Kidney Research and Clinical Practice

Original Article

Elevated serum immunoglobulin E level as a marker for progression of immunoglobulin A nephropathy

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Abstract

Background: Immunoglobulin E (IgE) has traditionally been associated with anaphylaxis and atopic disease. Previous studies reported that serum IgE levels are elevated in nephrotic syndrome and suggested IgE levels as a prognostic indicator in glomerular diseases. The aim of this study was to explore the association between serum IgE levels and renal outcome in patients with immunoglobulin A nephropathy (IgAN).

Methods: We included 117 patients with biopsy-proven IgAN. Renal progression was defined if a patient meets one of these criteria: (1) a negative value of delta estimated glomerular filtration rate (mL/min/1.73 m^2/mo) or (2) a rise in serum creatinine to an absolute level of ≥ 1.3 mg/dL (male) or 1.2 mg/dL (female). We defined delta changes in serum creatinine, estimated glomerular filtration rate, and proteinuria as a difference of values during the follow-up period.

Results: A total of 117 patients with IgAN were included. The serum IgE level was significantly high in the renal progressive group compared with the nonprogressive group. Sex and history of gross hematuria were significantly different between the high-IgE group and the low-IgE group. Regression analysis showed that a male sex, initial proteinuria, and change of proteinuria were significantly associated with serum IgE levels.

Conclusion: The serum IgE level is potentially associated with disease progression and pathogenesis of IgAN.

Introduction

Immunoglobulin A nephropathy (IgAN), characterized by IgA deposition in glomerular mesangium, is the most common primary glomerulonephritis (GN) worldwide [1] and the leading cause of GN in some countries, such as Korea [2]. Recent studies have shown that 35—50% of these patients exhibit disease progression to end-stage kidney disease within

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30 years despite treatments [3]. According to the Kidney Disease: Improving Global Outcomes guideline of 2012, proteinuria, blood pressure, and kidney biopsy findings at presentation are associated with the risk of end-stage renal disease and the doubling of serum creatinine (SCr) levels [4]. Among these, proteinuria of >1 g/d is a powerful independent predictor of accelerated decline of renal function [5,6]. Although the pathologic analysis of renal biopsies is the standard for the diagnosis of IgAN, the measurement of novel biomarkers in serum might be regarded as an alternative tool, providing meaningful information for the diagnosis and prognosis of this glomerular disease [7—11].

Immunoglobulin E (IgE) has traditionally been associated with anaphylaxis and atopic diseases. IgE production is characteristic of not only allergy but also infection by parasitic worms. The highest levels of IgE are often associated with atopic dermatitis, followed by atopic asthma, perennial allergic rhinitis, and seasonal allergic rhinitis. Measurement of total IgE levels in patients with allergic bronchopulmonary aspergillosis can be used to monitor disease activity and response to therapy. Total serum IgE level has been found to be of clinical relevance in nephrotic syndrome, where elevated levels of serum IgE were regarded as a predictor of the disease [12—14]. However, the clinical significance has rarely been studied in IgAN. The aim of this study was to explore the association between the serum IgE level in IgAN patients and their renal outcome.

