

Serum and urine galactose deficient-IgA1 as alternative biomarkers in the management of IgA nephropathy

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ABSTRACT

Introduction: Immunoglobulin A (IgA) nephropathy (IgAN) results from abnormal accumulation of immune complexes containing galactose deficient IgA1 (Gd-IgA1) in the kidneys. About 40% of patients develop end-stage kidney disease within 20 years of renal biopsy. At present, the diagnosis and risk stratification of patients (using the international IgAN risk prediction tool) rely on renal biopsy, which is an invasive procedure. Also, treatment decisions are still dependent on proteinuria, which is not specific for IgA nephropathy. We discussed the role of serum and urine Gd-IgA1 in the diagnosis of IgAN, its association with disease progression and changes with treatment in patients with IgA nephropathy.

Materials and Methods: A systematic search of PubMed and Scopus databases was done to identify the articles that are relevant to the topic including systematic reviews and original articles.

Results: Several studies showed that both serum and urine Gd-IgA1 differentiate IgA nephropathy patients from healthy people and other glomerulonephropathies. Thus, it is useful as a less invasive diagnostic biomarker, although detection methods varied between studies with different sensitivities. There are various reports of its use as a prognostic parameter. Evidence is emerging for its use as a monitoring parameter for treatment.

Conclusion: Galactose deficient IgA1 is a promising biomarker in the management of IgA nephropathy, although a more robust and standardised means of estimation is required.

KEYWORDS:

Biomarker; galactose deficient IgA1; glomerulonephritis; IgA nephropathy; serum; urine

INTRODUCTION

Immunoglobulin A (IgA) nephropathy (IgAN) is an immune-mediated glomerular disease first described by Jean Berger in 1968.¹ IgAN in the native kidney is defined as immunofluorescence or immunoperoxidase, dominant or codominant staining for IgA in the glomeruli.² Characteristically, IgA exhibits dominating staining whereas

IgG and/or IgM staining are less pronounced and varied.³ The IgA deposits are primarily composed of polymeric, structurally aberrant IgA of the IgA1 subclass.⁴ The global prevalence of IgAN is estimated at 2.5 per 100,000 people per year.⁵ This prevalence varies widely between different regions of the world. The number is higher in Asia: Exceeding 40% of biopsy-proven primary glomerular disease in Japan and China^{6,7} and least in Africa.⁸

The exact aetiology of this disease remains obscure. However, it is known to result from the accumulation of immune complexes containing abnormal IgA (galactose-deficient IgA1) in the glomeruli. Thus, its diagnosis depends on a renal biopsy and histology, which is an invasive procedure with substantial risks. The renal injury in IgAN takes different courses in different patients. While a few patients have a variable period of active disease followed by remission with complete resolution of urine abnormalities, about 40% progress slowly to end-stage kidney disease (ESKD). Others progress rapidly to ESKD.⁵ Ten-year renal survival rates vary from about 85% in Caucasians and Japanese⁹ to as low as 35% among Indians.¹⁰ These variations in progression have posed a challenge to the management of patients with IgAN. It is currently difficult to prospectively distinguish progressive from non-progressive disease in the early stages. This contributes to the risk of delayed treatment for progressors and exposure to immunosuppression and its deleterious side effects for IgA patients with stable disease. Traditionally, features including hypertension, persistent proteinuria > 1 g/day, and reduced estimated glomerular filtration rate (eGFR) are used as risk factors for progression. However, these features are not specific to IgAN. The risk stratification based on the Oxford classification requires a renal biopsy, which is an invasive process with its attendant complications. Efforts to address these drawbacks have recently produced the International IgA Nephropathy Risk Prediction Tool (IIgAN-PT) by Barbour et al.¹¹ This tool employs clinical, laboratory and histologic data obtained at the time of the biopsy for the prediction of disease progression. It is limited by several factors. It is dependent on renal biopsy, is recommended for the prediction of a 5-year outcome, and may not be used to determine treatment.¹¹ To overcome these challenges, it is necessary to utilize all available techniques and search for biomarkers that can address these gaps. In this paper, we discuss the role of galactose deficient IgA1 (Gd-IgA1) as a non-invasive alternative for diagnosing and predicting

