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Extraglomerular C3 deposition and metabolic impacts in patients with IgA nephropathy

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ORIGINAL ARTICLE

ABSTRACT

Background. The aim of the present study was to explore the significance of extraglomerular (Bowman's capsule and/or arteriole) C3 (ex-C3) deposits in IgA nephropathy (IgAN).

Methods. One hundred and seventy patients with IgAN were divided into two groups: Group A ($n = 79$), patients who did not have ex-C3 deposits, and Group B ($n = 91$), patients who had ex-C3 deposits.

Results. At the time of renal biopsy, Group B was characterized by a marked increase in diastolic blood pressure, total cholesterol, triglyceride and low-density lipoprotein-cholesterol compared with those of Group A. After 4 years, the estimated glomerular filtration rate (eGFR) in Group B was significantly worse than that of Group A. Upon examination by electron microscopy, the arteriolar dense deposits in Group B were found to occur in significantly higher amounts than in Group A. One hundred and thirty-four patients underwent a 3-year follow-up study after intervention and were re-divided by therapeutic factors as follows: 'conventional therapy', treatment with anti-hypertensive drugs and/or anti-platelet drugs, and 'aggressive therapy', additional treatment with either tonsillectomy or corticosteroid. Patients treated with conventional therapy in Group B had significantly higher body mass index and levels of C3 and CH50 compared with other Groups. Aggressive therapy was significantly effective in urinary protein reduction in both Group A and Group B. Except for the patients who received aggressive therapy in Group A, the levels of the eGFR gradually declined.

Conclusions. It appears that IgAN patients who have ex-C3 deposits have worse clinical outcomes.

INTRODUCTION

IgA nephropathy (IgAN) is the most common form of primary glomerulonephritis in the world, and the definitive diagnosis is determined from the results of renal biopsy. By immunofluorescence (IF) technique, mesangial deposition of IgA is also a conclusive factor for the diagnosis of IgAN. With

respect to complement deposition, C3 is highly detected in glomeruli, and the detection rate is >90% in patients with IgAN [1, 2]. These findings can be used to deduce that the complement activation leads to glomerular damage. However, although we also encounter the extraglomerular deposition of C3 in the results of routine histological study, these findings have received less attention in recent decades. Therefore, an important question that arises is whether the findings of extraglomerular C3 (ex-C3) deposition have clinical significance.

Mesangial proliferation is a characteristic finding which was observed by light microscopy (LM), and recent studies have indicated that histological modifications occur in obese patients with IgAN [3, 4]. Hyperinsulinemia and hyperleptinemia might increase growth factors, and angiotensin II might lead to glomerular enlargement and thickening of glomerular basement membrane. On the other hand, patients with protein-energy malnutrition show low concentrations of serum C3 and their nutritional rehabilitation results in the recovery of the levels of serum C3 to the normal range [5–7]. Recently, we have demonstrated that the serum concentration of C3 showed a strongly positive association with markers of metabolic syndrome (Mets), such as insulin, homeostasis model assessment, total cholesterol (TC), triglyceride (TG), low-density lipoprotein-cholesterol (LDL-c) and body mass index (BMI) [8]. These indicate that nutritional adequacy has a positive impact on the serum concentration. Thus, the pathophysiological role of metabolic condition is mandatory in the study of renal damage in IgAN.

In this study, we undertook clinical research to elucidate the significance of extraglomerular deposition of C3 in patients with IgAN and highlighted the metabolic impacts on the progression of this disease.

MATERIALS AND METHODS

The study included 170 patients who were diagnosed with IgAN and followed at the Division of Nephrology and Hypertension, Juntendo University Hospital. The study was conducted in accordance with the Declaration of Helsinki (1975) and was approved by the Institutional Review Board of Juntendo University. Based on clinical characteristics, all of the patients with Henoch–Schönlein purpura nephritis, hepatitis B-associated glomerulonephritis or systemic lupus erythematosus that was secondary to IgAN were excluded. Patients with diabetes mellitus [fasting blood glucose level (FPG) ≥ 126 mg/dL, random blood glucose level ≥ 200 mg/dL or currently on anti-diabetic medications] or autoimmune diseases were also excluded. Patient demographics are given in Table 1. There were 88 men and 82 women. The mean (±SD) age was 32.8 ± 11.1 years. Clinical data were collected at the time of biopsy and at the time of yearly check up. BMI was calculated by dividing the body weight (kg) by height^2 (m^2). The follow-up period was 4.0 ± 2.8 years.

