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Fluctuation of serum C3 levels reflects disease activity and metabolic background in patients with IgA nephropathy

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Abstract

Background: **We focused on the fluctuations of serum C3 levels throughout the clinical course of patients and investigated the relationship between these fluctuations and clinical findings.**

Methods: **IgA nephropathy patients (n = 122) were enrolled in the present study. Serum C3 and other clinical markers were compared at the time of renal biopsy and at last follow-up (6.67 ± 2.07 years). Patients were divided into 3 groups based on serum C3 levels: Group I with first C3 levels below the mean −1 SD, which turned into an increase at last observation; group II with first C3 levels more than the mean +1 SD, which turned into a decrease at last observation; and group III, with first C3 levels more than the mean +1 SD, which turned into an increase at last observation. First and last levels of clinical markers were compared among the 3 groups.**

Results: **Serum C3 levels of the patients whose renal symptoms, including hematuria, proteinuria and estimated glomerular filtration rate (eGFR), were improved, were significantly increased at last observation ($p<0.05$, $p<0.01$, $p<0.01$, respectively). Age, total cholesterol and triglyceride levels in group III were significantly higher than those in group I. Group II showed a significant reduction of urinary protein. Groups I and II maintained renal function, but group III showed a significant deterioration of renal function.**

Conclusions: **The levels and fluctuations of serum C3 might reflect the disease activity and metabolic alteration in patients with IgA nephropathy.**

Key words: *IgA nephropathy, Metabolic syndrome, Serum C3*

Introduction

IgA nephropathy (IgAN) shows the greatest frequency in Asians and whites, and is relatively rare in blacks. The detection of IgAN is often consequent to a chance finding of hematuria and/or proteinuria, but approximately 40% of patients have progressed to end-stage kidney disease (ESKD) about 20 years after a renal biopsy.

Although a definite diagnosis of IgAN can be achieved by renal biopsy, it has some contraindications when the clinical symptoms are scarce (instead of at the time of clinical diagnosis). Previously, we reported that the levels of serum IgA and the IgA/C3 ratio in IgAN patients were significantly higher than those in non-IgAN patients. In the chronic glomerulonephritis (CGN) patients, a serum IgA/C3 ratio of 3.01 or above was an indication of likely IgAN (1-3).

IgAN is not seen as a hypocomplementemic glomerulonephritis. Since serum C3 and C4 levels fluctuate within the normal range, the changes of serum complements have not been focused on in clinical practice. In recent years, it has been proposed that the activation of complement pathways in the renal tissues of IgAN patients primarily mediates the alternative pathway (AP), as well as the lectin pathway (LP) in some patients, and that the consumption of serum C3 occurs in both of these pathways (4-6). Furthermore, serum C3 levels do not increase despite the elevated levels of other complement components in IgAN, suggesting the possibility that the consumption of serum C3 might be increased compared with hepatic C3 production (7). On the other hand, serum C3 levels have been shown to closely reflect metabolic states such as body mass index (BMI), insulin resistance, total cholesterol (TC),

low-density lipoprotein cholesterol (LDL-c) and triglyceride (TG), leading us to undertake research into the metabolic background of patients with IgAN (8, 9).
In the present study, we focused on the fluctuations of serum C3 levels throughout the clinical course and then investigated the clinical significance of the changes of complement components in IgAN patients.

Patients and methods

Patients

Subjects included 122 patients (60 men, 62 women) who underwent a renal biopsy from 1992 to 2004 and who were diagnosed as suffering from IgAN, at the Division of Nephrology, Department of Internal Medicine, Juntendo University Faculty of Medicine. No restrictions were placed on the patients' age, but patients with systemic disease complications, such as systemic lupus erythematosus, diabetes mellitus, Henoch-Schönlein purpura nephritis or liver cirrhosis, were excluded from the study. A comparative investigation of the serum levels of IgA, C3, C4, CH50 and clinical data (hematuria, proteinuria, serum creatinine and estimated glomerular filtration rate [eGFR]) of the patients was conducted at the end of the observation period. Records of treatment such as with corticosteroids or renin-angiotensin system (RAS) inhibitors were also collected. This research was conducted in accordance with the protocol and in compliance with the moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki (1975).