Methods

Study population and study design

This is an observational retrospective study of a cohort of IgAN patients undergoing kidney biopsies, between 1995 and 2012 (Fig. 1). All patients in this study were diagnosed at Kyung Hee Medical Center an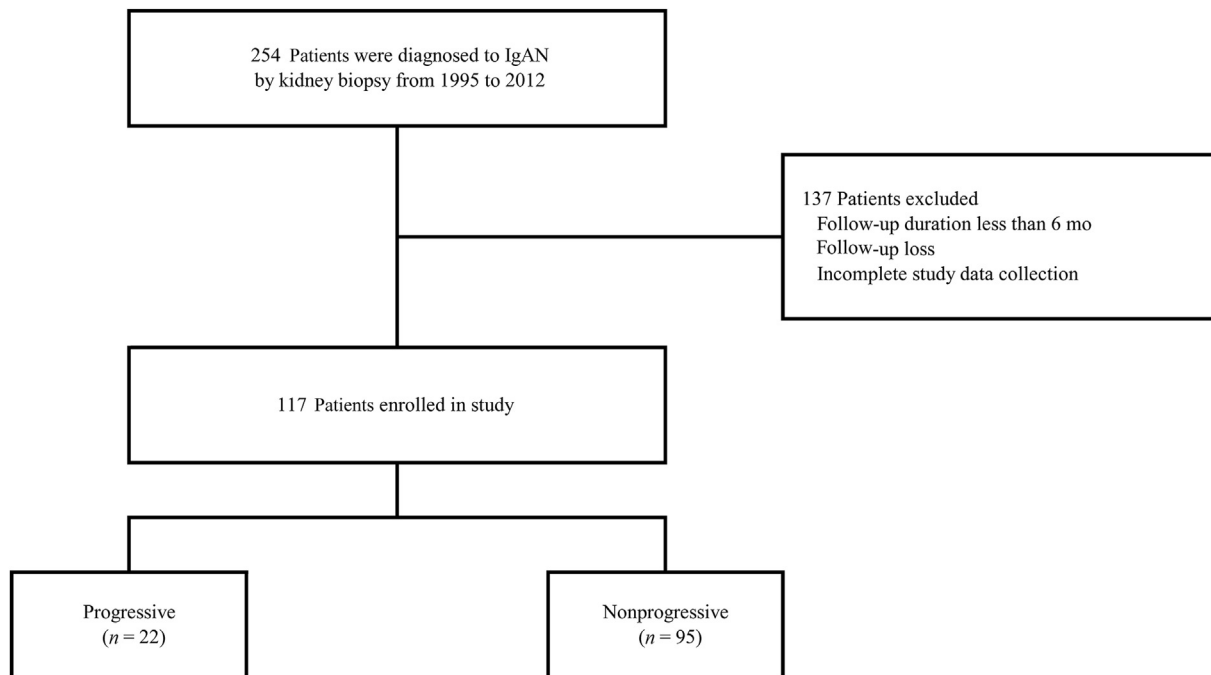d Kyung Hee University Hospital at Gangdong. A total of 117 patients, 67 (57.3%) men and 50 (42.7%) women, with IgAN were included (Table 1). The median age at the time of renal biopsy was 33 years (range, 12—68 years). We collected the data of patients' demographics and serum IgE levels via routine laboratory examination.

Table 1. Patient characteristics

Parameters	
Number of patients	117
Sex (male)	67 (57.3)
Age (y)	33.4
BMI (kg/m^2)	23.1 ± 3.6
Smoking	20 (17.1)
HTN	23 (19.7)
Serum IgE (IU/mL)	304 ± 607
Serum IgA (mg/dL)	334 ± 157
Period of follow-up (mo)	39 ± 33
Hb (g/dL)	13.3 ± 2.0
Albumin (g/dL)	3.8 ± 0.7
Total cholesterol (mg/dL)	186 ± 64
Initial serum Cr (mg/dL)	1.3 ± 1.0
Initial eGFR (mL/min/1.73 m^2)	84.8 ± 37.4
Initial UPCR (g/gCr)	1.8 ± 2.7
Final serum Cr (mg/dL)	1.8 ± 3.2
Final eGFR (mL/min/1.73 m^2)	90.5 ± 42.0
Final proteinuria (g/gCr)	0.8 ± 1.2
Gross hematuria	27 (23.1)
Renal progression	17 (14.5)
Pathologic stage	
Stage I	29 (24.8)
Stage II	62 (53.0)
Stage III	19 (16.2)
Stage IV	6 (5.1)
Stage V	1 (0.9)

Data are presented as *n* (%) or mean ± SD.
BMI, body mass index; Cr, creatinine; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; HTN, hypertension; IgA, immunoglobulin A; IgE, immunoglobulin E; UPCR, urine protein-to-creatinine ratio.

Figure 1. Study design and renal outcomes. IgAN, immunoglobulin A nephropathy.

Clinical data

We retrospectively analyzed the correlation between the serum IgE level and clinical parameters (age, sex, SCr, estimated glomerular filtration rate [eGFR], proteinuria, blood pressure, and history of gross hematuria). The eGFR was calculated using the Modification of Diet in Renal Disease formula: [eGFR = 175 × standardized $SCr^{-1.154}$ × $age^{-0.203}$ × 0.741 (if Asian) × 0.742 (if female)] [15]. Serum total IgE was determined by high-sensitivity nephelometry (BN II System; Siemens Healthcare Diagnostics, Deerfield, IL, USA).

