease. Am J Med Sci. 2021;361:176-94. doi: 10.1016/j.amjms.2020.10.003.
2. Suzuki H, Novak J. Special Issue: New Insights into the Pathogenesis and Therapies of IgA Nephropathy. J Clin Med. 2022;11. doi: 10.3390/jcm11154378.
3. Rawla P LF, Hashmi MF. IgA Nephropathy. [Updated 2023 Feb 19]. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK538214/.
4. Roberts IS. Pathology of IgA nephropathy. Nat Rev Nephrol. 2014;10:445-54. doi: 10.1038/nrneph.2014.92.
5. Mizdrak M, Kumrić M, Kurir TT, Božić J. Emerging Biomarkers for Early Detection of Chronic Kidney Disease. J Pers Med. 2022;12. doi: 10.3390/jpm12040548.
6. Hastings MC, Moldoveanu Z, Suzuki H, Berthoux F, Julian BA, Sanders JT, et al. Biomarkers in IgA nephropathy: relationship to pathogenetic hits. Expert Opin Med Diagn. 2013;7:615-27. doi: 10.1517/17530059.2013.856878.
7. Irabu H, Shimizu M, Kaneko S, Inoue N, Mizuta M, Ohta K, et al. Clinical Significance of Serum Galactose-Deficient IgA1 Level in Children with IgA Nephropathy. J Immunol Res. 2020;2020:4284379. doi: 10.1155/2020/4284379.
8. Kim JS, Hwang HS, Lee SH, Kim YG, Moon JY, Kong JY, et al. Clinical Relevance of Serum Galactose Deficient IgA1 in Patients with IgA Nephropathy. J Clin Med. 2020;9. doi: 10.3390/jcm9113549.
9. Lupușoru G, Ailincăi I, Sorohan BM, Andronesi A, Achim C, Micu G, et al. Serum soluble urokinase plasminogen activator receptor as a potential biomarker of renal impairment severity in diabetic nephropathy. Diabetes Res Clin Pract. 2021;182:109116. doi: 10.1016/j.diabres.2021.109116.
10. Rasmussen LJH, Petersen JEV, Eugen-Olsen J. Soluble Urokinase Plasminogen Activator Receptor (suPAR) as a Biomarker of Systemic Chronic Inflammation. Front Immunol. 2021;12:780641. doi: 10.3389/fimmu.2021.780641.
11. Yasutake J, Suzuki Y, Suzuki H, Hiura N, Yanagawa H, Makita Y, et al. Novel lectin-independent approach to detect galactose-deficient IgA1 in IgA nephropathy. Nephrol Dial Transplant. 2015;30:1315-21. doi: 10.1093/ndt/gfv221.
12. Dai L, Watanabe M, Qureshi AR, Mukai H, Machowska A, Heimbürger O, et al. Serum 8-hydroxydeoxyguanosine, a marker of oxidative DNA damage, is associated with mortality independent of inflammation in chronic kidney disease. Eur J Intern Med. 2019;68:60-5. doi: 10.1016/j.ejim.2019.07.035.
13. Jarrick S, Lundberg S, Welander A, Carrero JJ, Höijer J, Bottai M, et al. Mortality in IgA Nephropathy: A Nationwide Population-Based Cohort Study. J Am Soc Nephrol. 2019;30:866-76. doi: 10.1681/asn.2018101017.
14. Rodrigues JC, Haas M, Reich HN. IgA Nephropathy. Clin J Am Soc Nephrol. 2017;12:677-86. doi: 10.2215/cjn.07420716.
15. Floege J, Rauen T, Tang SCW. Current treatment of IgA nephropathy. Semin Immunopathol. 2021;43:717-28. doi: 10.1007/s00281-021-00888-3.
16. Habas E, Ali E, Farfar K, Errayes M, Alfitori J, Habas E, et al. IgA nephropathy pathogenesis and therapy: Review & updates. Medicine (Baltimore). 2022;101:e31219. doi: 10.1097/md.0000000000031219.
17. Selvaskandan H, Shi S, Twaij S, Cheung CK, Barratt J. Monitoring Immune Responses in IgA Nephropathy: Biomarkers to Guide Management. Front Immunol. 2020;11:572754. doi: 10.3389/fimmu.2020.572754.
18. Qing JB, Song WZ, Li CQ, Li YF. The Diagnostic and Predictive Significance of Immune-Related Genes and Immune Characteristics in the Occurrence and Progression of IgA Nephropathy. J Immunol Res. 2022;2022:9284204. doi: 10.1155/2022/9284204.
19. Imig JD, Ryan MJ. Immune and inflammatory role in renal disease. Compr Physiol. 2013;3:957-76. doi: 10.1002/cphy.c120028.
20. Reddy MA, Tak Park J, Natarajan R. Epigenetic modifications in the pathogenesis of diabetic nephropathy. Semin Nephrol. 2013;33:341-53. doi: 10.1016/j.semnephrol.2013.05.006.
21. Kato M, Natarajan R. Epigenetics and epigenomics in diabetic kidney disease and metabolic memory. Nat Rev Nephrol. 2019;15:327-45. doi: 10.1038/s41581-019-0135-6.
22. Ratti M, Lampis A, Ghidini M, Salati M, Mirchev MB, Valeri N, et al. MicroRNAs (miRNAs) and Long Non-Coding RNAs (lncRNAs) as New Tools for Cancer Therapy: First Steps from Bench to Bedside. Target Oncol. 2020;15:261-78. doi: 10.1007/s11523-020-00717-x.