Measurement and comparison of clinical data

Body weight and body height were measured at the time of renal biopsy, and a biochemical analysis, including TC, high-density lipoprotein cholesterol (HDL-c), LDL-c, TG, fasting plasma glucose (FPG) and HbA1c, was conducted at the central laboratory in the Juntendo University Hospital. Serum creatinine (s-Cre) was measured using an enzymatic method; serum IgA, C3 and C4 levels were measured using a turbidimetric immunoassay; and a serum complement hemolytic assay (CH50) was also completed using the relative turbidimetric method as a modification of the Mayer method. The Japanese eGFR equation of eGFR = $194 \times Cr^{-1.094} \times age^{-0.287}$ (×0.739 for females), where eGFR is in ml/min per 1.73 m^2, creatinine (Cr) in mg/dL, and age in years, was used for this study (10).
Patients were divided into groups based on the outcome of proteinuria, hematuria and renal function tests and therapeutic strategies. Serum C3 levels were compared among each group.
Patients were considered as positive for occult blood in urine if they showed 6-10 red blood cells (RBC) / high-power field (HPF) or more in urinary sediments, and they were divided into 3 groups as follows: a persistent hematuria group (16 or more RBCs/HPF) of 23 patients; an improved hematuria group (6-15 RBCs/HPF) of 22 patients; and a resolved hematuria group (1-5 RBCs/HPF) of 77 patients. Patients were considered as positive for proteinuria if they were 1+ or more according to qualitative testing (Tes-Tape). Patients were also divided into the following 3 groups: a persistent proteinuria group of 42 patients; a persistently negative proteinuria group of 40 patients; and a turning-to-negative proteinuria group of 40 patients. Quantitative proteinuria testing was also conducted. For our analysis of renal function, those with an eGFR decrease of 20% or more were included in the deteriorated renal function group (40 patients), and those with an eGFR decrease of less than 20% were included in the maintained renal function group (82 patients).
Furthermore, the patient's background, changes of levels of proteinuria and eGFR were compared by the dynamic pattern of serum C3 levels. All patients were divided into 3 groups based on serum C3 levels as follows: Group I (n = 19) with first C3 levels less than the mean –1 standard deviation (SD) (74.14 mg/dL), which turned into an increase at last observation (mean serum C3 level was increased from 65.56 ± 10.64 mg/dL to 113.58 ± 72.35 mg/dL); group II (n = 5), with first C3 levels more than the mean +1 SD (112.26 mg/dL), which turned into a decrease at last observation (mean serum C3 level was decreased from 125.31 ± 11.23 mg/dL to 104.82 ± 15.63 mg/dL); and group III (n = 11), with first C3 levels more than the mean +1 SD which turned into an increase at last observation (mean serum C3 level was increased from 124.65 ± 14.45 mg/dL to 131.60 ± 16.16 mg/dL). First and last clinical markers were compared among the 3 groups. There was no patient whose first C3 levels were less than the mean –1 SD, and whose C3 levels were found to have decreased at last observation in this study.

Statistical analysis

StatView for Windows, version 5.0 (SAS Institute Inc., Cary, NC, USA) and GraphPad Prism 5J for Windows, version 5.04 (GraphPad, San Diego, CA, USA) were used for the statistical analysis. Statistical analysis was conducted with the *t*-test, and the results were recorded as means ± SD. A p value <0.05 was regarded as significant.

Results

Clinical and laboratory data

The mean age at the time of diagnosis was 32.68 ± 11.50 years, and the mean observation period was 6.66 ± 2.07 years (Tab. I). Microscopic hematuria was observed in all patients at the time of renal biopsy. However, it was noted in only 45 patients at the end of the observation period. By the end of the observation period, 7 patients had ESKD and needed replacement therapy. Twenty-four patients were treated by steroid pulse therapy or orally administered corticosteroids, and 11 patients had a tonsillectomy. An RAS inhibitor (angiotensin-converting enzyme inhibitor or angiotensin receptor blocker) was administered in 50 patients.

Fluctuations of serum IgA and complement component levels in all IgAN patients

Serum IgA levels were decreased from 347.87 ± 120.60 mg/dL to 313.01 ± 102.47 mg/dL (p<0.001), and serum C3 levels were increased from 93.20 ± 19.06 mg/dL to 98.68 ± 16.07 mg/dL (p<0.01). Significant decreases were observed in both serum C4 levels (from 27.42 ± 8.24 mg/dL to 24.38 ± 10.65 mg/dL; p<0.05) and serum CH50 levels (from 43.11 ± 6.80 U/mL to 40.34 ± 8.34 U/mL; p<0.001) despite being within the cutoff range.

Fluctuations of serum C3 levels according to urinary findings

Serum C3 levels in the persistent hematuria group were increased from 90.60 ± 13.55 mg/dL to 94.60 ± 14.41 mg/dL, but were not significantly different. In the improved hematuria group, serum C3 levels were increased from 93.08 ± 20.14 mg/dL to 99.68 ± 21.31 mg/dL, but the increase was not significant. In the resolved hematuria group, serum C3 levels were significantly increased from 93.78 ± 20.04 mg/dL to 98.58 ± 14.91 mg/dL (p<0.05) (Fig. 1).