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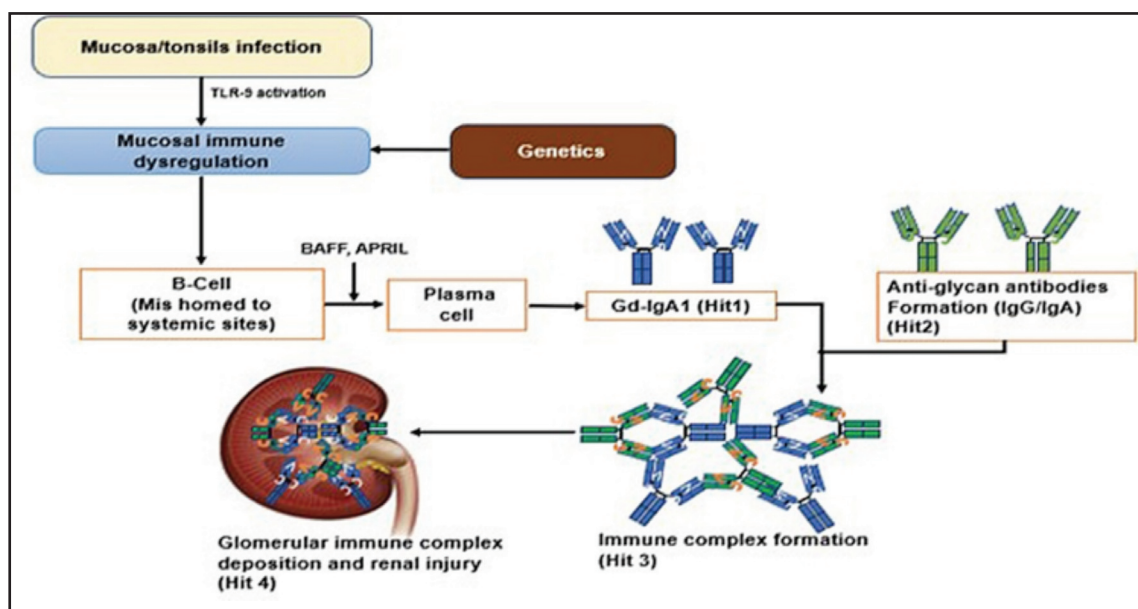


Fig. 1: Pathogenesis of IgAN. In genetically susceptible persons with mucosal immune dysregulation, repeated mucosa/tonsillar infection causes proliferation of plasma cells producing Gd-IgA1. Autoantibodies (IgG and IgA) and immune complexes are formed in response. These are subsequently deposited in the kidneys leading to renal injury.

disease progression in IgAN patients. We searched Google Scholar, PubMed and Scopus databases using several combinations of keywords. These include, 'immunoglobulin A nephropathy,' 'IgA nephropathy,' 'galactose deficient IgA1,' Gd-IgA1, glomerulonephritis, progression, biomarker, blood, urine and prognosis. The search was limited to original articles and reviews published in English. We screened and extracted those that analysed Gd-IgA1 as a diagnostic tool or its association with disease progression and treatment. The references were screened further to identify the relevant publications.

PATHOGENESIS

The exact mechanism involved in the pathogenesis of IgAN is not completely understood. Genetic predisposition,¹² environmental triggers,^{13,14} and immune dysregulation¹⁵ play different roles in IgAN (Fig 1). However, a multi-hit mechanism has been described.¹⁶

The Multihit Theory

Hit 1: Overproduction of galactose deficient immunoglobulin A of subclass 1 (Gd-IgA1). Normally, mucosal surface secretions contains polymeric IgA, whereas monomeric IgA is found in circulation. In genetically susceptible persons, there is an abnormal innate immunity response to mucosal infections and antigens. There is a 'mishoming' of differentiated plasma cells to the bone marrow which likely contributes to the the production of Gd-IgA1.¹⁷ Tonsillar TLR-9 activation increases the production of interleukin-6 (IL-6) and activation proliferation-inducing ligand (APRIL), which promote production of Gd-IgA1.¹⁸ This polymeric IgA1 lacks galactose on some O-glycans in the hinge region between the constant region domains 1 and 2 of the heavy chain. This deficiency causes the exposure of N-acetylgalactosamine (GalNac) or sialylated GalNac.^{19,20} The production of aberrant