After histological diagnosis, several therapeutic options including tonsillectomy (Ton), steroid pulse therapy (SP; methylprednisolone 500 mg/day for 3 days), steroid oral prescription (SO; prednisolone 0.5 mg/kg/day, every other day, for 6 months), renin–angiotensin system inhibitor, calcium channel blocker and anti-platelet drug (dipyridamole) were started.

Laboratory data

All blood samples were obtained from the antecubital vein after overnight fasting. Biochemical analysis, including hemoglobin, hematocrit, FPG, TC, TG, high-density lipoprotein-cholesterol (HDL-c), LDL-c, serum creatinine (s-Cr), uric acid (UA), albumin, immunoglobulin (Ig) G, IgA, IgM, C3, C4 CH50, C-reacting protein (CRP), urinary protein (uPro) and urinary α1-microglobulin, was examined. The degree of urinary sediment of red blood cells (uRBC) was scored in five phases as follows: 1–5 red blood cells (RBCs)/high power field (HPF): 1, 6–10 RBCs/HPF: 2 , 11–15 RBCs/HPF: 3, 16–20 RBCs/HPF: 4 and more than 21 RBCs/HPF: 5 [9]. The estimated glomerular filtration rate (eGFR) was calculated using the formula established by the Japanese Society of Nephrology: eGFR (mL/min/1.73m^2) = $194 \times Cr^{-1.094} \times age^{-0.287}$ (if female, ×0.739) [10].

Morphometric analysis

Paraffin-embedded sections were routinely stained with hematoxylin and eosin, periodic acid-Schiff, Masson's trichrome and periodic acid-silver methenamine. The activity and severity were graded by the classification system, according to the Japanese classification of IgA Nephropathy [11]. For the quantitation of the percentage of fibrotic (collagen-positive) area stained by Masson's trichrome, we used the KS400 image analysis system (KS400, Zeiss, Germany). LM analysis was performed by two pathologists and two nephrologists in a blinded fashion.

Staining for IgG, IgA, IgM, C3c and C1q on freshly frozen renal tissues was performed using corresponding fluorescence isothiocyanate-conjugated anti-sera (Dako, Copenhagen, Denmark). C3 deposition was reviewed by two experienced nephrologists and all patients were divided into two Groups—Group A: C3 deposition was limited in glomeruli, and Group B: C3 deposition was observed at both glomeruli and extraglomerular areas, namely Bowman's capsule and/or afferent and efferent arterial walls. In other words, patients with a mixed pattern of C3 staining can be designated as Group B.

Renal tissues were immediately fixed in 2% osmium and phosphate buffer saline for 2 h, then dehydrogenated by increasing the concentration of alcohol and embedded in Epok 812 (Oken-syoji, Tokyo, Japan). Approximately 1-μm-thick slices were prepared and stained with toluidine blue. One selected glomerulus was trimmed and ultra-thin sections (80–90 nm thickness) were prepared. They were double-stained with uranyl acetate and lead, and then observed by electron microscopy (Hitachi H-7100, Tokyo, Japan).

Statistical analysis

StatView for Windows (version 5.0; SAS Institute, Inc., Cary, NC, USA) and the GraphPad Prism 5J software for Windows (version 5.04; GraphPad, San Diego, CA, USA) were used for statistical analysis, and the two-sided P-value < 0.05 was taken as the level for statistical significance. All data were

