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EDUCATIONAL REVIEW

How to take advantage of easily available biomarkers in patients with IgA nephropathy: IgA and C3 in serum and kidney biopsies

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Abstract
IgA nephropathy (IgAN) is the most common glomerulonephritis worldwide. It is diagnosed based on clinical and histological features including predominant IgA deposits in kidney biopsy. The multi-hit theory, based on the production of GDIgA1 and anti-GDIgA1 antibodies, and complement activation via alternative and lectin pathways and also a genetic tendency are crucial in the pathogenesis of IgAN. The aim of the present review is to summarize the utility of routine diagnostic tests in IgA nephropathy, such as IgA and C3 in serum and kidney biopsy specimens, for predicting the disease progression. The paper also contains data on new markers used in the diagnosis and prognosis of IgA nephropathy.

Keywords IgA nephropathy · IgA · C3 · IgA deposits · C3 deposits

Introduction

IgA nephropathy (IgAN) is the most common glomerulonephritis worldwide. It is diagnosed based on clinical and histological features including predominant IgA deposits in kidney biopsy. IgAN reduces life expectancy by more than 10 years and leads to kidney failure in 20–40% of patients by 20 years after the diagnosis [1–3].

In patients after kidney transplantation, the disease recurs in 50% of cases within 10 years [1]. Hypertension, elevated serum creatinine concentration, proteinuria, old age, male sex, and the absence of macroscopic hematuria have been found to be independent predictors of an unfavorable outcome [4–6].

Various biomarkers have been used to predict the disease progression, including pediatric Prediction Tool models, and new predictors continue to be sought [7]. According to the WHO definition, a biomarker is any substance, structure, or process, which may be measured in an organism, or its products, which affects, indicates or predicts the frequency, or the outcome of a disease [8].

In the present review, we summarize the utility of traditional biomarkers in IgAN, such as IgA and C3, for predicting the disease progression, and discuss other substances, studied in the pathogenesis of IgAN, which are or may become new biomarkers.

Epidemiology and clinical presentation

IgAN is most common in Asia, where the prevalence is 30–60% in all kidney biopsies, compared to 20–30% in Europe and below 5% in Africa [9–11]. The disease course and its late sequelae are more severe in Asia compared to European populations [9, 12].

Clinical manifestations may vary and include asymptomatic microscopic hematuria, proteinuria with micro- or macroscopic hematuria, overt hematuria, nephritic syndrome, or even rapidly progressive glomerulonephritis. In pediatric patients with IgAN in Poland, the most frequent symptom was microscopic hematuria with non-nephrotic proteinuria observed in 50% of patients, isolated micro or macroscopic hematuria in 29%, and nephrotic proteinuria with micro- or macroscopic hematuria in 21% of cases. Macroscopic hematuria was noticed as a first symptom of IgAN in 29% of children and kidney failure in 39% [13]. The clinical course may vary between adults and children [14, 15]. In adults it is a slow disease, leading to kidney failure in 30–40% of patients. In children, it may present with mild symptoms, but 50% of patients require kidney replacement therapy by the age of 50 [14]. Proteinuria in adults reflects

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the presence of chronic lesions, while in children with IgAN, it is associated with glomerular proliferative lesions [15].

A kidney biopsy showing predominant IgA deposits is the only, albeit invasive diagnostic tool for IgAN. Histopathological specimens are evaluated using the Oxford MESTC classification: 1—present, 0—absent; M—mesangial hypercellularity; E—endocapillary hypercellularity; S—segmental sclerosis/adhesion; T—tubular atrophy/interstitial fibrosis T0 0–25%, T1 26–50%, T2 > 50%; and C—crescents, C0 0%, C1 1–25%, C2 > 25% [16, 17].

Pathogenesis of IgAN

The pathogenesis of IgAN is described by the multi-hit theory. This theory assumes that the initial pathogenetic event (first hit) is a production of galactose-deficient IgA1 (GdIgA1). In the hinge region, 3–6 glycans are attached but not all of them contain a galactose moiety, which is due to impaired expression or activity of glucosyltransferases involved in post-translation modification of IgA1 [18–21].

Available data also show that abnormal IgA1 glycosylation precedes clinically overt disease and is a hereditary risk factor for the development of IgAN.