IgA1 is associated with reduced activity of core1 β 1,3 galactosyltransferase (C1GalT1) and an increase in the activity of α 2,6 sialyltransferase II (ST6GalNAc-II) in IgA1 producing cells.¹⁶

Hit 2: The formation of glycan-specific autoantibodies against Gd-IgA1, especially IgG. The autoantibodies recognise glycan-containing epitopes on Gd-IgA1. They exhibit an A to S substitution in the complementarity-determining region 3 (CDR3) of the variable region of their heavy chains.²¹

Hit 3: Immune complex formation. The autoantibodies form immune complexes with Gd-IgA1. In IgAN patients, Gd-IgA1 exists predominantly in complexes with IgG or IgA.²² Moldoveanu et al. provided an evidence of the role of the immune complex in IgAN pathogenesis using a mouse model. They demonstrated that the administration of Gd-IgA1 complexed with IgG from IgAN patients produced the disease. Neither uncomplexed Gd-IgA1 and its autoantibodies nor those from healthy individuals produced the disease in the models.²²

Hit 4: Mesangial immune complex deposition. The characteristic position of the mesangial cells between the glomerular capillaries and the Bowman's capsule might explain their susceptibility to immune complex deposition. The mesangial cells in IgAN patients exhibit a mesangioproliferative phenotype and are more reactive to IgA1. These cellular inherent characteristics may be crucial for the onset of IgA nephropathy.²³

GALACTOSE DEFICIENT IgA1 IN DIAGNOSIS OF IgAN

The gold standard for the diagnosis of IgAN is renal biopsy with immunofluorescence or immunoperoxidase showing

dominant or codominant IgA staining. Increased serum levels of IgA are known to occur in about half of the IgAN patients.²⁴ The serum level of Gd-IgA1 is higher in IgAN than in healthy controls, both in children and adults.²⁴ However, other autoimmune-mediated glomerular diseases also show increased serum levels of Gd-IgA1.²⁶ Gd-IgA1 is deposited in the glomerular mesangium in a manner that is not dependent on its blood concentration and is excreted in urine.²⁷ Urinary Gd-IgA1 levels are significantly higher in patients with IgAN compared to non-IgAN chronic kidney disease (CKD) patients.^{27,28} In other studies, the urine of non-IgAN CKD showed a low level of Gd-IgA1 that was below detection on HAA-lectin Western blotting.^{28,29} Although urine Gd-IgA1 is believed to be more specific for IgAN, further studies comparing blood and urine levels in the same patients are required.

IgG and IgA autoantibodies specific for Gd-IgA1 are formed in response to circulating Gd-IgA1. Serum levels of these antibodies are elevated in IgAN patients.^{30,31} These antibodies are excreted in the urine in complexes with antigens, and their levels are high in the urine of IgAN patients.²⁹ Longitudinal studies that assess the utility of these biomarkers, especially the more specific urine components, are required.

RISK STRATIFICATION AND PROGNOSIS IN IgAN

Routine markers

Risk stratification of patients for disease progression continues to depend on renal biopsy and nonspecific measures such as blood pressure, eGFR and proteinuria. A study reported a remarkable difference in the 10-year risk of ESKD depending on the time average proteinuria (TAP). TAP of 1 g/day was associated with a 5% risk, whereas TAP > 3 g/day was associated with a 60% risk.³² TAP appears to be the most consistent predictor, even in populations where blood pressure, eGFR and 24-hour proteinuria were reported to have no association with the renal outcome.³³ The inability to distinguish between proteinuria caused by acute inflammation around the urinary tract and chronic glomerulonephritis is still a drawback. In a study involving French patients, the incidence of dialysis or death increased with increasing blood pressure, from 5% in normotensives to 42% in uncontrolled hypertensives.³⁴ The 2016 updated Oxford classification of IgAN includes histopathologic lesions (mesangial hypercellularity, endocapillary proliferation, segmental glomerulosclerosis, tubular atrophy and interstitial fibrosis, crescents [MEST-C]) which are proposed as independent risk factors for ESKD and/or a 50% decline in eGFR.³⁵ The S and T components have been most associated with progression, while the role of crescents in prognosis requires further clarification.^{36,37} Individually, these markers are insufficient; a patient with a low risk based on proteinuria alone may have an increased risk using the MEST, and vice versa.³⁸ This raises the need for a more specific parameter.