Table 1. Clinical background of all patients with IgAN

	Total	Group A	Group B	*P*-value
n	170	79	91	
Anthropometric variables				
Gender (M:F)	88:82	39:40	49:42	NS (χ^2)
Age (years)	32.8 ± 11.1	31.3 ± 10.8	34.1 ± 11.4	NS
BMI (kg/m^2)	22.0 ± 3.1	21.6 ± 3.1	22.2 ± 3.1	NS
Systolic blood pressure (mmHg)	116.3 ± 14.0	115.6 ± 14.3	116.8 ± 13.7	NS
Diastolic blood pressure (mmHg)	67.8 ± 11.0	66.5 ± 10.9	68.8 ± 11.0	$P < 0.05$
Biochemical variables				
s-Cr (mg/dL)	0.8 ± 0.3	0.8 ± 0.2	0.9 ± 0.3	NS
Estimated GFR (mL/min/1.73 m^2)	84.7 ± 25.1	88.0 ± 24.1	81.5 ± 25.8	NS
uPro (g/g creatinine)	1.0 ± 1.4	0.7 ± 0.8	1.2 ± 1.6	NS
uRBC (grade)	4.1 ± 1.4	4.3 ± 1.2	4.0 ± 1.5	NS
Urinary α1-microglobulin	7.4 ± 7.0	7.4 ± 7.3	7.5 ± 6.9	NS
UA (mg/dL)	5.7 ± 1.6	5.8 ± 1.5	5.7 ± 1.8	NS
Total protein (g/dL)	6.8 ± 0.6	6.7 ± 0.6	6.8 ± 1.6	NS
Albumin (mg/dL)	4.0 ± 0.5	4.1 ± 0.4	4.0 ± 0.5	NS
TC (mg/dL)	198.3 ± 37.1	192.1 ± 33.9	203.8 ± 39.2	$P < 0.05$
TG (mg/dL)	117.6 ± 71.1	108.7 ± 73.2	125.4 ± 68.6	$P < 0.05$
HDL-c (mg/dL)	60.9 ± 18.9	59.9 ± 14.8	61.7 ± 21.9	NS
LDL-c (mg/dL)	129.2 ± 36.5	123.3 ± 35.0	134.6 ± 37.3	$P < 0.05$
Hemoglobin (mg/dL)	13.5 ± 1.6	13.4 ± 1.3	13.5 ± 1.7	NS
Immunological variables				
CRP (mg/dL)	0.1 ± 0.2	0.1 ± 0.3	0.1 ± 0.1	NS
IgG (mg/dL)	1140.3 ± 281.9	1165.5 ± 295.8	1118.8 ± 269.1	NS
IgA (mg/dL)	312.3 ± 94.8	317.4 ± 99.9	307.8 ± 90.4	NS
IgM (mg/dL)	124.1 ± 64.3	136.5 ± 69.4	113.2 ± 57.8	$P < 0.05$
C3 (mg/dL)	98.8 ± 16.4	96.8 ± 16.5	100.5 ± 16.3	NS
C4 (mg/dL)	24.7 ± 6.9	24.1 ± 7.0	25.3 ± 6.8	NS
CH50 (unit/mL)	41.8 ± 6.7	40.5 ± 6.3	42.9 ± 6.8	NS
IgA/C3 ratio	3.2 ± 1.0	3.3 ± 1.0	3.1 ± 1.0	NS
Therapy				χ^2
Ton	32	17	15	NS
Ton+SP+SO	28	15	13	NS
SP+SO	15	6	9	NS
SO	4	1	3	NS
RAS-INH	72	30	42	NS
CCB	12	5	7	NS
Anti-platelets agents	152	70	82	NS

Continued

Table 1. Continued

	Total	Group A	Group B	*P*-value
Follow-up data				
Observation period (years)	4.0 ± 2.8	3.9 ± 2.9	4.0 ± 2.7	NS
				ANOVA[a]
Last s-Cr (mg/dL)	1.2 ± 1.8	1.1 ± 1.6	1.3 ± 2.0	<0.01
Last estimated GFR (mL/min/1.73 m^2)	76.9 ± 28.9	80.1 ± 27.9	73.8 ± 29.6	<0.01
Last uPro (g/g creatinine)	0.5 ± 0.9	0.5 ± 0.7	0.6 ± 1.0	<0.01
uRBC (grade)	2.3 ± 1.7	2.5 ± 1.7	2.3 ± 1.7	<0.01