In the pathogenesis of IgAN, synthesis of GDIgA1 and IgA is also significantly affected by APRIL (a proliferation-inducing ligand), homologous with B-cell activating factor (BAFF). APRIL is coded by the *TNFSF13* gene which is associated with IgA synthesis in the general population and in patients with IgAN [22, 23]. In mice, overexpression of BAFF resulted in an increased GDIgA1 level and more severe proteinuria and microscopic hematuria in IgAN [24]. An increased APRIL level leads to overexpression of its receptors on B cells and increased GDIgA1 production, which plays a role in the pathogenesis of IgAN [22].

However, an elevated GDIgA1 level is not sufficient to induce IgAN [25–27]. The presence of GDIgA1 leads to the formation of specific IgA or IgG antibodies (second hit). Anti-GDIgA1 IgG level correlates with the severity of disease and proteinuria [21]. Another major contributing factor is the genetic effect of MHC class II antigens, HLA-DQB1, DQA, and DRB1, of which *DQB1*0602* reduces the risk of incident IgAN by 50% [21, 28].

Production of anti-GDIgA1 may be induced by exposure to infectious or dietary antigens in patients with susceptibility alleles, which are discovered in GWAS (genome-wide association study) [25, 26]. The formation of circulating immune complexes or deposits of abnormally glycosylated IgA1, which bind to anti-glycan antibodies and form in situ immune complexes in the mesangium, constitutes the third hit. However, circulating complexes may also be identified in healthy subjects or those with IgA vasculitis without nephropathy [21]. IgA-IgA complexes are considered non-nephritogenic. IgA-IgG complexes are relatively large and do not enter the Disse space and thus are not catabolized by the ASGPR receptor (asialoglicoprotein receptor), specific for IgA1, but enter the kidney circulation. They bind to the mesangium more effectively than IgA1 present in a non-immune complex form [21, 29, 30], which results in cellular and mesangial matrix proliferation, and production of cytokines including tumor necrosis factor (TNF), interleukin-6, and transforming growth factor (TGF) beta, which activate the alternative complement pathway and change glomerular permeability by modifying podocyte gene expression (fourth hit) [21, 25, 31–34].

In addition, the binding of soluble CD89 with circulating polymeric IgA1 may increase the nephritogenicity of immune complexes [25, 35, 36]. The receptor for transferrin (CD71) and transglutaminase 2 (TGase 2) on mesangial cells effectively binds immune complexes containing GDIgA1 [21, 35, 37, 38] which results in additionally increased mesangial expression and leads to the complement system activation [25]. The role of genetic factors is also important, and the existence of susceptibility alleles has been confirmed in genome-wide association studies [25–27]. The pathogenesis of IgAN is shown in Fig. 1.

The available literature also suggests a major role of the complement system in IgAN. Complement activation increases the inflammatory process and leads to kidney tissue damage. Complement activation in IgAN occurs via the alternative or the lectin pathway (MBL, mannose binding lectin), resulting in the presence of C3 and the absence of C1q in kidney biopsy specimens. The distribution of C3 follows that of IgA in as many as 90% of kidney biopsy specimens [3, 39]. Activation of the alternative pathway is inhibited by FH (factor H) and stimulated by FHR1-5 (factor H related protein 1–5).

Activation of the lectin pathway by MBL deposition was observed in 20–25% of cases. It also determined more severe kidney damage [40]. A marker of the activation of this pathway is the presence of C4d in kidney biopsy specimens, which was associated with worse patient outcomes during 20-year follow-up in Spanish studies [41, 42]. Complement activation pathways are shown in Fig. 2.

In genetic GWAS studies the presence of *CFHR1*/*CFHR3* (complement factor H-related protein 1/complement factor H-related protein 3) deletion results in a lower FHR1 level and protects from excessive complement activation, as *CFHR1* and *CFHR3* compete with FH for binding with C3b, which is the key activator of the terminal complement pathway [25]. The presence of homozygosity of this deletion reduces the risk of IgAN by 45% and by 26% in heterozygosity [26].