Galactose deficient-IgA1 and disease progression

Different studies have used various study outcomes to define disease progression in IgAN. These include a doubling of serum creatinine, a 30 to 50% decline in eGFR, ESKD, the

onset of renal replacement therapy, transplantation and death. Several others use a composite of these outcomes. This is in part due to the slowly progressive nature of the disease in most patients.

Association of Gd-IgA1 and eGFR/renal failure

Elevated Gd-IgA1 levels have been associated with an increased risk of disease progression. In a study involving 91 Czechs, high levels of serum native and neuraminidase-treated Gd-IgA1 measured by lectin-dependent ELISA, predicted a faster renal function decline and poor renal survival.³⁰ Elevated serum Gd-IgA1 was negatively correlated with eGFR and was an independent predictor of chronic kidney disease progression in a study among 230 Korean patients.²⁶ Gd-IgA1 was reported to be an independent predictor of renal failure even after adjustment for eGFR and time-average proteinuria.³⁹ Gd-IgA1 level is also negatively correlated with eGFR.^{26,40} Renal survival decreased with increasing Gd-IgA1 quartile.²⁶

Association of Gd-IgA1 and proteinuria

Proteinuria is currently used as a risk factor for IgAN patients. There are conflicting reports about the association of Gd-IgA1 with proteinuria. While some studies have reported a positive correlation between Gd-IgA1 and urine protein creatinine index (UPCI),⁴⁰ others have reported no association between these parameters during diagnosis.²⁴

Association of Gd-IgA1 and histology

Some studies have shown that Gd-IgA1 can be used in the risk stratification of IgAN. Higher serum and urine Gd-IgA1 levels were shown to be associated with segmental sclerosis and tubular interstitial fibrosis during diagnosis.^{27,42} In a study involving 84 biopsy-proven IgAN patients, Gd-IgA1 and complement proteins were evaluated as predictors of disease progression. There were significantly elevated levels of Gd-IgA1 in patients with tubular atrophy and interstitial fibrosis. Gd-IgA1 and factor Ba independently predicted higher T scores on multivariate analysis signifying that these biomarkers were reflective of the Oxford classification of IgAN, which are reported as important predictors of ESKD.⁴⁰

Association of Gd-IgA1 and other parameters

The human mesangial cells have a phenotype that is sensitive to stimulation with IgA1.⁴² Patients with higher serum Gd-IgA1 levels may experience faster disease progression to ESKD, owing to a more pronounced mesangial cell inflammatory response and, as a result, more severe histologic changes.^{27,40,42} In an *in vitro* study, primary human mesangial cells were stimulated using IgA1 derived from the serum of patients with IgAN. A higher serum Gd-IgA1 concentration was linked to a more severe mesangial cell inflammatory response, including increased MCP-1 and IL-6 production.⁴² Elevated Gd-IgA1 was also associated with IgAN recurrence after renal transplant.⁴³

METHOD FOR DETECTING BIOMARKERS

Western Blot

Helix aspersa agglutinin (HAA) lectin western blotting after SDS-PAGE detects the presence of Gd-IgA1 in the urine samples of patients with IgAN but not in the urine samples of

Table I: Summary of laboratory findings during admission

Author	Population	Sample size	Sample	Assay method	Sensitivity	Specificity	AUC: ROC	PPV	NPV	Reference
Moldoveanu et al., 2007	Caucasian USA	153 IgAN	Serum	HAA lectin-based ELISA	76.5%	94%	0.902	88.6	78.9	24
Yanagawa et al., 2014	Japanese	153 healthy controls 135 IgAN	Serum	HAA lectin-based ELISA with neuraminidase treatment	89%	92%	0.965			30
Rahman et al., 2021	Indian	40 IgAN 38 controls	Serum	Non-lectin (KM55) ELISA	75.3%	85%	0.85	90.9	63	41
Chen et al., 2019	Chinese	1210 IgAN	Plasma	Helix pomatia-based ELISA with neuraminidase treatment	54%	90%				45
Bagchi et al., 2019	Indian	136 IgAN and 110 controls (60 non-IgA glomerular diseases, 50 healthy volunteers).	Serum	Non-lectin ELISA	74.3%	72%	0.7865	87.8	50.7	46
Jiang et al., 2015	Chinese children	72 IgAN, 30 healthy controls,	Serum	Vicia villosa lectin ELISA	87.5%	83.3%	0.976	92.6	73.5	47
Martin-penagos et al., 2021	Spanish	49 IgAN	Serum	Non-lectin (KM55) ELISA	75.5%	54.1%	0.625			48