Values expressed as percent or mean ± SD.
BMI, body mass index; GFR, glomerular filtration rate; RBCs, red blood cells, HDL, high-density lipoprotein; LDL, low-density lipoprotein; CRP, C-reactive protein; Ton, tonsillectomy; SP, steroid pulse therapy; SO, steroid oral prescription; RAS-INH, renin–angiotensin–aldosteron system-inhibitor; CCB, calcium channel blocker; uPro, urinary protein; s-Cr, serum creatinine; uRBC, urinary sediment of red blood cells; TC, total cholesterol; TG, triglyceride; UA, uric acid.
[a]One-factor repeated measures ANOVA.

expressed as mean ± SD. The relationship between categorical variables were analyzed using χ^2 test. One-factor repeated measures or two-factor factorial analysis of variance (ANOVA), followed by pair-wise comparisons with Scheffé's *F* analysis when total ANOVA indicated a significant difference, were used in the comparisons between Grouped items, respectively.

RESULTS

Figure 1 shows the representative photographs of immunohistochemistry. We divided all patients into two groups—Group A: C3 deposition was limited in glomeruli, and Group B: C3 deposition was observed at both glomeruli and extraglomerular areas, namely in Bowman's capsule and/or afferent and efferent arterial walls.

Seventy-nine patients presented only glomerular deposition of C3 (Group A), and 91 patients presented not only glomerular deposition of C3 but also extraglomerular deposition of C3 (Group B) (Table 1).

Background and comparison of clinical parameters between Group A and Group B

At the time of renal biopsy, there was no difference in gender, age, BMI, systolic blood pressure, s-Cr, eGFR, uPro, uRBC, urinary α1-microglobulin, UA, CRP, IgG, IgA, C3, C4 and CH50 between Group A and group B. Mean diastolic blood pressure in Group B was significantly higher than that in Group A ($P < 0.05$). Serum concentrations of TC, TG and LDL-c in Group B were significantly higher than those in Group A (Figure 2) ($P < 0.05$).

Ton was performed in 32 patients; a combination therapy of Ton, SP and SO was performed in 28 patients, and combination therapy of SP and SO was performed in 15 patients. SO was taken in four patients. 89.4% of patients were prescribed dipyridamole and 42.3% of patients were given RAS inhibitors. There were no significant differences in the therapeutic strategies between Group A and Group B.

The last follow-up data were recorded at 3.9 ± 2.9 years after the renal biopsy for Group A and 4.0 ± 2.7 years for Group B. As for the parameters including s-Cr, eGFR, uPro and uRBC, one-factor repeated measures ANOVA revealed that these two groups were significantly independent groups ($P < 0.01$) (Table 1).

Comparisons of morphometric findings

The grading of Oxford classification of IgAN was adapted to all patients but the results presented no statistical differences between Group A and Group B (Table 2). Glomerular changes, including mesangial proliferation, sclerosis, crescent formation, double contour and lobulation, presented no differences between them. Arteriosclerosis was observed in 27 patients of Group A and 35 patients of Group B, but there was no difference between two groups. Mean percentages of fibrotic areas in whole areas of renal specimens presented no statistical difference in the two groups. More than half of the patients (91 out of 170) presented immunoglobulin (IgG, IgM) co-deposition with IgA in their glomeruli, but there was no significant difference. Bowman's capsule depositions of immunoglobulins in Group B tended to be higher than those in Group A. By EM study, the glomerular and Bowman's capsule dense deposits tended to be found in more patients in Group B but had no significant difference. Arteriolar dense deposition was observed significantly more in patients in Group B than in Group A ($P < 0.05$).

Localization of C3 deposition and therapeutic factors

Patients of Group A and Group B were divided by therapeutic modality (Table 3). Treatment with anti-hypertensive drugs and/or anti-platelet drugs was defined as 'conventional therapy', and additional treatment with either Ton or