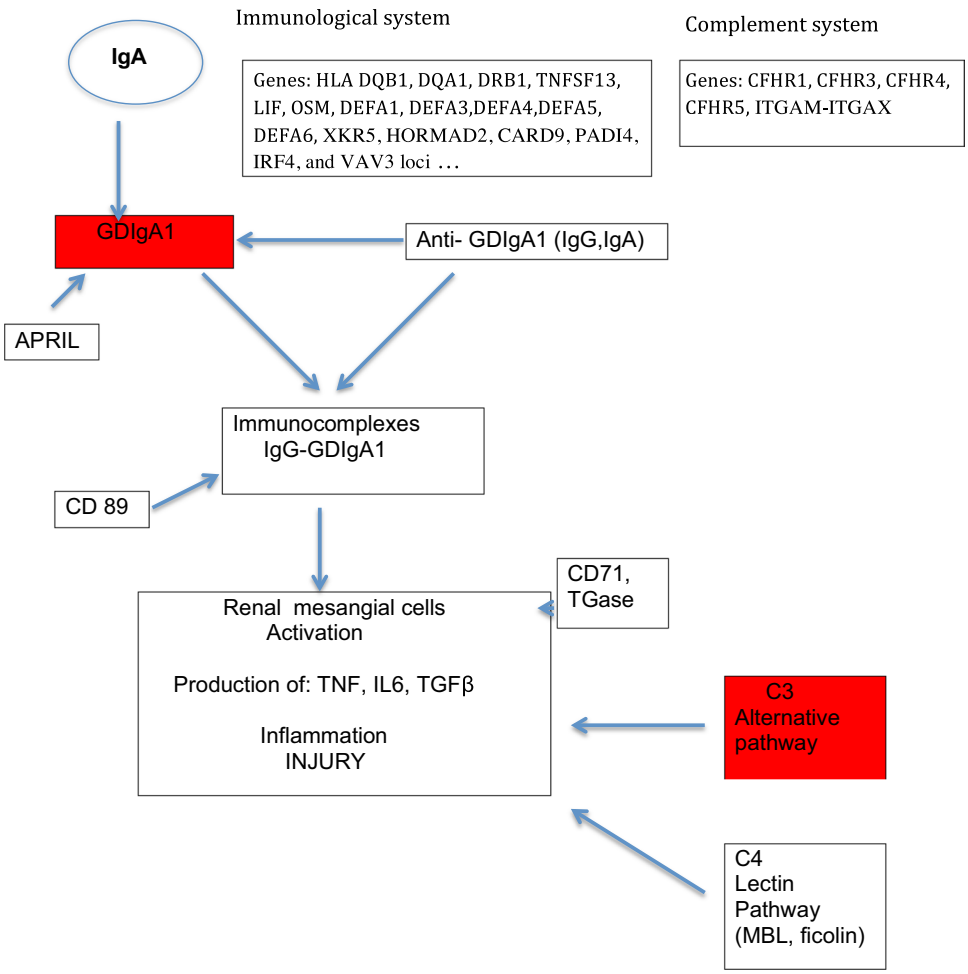

Fig. 1 Multi-hit pathogenesis of IgA nephropathy. GDIgA1 - galactose deficient IgA1; APRIL - a proliferation-inducing ligand; TGase transglutaminase 2; TNF - tumor necrosis factor; IL6 - interleukin 6; TGFβ tumor necrosis factor beta; MBL - mannose binding lectin

Serum biomarkers

IgA

Japanese data indicate that an elevated serum IgA level is found in 50–70% of adults and in only 16% of children with IgAN [43] while in the Polish pediatric population, IgA levels above the reference range were found in 52% of patients [44].

In the study by Tomino et al., multivariate analysis did not show the prognostic significance of elevated serum IgA level but the cutoff of > 315 mg/dL may serve as a diagnostic standard in adult patients [45].

In the present author's study of 89 children, elevated serum IgA level at baseline was significantly more frequently associated with M1 and S1 using the Oxford classification but the Kaplan–Meier curve did not show a relation between kidney survival and baseline IgA level [43]. In another study, pre-biopsy IgA level was significantly higher in children with IgAN without proteinuria compared to those with either nephrotic or non-nephrotic proteinuria [44].

Some authors point to the importance of biomarker panel differentiating IgAN from other kidney diseases. Yanagawa et al. compared serum levels of IgA, IgG, Gd-IgA1, Gd-IgA1-specific IgG, and Gd-IgA1-specific IgA in 135 IgAN adult patients, 79 patients with chronic kidney disease (CKD), and 106 healthy controls. Forty-one percent of IgAN patients have been found to have higher serum levels of IgA, and in 91% higher serum levels of IgG anti-GDIgA1 [46].

The studies on the importance of serum IgA are now of historic interest, and current research focuses on the importance of GDIgA1 and anti-GDIgA1. While these tests are not yet readily available in routine practice in all nephrological centers, they may replace IgA assays for the diagnosis, monitoring, and prognostication of IgAN in the future.