Definition of renal progression

The initial measurement of SCr was obtained at the time of the renal biopsy. The SCr measured at the last follow-up visit was used when defining IgAN progression. SCr values were considered normal if they were ≤ 1.2 mg/dL. We defined delta changes in SCr, eGFR, and proteinuria as follows: delta SCr (mg/dL/mo) = [(final SCr level − initial SCr level)/duration of follow-up], delta eGFR (mL/min/1.73 m^2/mo) = [(final eGFR level − initial eGFR level)/duration of follow-up], and delta proteinuria (g/gCr/mo) = [(final urine protein level − initial urine protein level)/ duration of follow-up]. Renal progression was defined if a patient meets one of these criteria: (1) a negative value of delta eGFR (mL/min/1.73 m^2/mo) or (2) a rise in SCr to an absolute level of ≥ 1.3 mg/dL (male) or 1.2 mg/dL (female).

Statistical methods

Continuous variables are expressed as the mean ± standard deviation or median (interquartile range). Differences between the 2 groups were assessed using the Student *t* test; the χ^2 test was used for categorical variables. To evaluate the association between serum IgE and clinical variables, we used a univariate linear regression model. A *P* value < 0.05 was considered statistically significant. The statistical analysis was performed with the SPSS program for Windows (version 14.0; SPSS Inc., Chicago, IL, USA).

Results

Baseline clinical characteristics

A total of 117 patients were enrolled in this study. Among the patients, 67 were male (57.3%) and 50 were female (42.7%). The mean age was 33.4 ± 13.0 years, and the mean follow-up period was 39 ± 33 months. The mean initial eGFR and urine protein creatinine values were 84.8 ± 37.0 mL/min/1.73 m^2 and 1.8 ± 2.7 g/gCr, respectively. The distribution in glomerular grades of the 117 patients, using the H.S. Lee grading, was as follows: grade I, 29 patients (24.8%); grade II, 62 patients (53.0%); grade III, 19 patients (16.2%); grade IV, 6 patients (5.1%); and grade V, 1 patient (0.9%). The mean level of serum IgE was 304 ± 607 IU/mL (Table 1).

Progression of IgAN

Among 117 patients, 86 (73.5%) had normal SCr levels and 31 (26.5%) had elevated levels at the time of the renal biopsy. IgAN progression was found in 14 of the 117 patients (12%). Patients with progression had initially higher levels of serum IgE, SCr,

Table 2. Comparison between progressive and nonprogressive patients

Parameters	Nonprogressive	Progressive	*P*
Patient number	103	14	
Sex	55 (53.4)	12 (85.7)	0.010
Age (y)	31.5 ± 13.5	41.6 ± 12.7	0.001
BMI (kg/m^2)	22.8 ± 3.4	25.7 ± 3.9	0.004
Smoking	14 (13.6)	6 (42.9)	0.019
HTN	15 (14.6)	8 (57.1)	< 0.001
Initial serum IgE (IU/mL)	238 ± 290	590 ± 1,247	0.014
Initial serum IgA (mg/dL)	330 ± 155	346 ± 168	0.685
Initial Hb (g/dL)	13.5 ± 1.9	12.4 ± 2.3	0.018
Initial serum Cr (mg/dL)	1.1 ± 0.8	2.1 ± 1.3	< 0.001
Initial eGFR (mL/min/1.73 m^2)	91.8 ± 33.8	54.4 ± 37.1	< 0.001
Initial proteinuria (g/gCr)	1.4 ± 2.2	3.4 ± 3.8	0.002
Final proteinuria (g/gCr)	0.6 ± 1.0	2.7 ± 1.5	< 0.001
Delta serum Cr (mg/dL)	−0.01 ± 0.04	0.1 ± 0.2	< 0.001
Delta eGFR (mL/min/1.73 m^2)	0.8 ± 2.7	−0.6 ± 0.7	0.014
Delta proteinuria (g/gCr)	−0.03 ± 0.08	−0.04 ± 0.09	0.544
Pathologic stage	2.0 ± 0.8	2.3 ± 1.0	0.152
Gross hematuria	25 (24.2)	3 (21.4)	0.549
Use of immunosuppressants	8 (7.8)	6 (42.9)	< 0.001

Data are presented as *n* (%) or mean ± SD.
BMI, body mass index; Cr, creatinine; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; HTN, hypertension; IgA, immunoglobulin A; IgE, immunoglobulin E.

and proteinuria and frequently had a history of hypertension and use of immunosuppressants (Table 2). End-stage renal disease (requiring dialysis or kidney transplantation) developed in 8 patients (6.8%).