AUC: area under the curve, ROC: receiver operating characteristics, PPV: positive predictive value, NPV: negative predictive value, HAA: helix aspersa agglutinin, ELISA: enzyme-linked immunosorbent assay

patients with other proteinuric diseases.²⁸ This method is, however, cumbersome and expensive.

Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS)
The O-glycosylation patterns of IgA1 can be analysed using LC-MS/MS. IgA1 extracted from plasma using immunoaffinity beads is first de-N-glycosylated, then reduced. This is followed by trypsin digestion and O-glycopeptide enrichment through hydrophilic interaction liquid chromatography. There is a significant difference in the O-glycosylation pattern between IgAN, disease controls and healthy controls. IgAN patients had significantly lower GalNAc and galactose numbers in the hinge region of IgA1. This distinguishes them from other non-IgAN CKD.⁴⁴

Enzyme-Linked Immunosorbent Assay (ELISA)

Several lectin-based ELISA methods have been employed for the estimation of Gd-IgA1. *Helix aspersa agglutinin* (HAA) ELISA quantitation was first reported by Moldoveanu et al.²⁴ There are currently no standard means of estimating the Gd-IgA1 level. The different lectin-dependent ELISA methods in current use recognise galactose deficiency at different amino acid levels (serine vs. threonine). HAA-lectin-based ELISA is limited by the fact that its stability and bioactivity are dependent on the product lot. The procedure is also cumbersome. Several other lectin-based methods, such as *helix pomatia* and *Vicia villosa* lectin, have been used with different sensitivities and specificities, with the highest reported for the HAA lectin-based method (Table I).

TREATMENTS IN IgAN

There is currently no known cure for IgAN. The Kidney Disease Improving Global Outcome (KDIGO) 2021 guidelines recommended that, for all patients who do not have a variant form of IgAN, management should focus on optimising supportive care. The target systolic blood pressure is < 120 mmHg. The guideline recommends the use of angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) as the first line for blood pressure and proteinuria control. Irrespective of hypertension status, all patients with proteinuria > 0.5 g/day should be treated with ACEI/ARB. ACEI/ARB can be titrated to the maximum tolerated dose. Other supportive therapy includes control of protein intake, avoidance of nephrotoxins, smoking cessation and control of all components of the metabolic syndrome. The addition of a 6-month course of corticosteroids is recommended in cases of persistent proteinuria (> 0.75–1 g/day) despite 90 days of optimised supportive care and an eGFR >30 ml/min/1.73m². Cyclophosphamide and steroids are employed in addition to supportive therapy in cases of rapidly progressive IgAN.⁴⁹ Given that these treatment decisions are largely based on proteinuria which is nonspecific for IgAN, a more specific surrogate is required.

Galactose Deficient IgA1 in Treatment

Since Gd-IgA1 is central to the pathogenesis of IgAN, its association with therapy has been investigated in many studies. Nakata et al.⁵⁰ demonstrated a decline in serum Gd-IgA1 concentration and haematuria after tonsillectomy alone in 59% of a cohort of Japanese IgAN patients. When steroids were added to tonsillectomy, more patients improved