Serum complement component C3

Due to the role of complement activation in the pathogenesis of IgAN, studies in recent years also evaluated the prognostic importance of C3 level. In a Korean study of 343 adult patients with IgAN by Kim et al., serum C3 level < 90 mg/

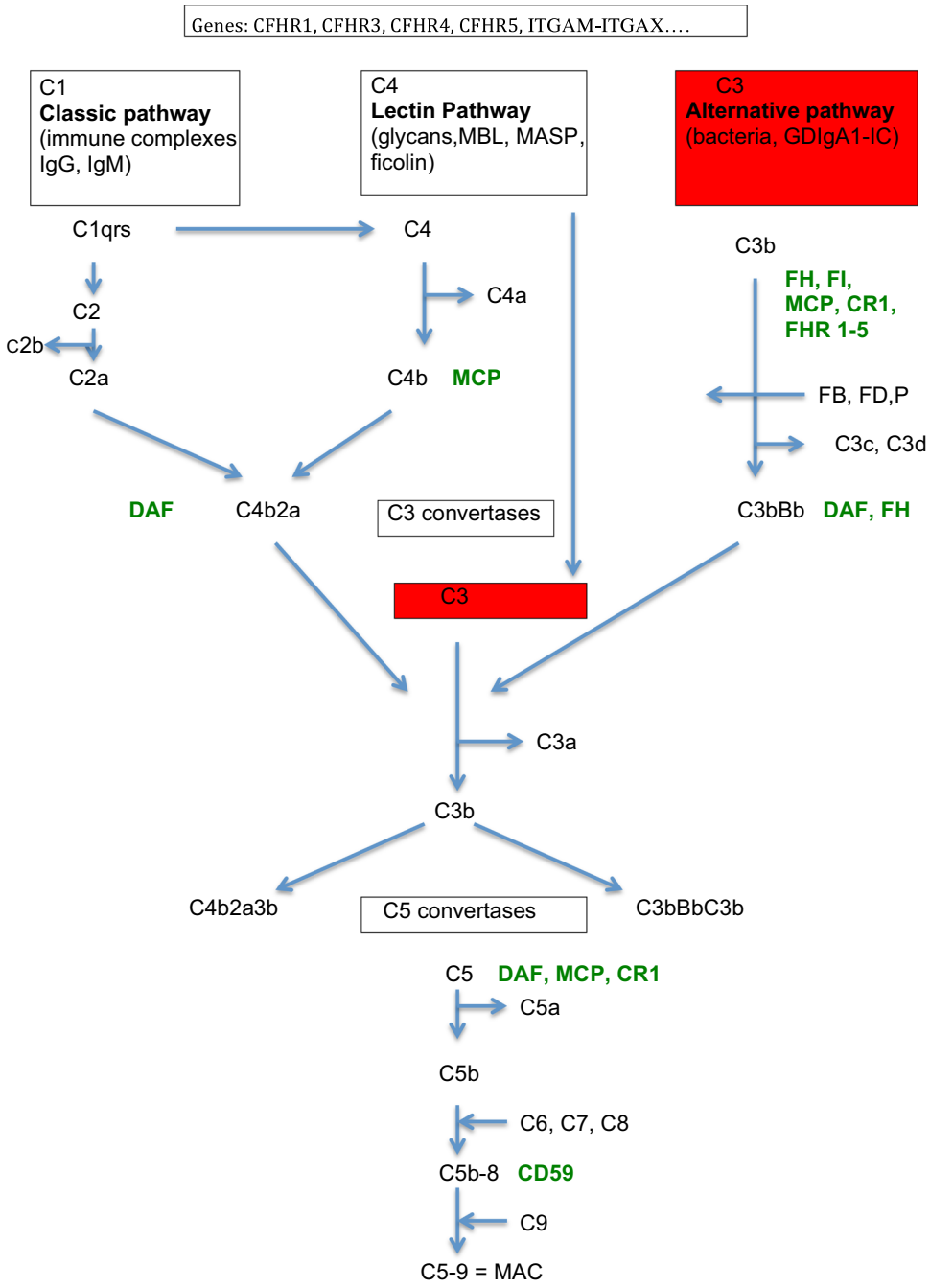

Fig. 2 Complement activation pathways. MBL - mannose binding lectin; MASP - mannose associated serine proteases; GDIgA1-IC - galactose deficient IgA1 immunocomplexes; MCP(CD46) - membrane cofactor protein; FH - factor H; FI - factor I; CR1(CD35) - complement receptor 1; FHR 1–5 - factor H related proteins 1–5; FB - factor B; FD, - factor D; P - properdin; DAF(CD55) - decay-accelerating factor. Regulators are in green

dL was found to be an independent predictor of poor outcomes [47].