Correlations between serum IgE and clinical variables

The serum IgE level was significantly high in the renal progressive group compared with the nonprogressive group (801 ± 1,520 vs. 236 ± 293 IU/mL, *P* < 0.001; Table 2). Male sex (70.0% vs. 43.9%, *P* = 0.004) was significantly different between the high-IgE group and the low-IgE group. However, no significant differences were seen for delta SCr (mg/dL/mo), delta eGFR (mL/min/1.73 m^2/mo), delta proteinuria (g/gCr/mo), and pathologic findings (Table 3). Univariate linear regression analysis showed that male sex (standardized β = 0.308, *t* = 2.246, *P* = 0.028), initial proteinuria (standardized β = 0.617, *t* = 2.712, *P* = 0.008), final proteinuria (standardized β = 0.321, *t* = 3.086, *P* = 0.003), and delta proteinuria (standardized β = 0.404, *t* = 2.246, *P* = 0.028) were significantly associated with serum IgE levels (Table 4).

Discussion

The present study showed that the serum IgE level was significantly high in the renal progressive group compared with the nonprogressive group. Serum IgE were also positively correlated with initial and delta proteinuria.

IgE has the lowest abundance *in vivo*, and its levels are tightly regulated. Concentrations of free serum IgE are

Table 3. Comparison of clinical variables according to the levels of plasma IgE in patients with IgAN

Parameters	IgE < 109 IU/mL	IgE ≥ 109 IU/mL	P
Patient number	57	60	
Albumin (g/L)	3.8 ± 0.5	3.7 ± 0.8	0.503
Hb (g/dL)	13.1 ± 2.0	13.5 ± 2.1	0.296
Sex	25 (43.9)	42 (70.0)	0.004
Age (y)	34.3 ± 12.4	32.6 ± 14.7	0.501
BMI (kg/m^2)	22.9 ± 3.8	23.3 ± 3.4	0.623
Smoking	8 (14.0)	12 (20)	0.394
HTN	10 (17.5)	13 (21.7)	0.578
Initial serum Cr (mg/dL)	1.2 ± 0.8	1.4 ± 1.1	0.169
Initial eGFR (mL/min/1.73 m^2)	86.3 ± 38.2	83.3 ± 36.8	0.663
Initial proteinuria (g/gCr)	1.6 ± 2.6	2.0 ± 2.9	0.467
Final proteinuria (g/gCr)	1.0 ± 1.5	0.7 ± 1.0	0.263
Delta serum Cr (mg/dL)	0.004 ± 0.045	0.022 ± 0.166	0.422
Delta eGFR (mL/min/1.73 m^2)	0.2 ± 1.6	0.9 ± 3.1	0.179
Delta proteinuria (g/gCr)	−0.015 ± 0.061	−0.043 ± 0.100	0.068
Initial serum IgA (mg/dL)	327 ± 139	338 ± 173	0.699
Pathology (stage)	2.1 ± 0.8	2.0 ± 0.9	0.571
Gross hematuria	17 (29.8)	6 (10.0)	0.095
Use of immunosuppressants	6 (10.5)	8 (13.3)	0.644
Renal progression (%)	8 (14.0)	6 (10.0)	0.507

Data are presented as *n* (%) or mean ± SD.
BMI, body mass index; Cr, creatinine; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; HTN, hypertension; IgA, immunoglobulin A; IgAN, IgA nephropathy.