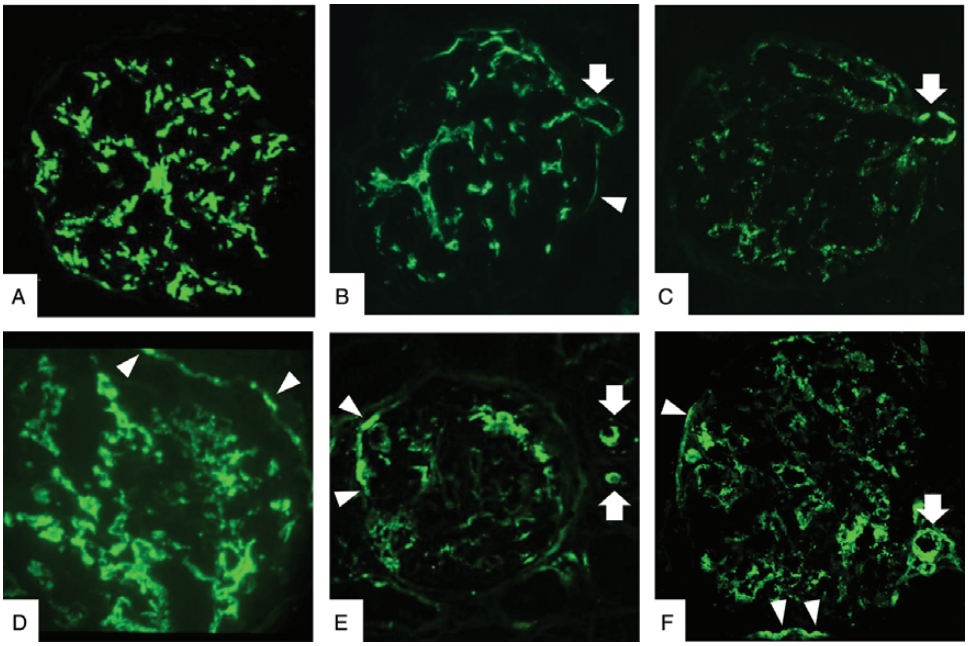

FIGURE 1: Staining pattern of C3 deposition of IgAN (×200). (**A**) Representative photograph of Group A. These glomeruli have intraglomerular (mesangial pattern) deposition only. (**B**–**F**) Representative photographs of Group B. These glomeruli have mesangial and extraglomerular deposits (arrow: afferent and efferent arteriolar deposition; arrow head: Bowman's capsule deposition).

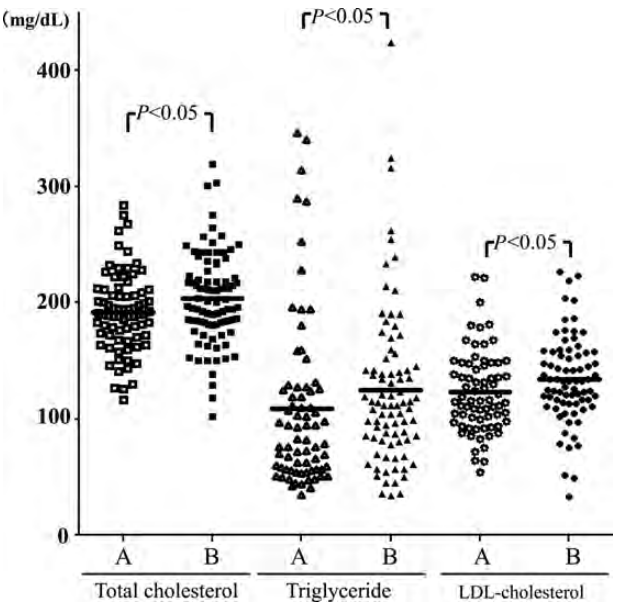

FIGURE 2: Distribution of lipid levels in all patients. The patients (**B**) who had ex-C3 deposits presented higher levels of TC, TG and LDL-c than patients (**A**) who presented only glomerular C3 deposition ($P < 0.05$).

corticosteroid therapy (SP and SO) was defined as 'aggressive therapy'. Data were collected for 134 patients who had three-point data for every year during the 3 years after renal biopsy. Aggressive therapy was performed for the patients who presented high excretion of uPro in both groups. With regard to eGFR, patients who had high levels of eGFR in Group A and low levels of eGFR in Group B underwent aggressive therapy. Patients who were treated with conventional therapy in Group B had significantly higher BMI and levels of C3 and CH50 than the other three groups ($P < 0.05$).

During the 3 years of observation, the levels of uPro and uRBC were gradually ameliorated and four groups were significantly independent ($P < 0.01$) (Figure 3). Patients with aggressive therapy presented rapid reduction of uRBC and uPro in both Group A and Group B. Only patients who underwent aggressive therapy in Group A maintained levels of eGFR during the 3 years (Figure 4). The eGFR of other groups gradually declined. In the first year, the eGFR of patients who were given aggressive therapy in Group B presented good initial response for aggressive therapy, but gradually declined 2 and 3 years after.