In contrast to adults, the Polish study of 166 children from the Polish Pediatric IgAN Registry did not show such an association for C3 level below the reference range, although, in children with serum C3 level below the reference range, the glomerular filtration rate (GFR) at follow-up was lower compared to the group with normal baseline serum C3 level ($p = 0.07$). It may result from the fact that a low baseline serum C3 level was found in only 8% of patients in the study group [48].

In another pediatric study, a significantly lower C3 level was found in the T1 group compared to the T0 group ($p < 0.05$), with no significant differences between M1, E1, and S1 vs. M0, E0, and S0, respectively [44].

Current studies focus on activated C3 (actC3), which is present in 50% of patients. Based on the studies by Zwirner et al., elevated actC3 level is a predictor of disease progression and loss of kidney function with 75% sensitivity and 89% specificity [3, 49].

In addition, other types of biomarker activity, of alternative pathways of complement activation, have been studied

in IgAN patients, such as urinary MAC, FH and P levels. Onda et al. have shown that MAC and FH in urine correlates with creatinine levels, proteinuria, presence of glomerular fibrosis, and sclerosis and may be useful as a marker of kidney failure in patients with IgAN [50].

Lower level of MBL in adult patients (< 100 ng/ml) is associated with more frequent infections with gross hematuria and independently with poor outcome (hazard ratio 5.18; 95% *CI* 2.50–10.72; $p < 0.001$). High level of MBL (> 3540 ng/ml) is associated with heavy proteinuria and higher percentage of crescents. This data points to the importance of MBL in pathogenesis of IgAN in various mechanisms [51].

A Chinese genetic study that included 1543 adult patients with IgAN confirmed an association between *CFHR1* and *CFHR3* deletion and CFH and C3 level. CFH positively correlated with levels of C3 and negatively with mesangial C3 deposits. CFH, *CFHR1*, and *CFHR3* affect complement activation in IgAN [29, 52].

IgA/C3 ratio

The IgA/C3 ratio may help differentiate between IgAN and other glomerulopathies. In a Japanese study that included 195 patients with IgAN, 111 patients with other glomerulonephritides, and 418 healthy subjects, serum IgA/C3 ratio was the highest in patients with IgAN. Serum IgA/C3 in patients with IgAN was affected by both reduced C3 level and elevated IgA level [45]. In addition, studies from Asia also propose the IgA/C3 ratio as a prognostic marker. Higher values of IgA/C3 are associated with more severe histological lesions, and poor outcomes with worse kidney function, persistent proteinuria, and hematuria [3, 53–55].

In a Chinese study of 217 adult patients with IgAN, among whom 9.7% reached the endpoint of doubling of serum creatinine or kidney failure by 36 months, multivariate analysis showed that serum IgA/C3 ratio ≥ 3.32 was an independent adverse prognostic factor (*RR* = 4.31, 95% *CI* 1.33–13.96) [56]. In a European pediatric population of 89 children with IgAN, a prognostic value of the IgA/C3 ratio for kidney survival was not confirmed but the IgA/C3 ratio was shown to be a predictor of kidney biopsy specimen grading by the Oxford histological classification [44], as shown below (Table 1).

In another pediatric study of 44 Japanese children with IgAN, a prognostic value was shown for a combination of the IgA/C3 ratio > 2.68 and grade ≥ 2 C3 deposits in kidney biopsy [55]. In a European study of 95 adult patients with IgAN, it was confirmed that an IgA/C3 serum ratio > 2.91 may be considered an adverse prognostic factor for kidney survival with a specificity of 68% and sensitivity of 55% [57]. In a group of Japanese patients treated with steroids and tonsillectomy, a higher IgA/C3 ratio was associated with a higher number of recurrences [58].

Kidney histology

IgA deposits

Predominant IgA deposits in kidney biopsy are necessary for the diagnosis of IgAN. However, asymptomatic isolated IgA deposits were found in 6.9% of patients in the study by Varis et al. that included 753 kidney biopsies, and in 16.1% of patients in a Japanese study [59, 60]. It is unclear whether mesangial IgA deposits directly cause hematuria. Another study did not find an effect of severity of mesangial deposits and glomerular damage [61].