in terms of haematuria and serum Gd-IgA1. However, the changes in proteinuria and creatinine levels were not appreciable. The study was limited by its relatively small sample size and a very short (2 to 3 weeks) study duration post-tonsillectomy. The patients who showed improvements with tonsillectomy alone were those with a higher expression of tonsillar TLR9. This indicates that the palatine tonsils are possibly a major site of cells producing Gd-IgA1. The 'mishoming' of these cells to other lymphoid organs may explain, in part, the different responses observed to tonsillectomy alone.⁵⁰ The level of Gd-IgA1 was shown to be significantly reduced after 3 to 6 months of immunosuppression (including oral and/or systemic steroid or cyclosporine) in a cohort of Taiwanese IgAN patients.⁵¹ Prednisolone therapy showed a significant difference in serum levels of Gd-IgA1 from the baseline to 6 months post-transplant in a prospective study involving 36 post-transplant IgAN patients. Samples were taken before transplant, 3 months and 6 months post-transplant. Gd-IgA1 concentration was reduced with increasing doses of prednisolone. This difference was not seen with mycophenolate mofetil therapy.⁵²

Another study compared the effect of standard IgAN therapy (ACEI/ARB and controlled blood pressure) and standard therapy plus rituximab on the level of serum Gd-IgA1. Neither of the patient groups had a reduction in Gd-IgA1.⁵³

Novel Therapies

Gd-IgA1 is believed to be produced by B-cells derived from the mucosa-associated lymphoid tissues. These include the Peyer's patches in the ileum. A targeted release formulation of the glucocorticosteroid, budesonide (Nefecon), was formulated to be released at the distal ileum, where it may target B-cells primed to produce Gd-IgA1. NeflgArd, a phase 3 randomised, double-blind, placebo-controlled multicentre clinical trial, enrolled 199 IgAN patients who were given Nefecon or a placebo for 9 months, followed by 3 months of observation. At the end of the follow-up, there was a significant improvement in eGFR and proteinuria. There was a mean 3.87 ml/min/1.73 m² preservation of eGFR and 27% lower urine protein creatinine ratio levels in the Nefecon group compared to the placebo group. Although the drug was well tolerated, a major limitation of this drug is its cost.⁵⁴ The drug has been approved for IgAN treatment by the FDA.

Other B-cell targeted agents for the treatment of IgAN are under investigation. Telitacept and atacicept are human recombinant fusion proteins that target B-cell activating factor (BAFF) and APRIL. They bind to BAFF and APRIL and cause a reduction in B-cell count. They also cause disruptions in B-cell activation, maturation and differentiation.⁵⁵ In the randomised phase II JANUS trial, Baratt et al., demonstrated that atacicept produced a significant dose-dependent reduction in serum Gd-IgA1, IgG and IgM. At 24 weeks of study, IgAN patients who received weekly 75 mg subcutaneous atacicept, had a 60% reduction in baseline Gd-IgA1. This is significant especially when compared to the 25% reduction seen in the 25 mg atacicept group and a 2% increase seen in the placebo group.⁵⁶ The patients in the atacicept groups also improved in terms of proteinuria with a relatively stable eGFR at 72 weeks.

Other drugs that inhibit the B-cell activity that have been investigated include rituximab and belimumab. Although these are capable of reducing B-cell count, they did not reduce the production of Gd-IgA1.⁵³

FUTURE PERSPECTIVES

Increased serum and urine levels of galactose-deficient IgA1 are characteristic features of IgAN. More research is needed to understand the differences in levels observed across different groups, as well as their roles in prognosis and therapy. The use of Gd-IgA1 to predict the progression of the disease is currently limited by the small sample sizes in most of the studies and the difficulties in comparing the studies due to differences in the methods of assay. The reported sensitivity and specificity of the HAA-lectin-based ELISA, 76.9% and 94%,²⁴ 89% and 92%²⁹ are higher than the helix pomatia-based ELISA, at 54% and 90%⁵⁰ respectively. This makes comparison difficult and may not replace a renal biopsy yet. Thus, there is a need for a more robust and standardised method. The biomarker is yet to be studied in diverse populations to determine its utility in different populations. This is crucial considering the difference in progression among different ethnic groups. It may be possible to extend the applicability of the international IgAN prediction tool through the addition of biomarkers. In a pilot study by Pawluczyk et al, incorporating micro-RNA (miR-204) improved the predictive performance of the tool.⁵⁷ The tool may also be modified for different ethnic groups. Joo et al adjusted the race coefficient of the tool to a Korean coefficient. This improved the accuracy of the tool for that ethnic group.⁵⁸ These need to be tested in future studies.

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