DISCUSSION

To explore the clinical significance of ex-C3 deposition, we divided patients into two groups based on whether patients had ex-C3 deposition or not. Several studies have indicated that patients' backgrounds, such as higher age, male gender, obesity and insulin resistance, are associated with histological modification in the patients with IgAN [3, 4]. In our study, we first excluded diabetic patients, and age and gender showed no statistical significance between the groups. There was no significant difference in BMI between the groups, because 14.7% of our patients who had higher BMI (>25) had lower BMI when compared with previous reports [3, 4]. The levels of diastolic blood pressure, TC, TG and LDL-c were significantly higher in patients with ex-C3 deposit. Together with the last follow-up data, the ANOVA showed that both groups were significantly different. Thus, it is possible to envisage a scenario

Table 2. Pathological background of all patients with IgAN

	Group A	Group B	*t*-test[a]	χ^2
Light microscopic findings				
Total glomeruli (*n*)	16.0 ± 8.2	15.5 ± 7.3	NS	
Histological grade[b] (I:II:III:IV) (*n*)	53:24:13:1	50:19:10:0		NS
Number of global sclerosis	1.6 ± 2.2	1.9 ± 2.4	NS	
Number of segmental sclerosis	0.7 ± 1.6	0.5 ± 0.9	NS	
Number of crescent	1.4 ± 1.9	1.3 ± 2.1	NS	
Double contour (*n*)	14	27		NS
Lobulation (*n*)	6	9		NS
Arteriole sclerosis (*n*)	27	35		NS
Tubular atrophy score (0:1:2:3:4)	24:48:2:1:2	25:56:6:0:3		NS
Interstitium infiltration area (%)	4.9 ± 5.7	5.7 ± 6.4	NS	
IF findings				
Glomrular deposition (*n*)				
IgA + IgG	15	16		NS
IgA + IgM	12	19		NS
IgA + IgG + IgM	14	15		NS
Bowman's capsule deposition (*n*)				
IgG	6	12		NS
IgA	0	2		NS
IgM	0	1		NS
C3	0	62		$P < 0.01$
Arteriolar C3 deposition (*n*)	0	30		$P < 0.01$
Tubular C3 deposition (*n*)	14	14		NS
Electron microscopic findings				
Glomerular dense deposit (*n*)				
Subepithelial	6	10		NS
Subendothelial	0	3		NS
Intra-GBM	5	7		NS
Bowman's capsule deposit (*n*)	0	4		NS
Arteriole wall deposit (*n*)	0	6		$P < 0.05$

Values expressed as percent or mean ± SD.
GBM, glomerular basement membrane; IF, immunofluorescence.
[a]Mann-Whitney.
[b]Japanese Classification of IgA Nephropathy.

in which the mechanisms of ex-C3 deposition might be associated with not only immunological but also metabolic factors.

Several reports have stated that various types of renal disease presented granular deposits of C3 in the extraglomerular vessels [12, 13]. Pollock *et al.* [12] concluded that most patients with afferent arteriolar deposition of C3 had a marker of a distinct hereditary disease, such as thin basement membrane disease (TBMD). We firstly excluded patients of TBMD (all patients were confirmed by EM study to have a normal thickening of glomerular basement membrane). Based on the study of staining for other serum proteins in renal specimens, Valenzuela *et al.* [13] suggested that passive diffusion probably does not explain C3 deposition. As mentioned above, a drainage pathway of immune complex is assumed.