Table 4. Clinical variables for association with serum IgE (linear regression model)

Parameters	Standardized β	t	P
Albumin (g/L)	−0.058	−0.402	0.689
Hb (g/dL)	−0.105	−0.723	0.472
Sex (male, %)	0.308	2.272	0.028
Age (y)	−0.032	−0.218	0.828
Initial serum Cr (mg/dL)	−0.137	−0.767	0.445
Initial eGFR (mL/min/1.73 m^2)	−0.185	−0.941	0.350
Initial proteinuria (g/gCr)	0.616	2.719	0.008
Final proteinuria (g/gCr)	0.321	3.086	0.003
Delta serum Cr (mg/dL)	0.084	0.638	0.525
Delta eGFR (mL/min/1.73 m^2)	0.145	1.058	0.293
Delta proteinuria (g/gCr)	0.404	2.417	0.028
Serum IgA (mg/dL)	0.584	0.584	0.561
Gross hematuria (%)	−1.026	−1.026	0.308
Systolic blood pressure (mmHg)	−0.472	0.638	0.638
Pathologic stage	−1.864	0.066	0.066

Cr, creatinine; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; IgA, immunoglobulin A; IgE, immunoglobulin E.

~50−200 ng/mL of blood in healthy humans compared with ~1−10 mg/mL of blood for other immunoglobulin isotypes [16]. Increased IgE production has been documented in various autoimmune, inflammatory, and genetic diseases [17,18]. Despite the importance of IgE in allergic pathogenesis and helminth immunity, the mechanism by which IgE is produced and regulated is poorly understood. The classic pathway to IgE switching involves uptake of allergens by dendritic cells, allowing for the presentation of antigenic determinants to T cells. The subsequent stimulation of specific CD4+ T cells leads to the production of interleukin (IL)-4 and enhanced stimulation of B cells. IL-4 and IL-13 receptors signal to induce Cε germline transcripts, rearrangement of the IgE genomic locus, and production of IgE antibodies. IgE typically binds not only to mast cells and basophils but also to low-affinity receptors on inflammatory cells and platelets, with the release of inflammatory mediators and chemotactic factors, which have been thought to cause GN. Evidence supporting the role of type I hypersensitivity in the pathogenesis of GN comes from reports of high levels of serum IgE and its deposition in the kidney [19,20] and renal mast cells in IgAN [21].

The exact pathogenesis of IgAN is still not well defined. The multihit pathogenesis model proposed integrates findings from studies of galactose-deficient IgA1, antiglycan response, formation and deposition of IgA1-containing immune complexes, and mechanisms of immune complex−mediated tissue injury. Recently, a genome-wide association study of IgAN showed the interpopulation differences in genetic risk. Interestingly, the risk alleles with largest effects tend to have the greatest population differentiation and contribute most to the observed geographic patterns. The geospatial distribution of risk alleles is highly suggestive of multilocus adaptation, and the genetic risk correlates strongly with variation in local pathogens, particularly helminth diversity [22]. The enhanced IgA response, conferred by genome-wide association study risk alleles, is likely protective against these pathogens, but it can also explain the association of mucosal infections as a common trigger for IgAN. Given the fact that one of the main functions of IgE is providing immunity to parasites, such as helminths like *Schistosoma mansoni* [23] and *Trichinella spiralis* [24], it is possible that the correlation of the serum IgE level and IgAN progression in this study reflects how intestinal worm infections pertain to the pathogenesis of IgAN. Immunologic explanations have been proposed for both the suppression and induction of allergic diseases by helminth infection [25−27]. However, our study did not assess the mechanism of altered production of IgE in IgAN and disease progression; hence, such further prospective studies are needed.

Our study has certain important limitations. First, factors, such as allergic diseases, autoimmune disorders, and parasitic infections, are causes of elevated serum IgE [28]. Unfortunately, this study did not evaluate these factors besides IgAN. Second, the number of enrolled patients with IgAN was small, and the follow-up duration was varied and too short in some cases. Further study is required with large number and long-term follow-up. Third, multivariate analysis for risk factors for IgAN progression could not be performed because of the small number of disease progression events. Fourth, the retrospective nature of our study raises the possibility of biases in patient selection and does not definitively show that serum IgE itself caused the disease and/or its progression because of the observational study design.

In conclusion, the present study shows that the serum IgE level is elevated in a renal progression group of IgAN patients, suggesting that the serum IgE level is associated with renal progression in IgAN patients. Future prospective and controlled studies are needed to elucidate immunopathogenesis of the increased serum IgE level in IgAN.

Conflicts of interest

All authors have no conflicts of interest to declare.

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