IgA deposits persist in some patients despite clinical remission of disease [62].

In a study by Polish researchers of 81 children with IgAN, we also found no correlation of the severity or location of IgA deposits on histopathological examination, with proteinuria, creatinine and GFR, although the percentage of children with GFR < 90 was significantly higher in the group of children with IgA + 3, + 4 versus + 1, + 2 [63].

On histopathological examination, kidney GDIgA1 is also identified using KM55 antibodies. According to US authors, immunostaining does not differentiate primary from secondary forms of IgAN, although negative or low staining may be indicative of secondary or incident IgAN without signs of nephritis, and thus may help exclude primary IgAN (especially when GD-IgA1 ≤ + 1) [64].

Roos et al. found deposits of IgA1 but not IgA2 in kidney bioassays of IgAN patients [65]. Their study also showed the presence of MBL I L-ficolin in glomeruli, which is not

Table 1 Expected IgA/C3 ratio values for specific MEST score values

MEST score	Expected IgA/C3 ratio	Sensitivity (95% *CI*)	Specificity (95% *CI*)
< 1	1.55	0.74 (0.33–0.83)	0.74 (0.33–0.83)
< 2	2.15	0.74 (0.33–0.83)	0.57 (0.39–0.74)
< 3	2.26	0.74 (0.33–0.83)	0.57 (0.39–0.74)
< 4	Only 4 results		

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necessarily associated with increased serum concentrations. The biopsy finding of these lectin pathway activators was associated with increased mesangial proliferation, extracapillary proliferation, glomerular sclerosis, and interstitial infiltration, as well as increased proteinuria. These studies confirm the involvement of MBL and L-ficolin in IgAN progression. IgA polymers can activate the lectin pathway by binding to MBL through glycans present in a heavy chain of IgA [40, 65].

C3 deposits

The concomitant presence of C3 deposits in kidney biopsy are currently considered confirmatory for IgAN, in contrast to asymptomatic IgA deposits. In IgAN, C3 deposits are present together with IgA deposits in 90% of biopsies [3]. In the study by Caliskan et al. in 156 adult patients, grade ≥ 2 C3 deposits were significantly more commonly accompanied by a reduced serum C3 level, and the number of patients with GFR (glomerular filtration rate) reduction by > 50% compared to baseline was also higher in the group with grade ≥ 2 C3 deposits [6]. In the study by Kim and Koo of 343 adult patients, 21% showed grade ≥ 2 C3 deposits. An effect of grade ≥ 1 C3 deposits was also shown on the occurrence of kidney failure or doubling of serum creatinine [47].

Similarly, in the current author's study in a pediatric population of 148 patients, reduced kidney survival was shown in the group with grade ≥ 1 C3 deposits in kidney biopsy, as well as in boys and patients with baseline GFR < 90 mL/min [48].

Proteomic studies by Paunas et al. also confirmed an association between the presence of C3 deposits and progression of IgAN [66, 67].

C4d staining may be useful in differentiating between patients with a good and unfavorable prognosis. Espinisa et al. showed that 10-year kidney survival was 43.9% in C4d-positive patients versus 90.9% in C4d-negative patients (log-rank, $p = 0.0005$) [41]. Deposits of other elements of the alternative complement pathway such as FH, C5, and properdin may also be found in kidney biopsy [34]. The available data on the utility of IgA and C3 as prognostic markers are summarized in Table 2.

Summary

The present review discusses the utility of widely available, routine testing for IgA and C3 in serum and kidney biopsy specimens for the diagnosis and prognostication

Table 2 The utility of IgA and C3 for the evaluation of prognosis in IgA nephropathy