Table 3. Clinical data of four groups which were divided according to the therapeutical methods in patients with IgAN

	Group A		Group B		ANOVA[a]	*Post hoc* comparisons (Scheffe's test)
	Aggressive Tx	Conventional Tx	Aggressive Tx	Conventional Tx		
n	23	34	30	47		
Age (years)	27.8 ± 8.0	33.6 ± 11.5	31.5 ± 8.1	35.5 ± 13.1	$P < 0.05$	NS
BMI (kg/m^2)	20.6 ± 2.9	21.9 ± 3.1¶	21.0 ± 2.7†	23.1 ± 3.2‡	$P < 0.01$	‡ versus ¶ and †, $P < 0.05$
Diastolic blood pressure (mmHg)	63.3 ± 8.6	67.5 ± 12.4	65.0 ± 8.8	70.7 ± 11.9	$P < 0.05$	NS
Total protein (g/dL)	6.6 ± 0.5	6.8 ± 0.5	6.6 ± 0.6	6.9 ± 0.6	$P < 0.05$	NS
Albumin (mg/dL)	3.8 ± 0.3	4.1 ± 0.4	3.9 ± 0.5	4.1 ± 0.4	$P < 0.05$	NS
uPro (g/g creatinine)	1.12 ± 0.88	0.60 ± 0.86¶	1.71 ± 2.12†	0.65 ± 0.62‡	$P < 0.01$	† versus ¶ and ‡, $P < 0.05$
uRBC (grade)	4.61 ± 0.99	4.00 ± 1.26	4.27 ± 1.34	3.81 ± 1.26	NS	—
Estimated GFR (mL/min/1.73 m^2)	91.8 ± 24.6	85.7 ± 21.2	81.2 ± 27.8	82.8 ± 23.6	NS	—
C3 (mg/dL)	98.2 ± 13.1	93.4 ± 15.5¶	96.8 ± 11.9	104.0 ± 17.8‡	$P < 0.05$	¶ versus ‡, $P < 0.05$
CH50 (unit/mL)	41.2 ± 4.5	39.2 ± 6.9¶	42.0 ± 5.5	43.8 ± 7.5‡	$P < 0.05$	¶ versus ‡, $P < 0.05$

Values expressed as mean ± SD.
Tx, therapy; BMI, body mass index; GFR, glomerular filtration rate; uPro, urinary protein; uRBC, urinary sediment of red blood cells.
[a]Two-factor factorial ANOVA.

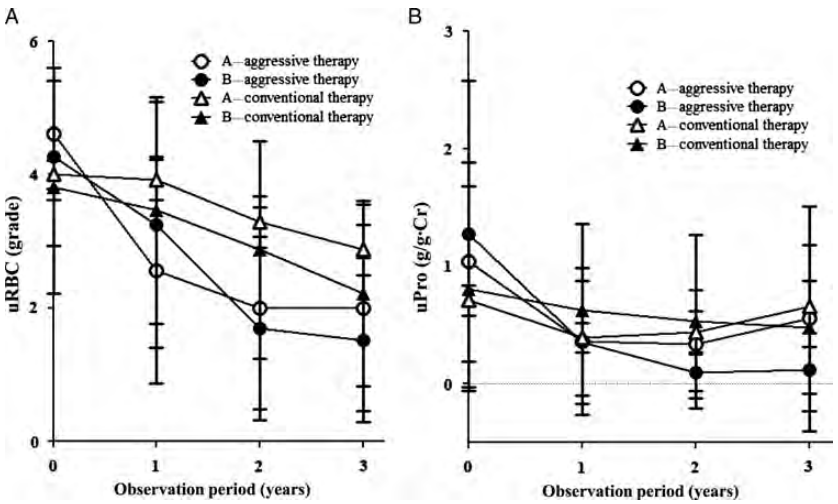

FIGURE 3: Yearly progression of uRBC and uPro in four groups. Statistical differences between four groups were analyzed by two-factor repeated measures ANOVA. (**A**) Sediment grades of uRBC were significantly different in the four groups in categories 'group' ($P < 0.01$) and 'observation period'($P < 0.01$). (**B**) uPro amounts were significantly different between four groups in categories 'group' ($P < 0.01$) and 'years' ($P < 0.01$).