	Importance	References
Serum	IgA	
	No prognostic significance	[43, 45]
	Serum IgA > 315 mg/dL may serve for diagnostic purposes	[45]
	Serum IgA higher in M1 and S1	[43]
	Higher level in children without proteinuria	[44]
	C3	
	SerumC3 < 90 mg/dL in adults is an independent adverse prognostic factor	[47]
	C3 below the reference range in children — trend for lower GFR at 4 years of follow-up	[48]
	Serum C3 level correlates negatively with the severity of C3 deposits in kidney biopsy	[47]
	Elevated C3 level in patients with protective *CFHR1/CFHR3* deletion	[29, 52]
	Progressive loss of renal function with elevated actC3	[3, 49]
	IgA/C3	
	Highest in IgAN compared to other glomerulopathies	[45, 53],
	The higher the level, the higher the recurrence rate	[58]
	Value ≥ 3.32 independent risk factor for progression in adults	[56]
	Cutoff values related to MEST score have been determined in children: IgA/C3 < 3	[44]
	Prognostic value in children when IgA/C3 > 2.68 and grade ≥ 2 C3 deposits	[55]
	Prognostic value when > 2.91 in adults	[57]
Kidney Biopsy	IgA deposits	
	Predominance confirms the diagnosis of IgAN	[1–6, 9]
	Absence of association of severity of mesangial deposits and glomerular damage	[61]
	GD-IgA1 are present in primary and secondary IgAN, but negative or up to + 1 immunostaining can help exclude primary IgAN	[64]
	C3 deposits	
	The presence of C3 deposits confirms IgAN	[3]
	Severe (grade ≥ 2) C3 deposits associated with worse renal survival	[6, 47], [44
	The severity of C3 deposits correlates with the presence of M1 and T1-2 in kidney biopsy	[47, 53]
	Association between the severity of C3 deposits and disease progression in a proteomic study	[66]

of IgAN, but studies show that even more important are GDIgA1 and anti-GDIgA1 that have been established as more sensitive and specific markers.

Regarding the complex mechanisms of IgAN pathogenesis, it is also important to consider the possible utility of other novel biomarkers resulting from activation of the alternative and lectin pathway of complement and genetic tests. Therefore, it seems that panels of biomarkers may be the future for the diagnosis and prognosis of IgAN in children and adults.

Key summary points

- IgA nephropathy (IgAN) is the most common glomerulonephritis worldwide. It is diagnosed based on clinical and histological features including predominant IgA deposits in kidney biopsy.
- The pathogenesis of IgA nephropathy is described by the multi-hit theory, in which immune, genetic, and environmental factors, as well as activation of the complement system by alternative and lectin pathways, play a role.
- Routine testing for IgA and C3 in serum and kidney biopsy specimens for the diagnosis and prognostication in IgAN are useful. Studies also show an important role for GDIgA1 and anti-GDIgA1, which have been found to be more sensitive and specific markers.
- Regarding the complex mechanisms of IgAN pathogenesis, it is also important to consider the possible utility of other novel biomarkers resulting from activation of the alternative and lectin pathway of complement and genetic tests. Therefore, it seems that panels of biomarkers may be the future for the diagnosis and prognosis of IgAN in children and adults.

Multiple choice questions (more than 1 answer may be correct) (answers can be found after the reference list).

1. IgA nephropathy:
   a. is the most common nephropathy in the world
   b. can lead to kidney failure in 20–40% of patients within 20 years
   c. is most prevalent in Asians, followed by Caucasians, and relatively rare in Africans
   d. kidney biopsy is the gold standard diagnostic method
   e. the diagnosis is made based on elevated serum IgA level
2. Clinical manifestations of IgA nephropathy include:
   a. erythrocyturia or hematuria
   b. proteinuria
   c. asymptomatic leukocyturia
   d. hypertension
   e. kidney failure
3. Factors important in the pathogenesis of IgA nephropathy include:
   a. formation of oligoglycosylated IgA1
   b. formation of anti-glycan antibodies
   c. genetic predisposition
   d. complement activation by the classical pathway
   e. complement activation by the alternative pathway
4. Serum IgA level:
   a. may be elevated in about 50% of patients with IgA nephropathy
   b. has no prognostic significance
   c. indicates GDIgA1
   d. is related to creatinine level
   e. is associated with lower proteinuria
5. C3 complement component:
   a. serum C3 level < 90 mg/dL in adults is an adverse prognostic factor
   b. serum C3 level correlates positively with the severity of C3 deposits in kidney biopsy
   c. elevated C3 level is present in patients with the protective *CFHR1/ CFHR3*deletion
   d. severe C3 deposits in kidney biopsy are associated with better kidney survival
   e. may be a component of IgA/C3 and have prognostic significance

Declarations

Conflict of interest The author declares no competing interests.

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Answers 1. a, b, c, d; 2. a, b, d, e; 3. a, b, c, e; 4. a, b; 5. a, c, e