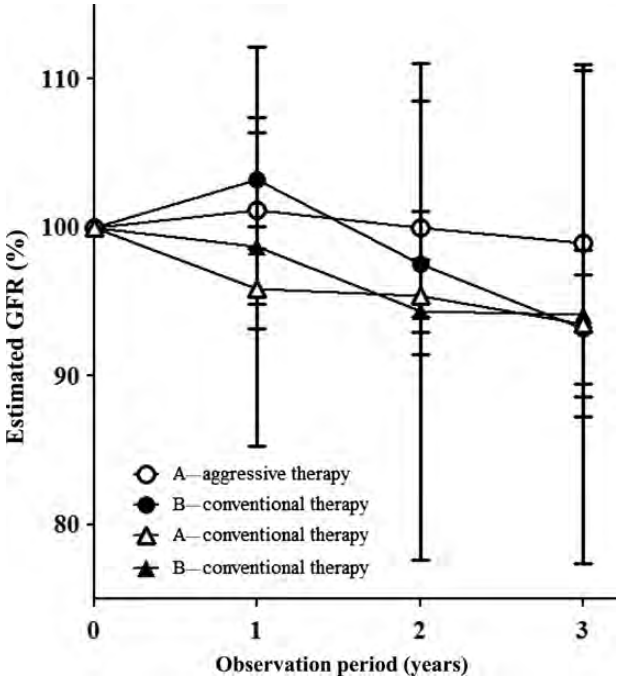

FIGURE 4: Yearly progression of the eGFR in four groups. Statistical differences between four groups were analyzed by two-factor repeated measures ANOVA. The eGFR was significantly different in the four groups in the category 'observation period' ($P < 0.01$).

Because the intraglomerular mesangial matrix is continuous to the extraglomerular mesangial matrix in the juxtaglomerular region, as shown in several tracer injection studies, arteriolar C3 deposits might be derived from paramesangial areas [14, 15]. The origins of C3 located at Bowman's capsules, where the deposit is away from the glomerular hilar portion, have yet to be defined. We have not addressed this question, but speculate that an immune complex that consists of C3 is able to translocate from the paramesangial portion to Bowman's capsule through the adhesive lesion between the glomerular capillaries and Bowman's capsules.

The IF study also revealed that the patterns of glomerular immunoglobulin co-deposition with IgA show no differences between the groups. However, Bowman's capsule depositions of immunoglobulin were well observed in the patients with ex-C3 deposit. On the other hand, EM findings showed more glomerular dense deposits and Bowman's capsule in patients who had extraglomerular deposits of C3. There were significantly more arteriolar dense deposits in patients with ex-C3 deposits. Since our recent ultra-structural study indicated that the presence of electron dense deposits in regions other than the paramesangial areas is associated with histological damage and renal status in IgAN [16], we recognize that the findings of ex-C3 deposits might provide a useful marker for predicting the worse prognosis of IgAN.

Among those in the ex-C3 deposit group, patients who were treated with conventional therapy presented high BMI and high levels of C3 and CH50. We and another investigators have identified associations between hyperinsulinemia, fasting plasma glucose, BMI and serum concentration of C3 [9, 17–19]. On the other hand, complement cascade is activated within the sites of connective tissues and atherosclerotic lesion [20, 21]. This implies that metabolic factor might impact the deposition of C3 into vascular wall components. Since recent studies have indicated that each of the disorders associated with Mets can lead to renal disease, and aggravate the renal function [22, 23], early detection and treatment of overweight or obesity should be an important target in the therapeutic approach of IgAN.

Ton combined with SP points to the possibility of complete remission of IgAN [24]. In our country, uProt >0.5 g/day and eGFR >60 mL/min/1.73 m^2 is a provisionary criterion for Ton combined with SP, but the adequate adaptation of these aggressive therapy has not been clearly defined. From the viewpoint of the reduction of uProt and uRBC, the aggressive therapy was effective whether the patients had ex-C3 deposits or not. Even the conventional therapy also led to amelioration of the degree of uProt and uRBC, and the effect of aggressive therapy was seemingly speedier in the degree of uRBC. After 3 years, the aggressive therapy retarded the eGFR only in patients who had no ex-C3 deposits. Intriguingly, the early phase of aggressive therapy yielded a good initial response in eGFR patients with ex-C3 deposits, but the effectiveness gradually decreased. On the other hand, conventional therapy could not retard the worsening tendency of the eGFR, whether the patients had ex-C3 deposits or not. Except for the patients who had no ex-C3 deposits, a new therapeutic strategy is needed.

In conclusion, we need to pay particular attention to IgAN patients who have ex-C3 deposit and need to develop a new therapeutic approach.

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CONFLICT OF INTEREST STATEMENT

None declared.

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