In the persistent proteinuria group, serum C3 levels were increased from 97.53 ± 16.67 mg/dL to 100.65 ± 17.09 mg/dL, but did not exhibit a significant difference. In the persistently negative proteinuria group, serum C3 levels were increased from 95.12 ± 20.52 mg/dL to 97.16 ± 18.04 mg/dL, but did

TABLE I
CLINICAL AND LABORATORY DATA FOR PATIENTS WITH IgA NEPHROPATHY (n = 122)

	At time of diagnosis	At end of observation period	p Value
Age, years	32.68 ± 11.50	39.36 ± 11.24	
Male/female, no.	60/62	60/62	
Microscopic hematuria, no. (%)	122 (100%)	45 (36.89%)	
Proteinuria, no. (%)	82 (67.21%)	42 (34.43%)	
Proteinuria (g/g cre)	0.67 ± 1.10	0.50 ± 1.37	NS
Serum creatinine, mg/dL	0.80 ± 0.23	1.08 ± 1.15	<0.01
eGFR, ml/min per 1.73 m^2	85.89 ± 22.71	74.17 ± 29.03	<0.001
Systolic blood pressure, mm Hg	117.86 ± 16.36	118.09 ± 13.12	NS
Diastolic blood pressure, mm Hg	68.15 ± 11.46	71.85 ± 11.32	<0.05
Serum IgA, mg/dL (reference range 110-410)	347.87 ± 120.60	313.01 ± 102.47	<0.001
Serum C3, mg/dL (reference range 69-128)	93.20 ± 19.06	98.68 ± 16.07	<0.01
Serum IgA/C3 ratio	3.90 ± 1.59	3.19 ± 1.04	<0.001
Serum C4, mg/dL (reference range 14-36)	27.42 ± 8.24	24.38 ± 10.65	<0.05
Serum CH50, U/mL (reference range 25.0-54.0)	43.11 ± 6.80	40.34 ± 8.34	<0.001

Values are expressed as means ± SD, or number (%) of patients.
cre = creatinine; eGFR = estimated glomerular filtration rate; NS = not significant.

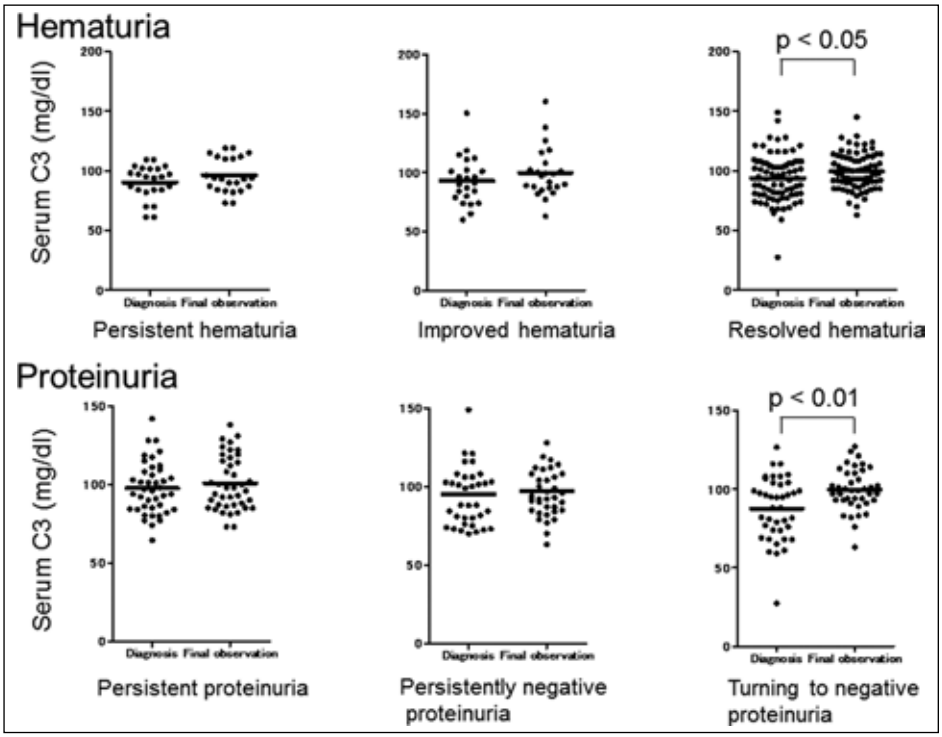

Fig. 1 - Fluctuations of serum C3 levels according to changes of hematuria and proteinuria during entire follow-up period (persistent hematuria, improved hematuria and resolved hematuria, persistent proteinuria, persistently negative proteinuria and turning-to-negative proteinuria).

not exhibit a significant difference. In the turning-to-negative proteinuria group, serum C3 levels were significantly increased from 87.61 ± 19.93 mg/dL to 99.60 ± 13.35 mg/dL ($p<0.01$) (Fig. 1).

Fluctuations of serum C3 levels according to renal function

In the deteriorated renal function group, serum C3 levels were increased from 93.14 ± 17.90 mg/dL to 97.30 ± 18.13 mg/dL, but did not exhibit a significant change. In the maintained renal function group, serum C3 levels were significantly increased from 93.23 ± 19.70 mg/dL to 99.37 ± 15.04 mg/dL ($p<0.01$) (Fig. 2).

Fluctuations of serum C3 levels according to therapeutic strategies

In the corticosteroids administration group (n = 24), serum C3 levels were increased from 96.51 ± 16.61 mg/dL to 97.79 ± 16.52 mg/dL, but did not exhibit a significant difference. In the non-corticosteroids administration group (n = 98), serum C3 levels were significantly increased from 92.38 ± 19.60 mg/dL to 98.90 ± 16.03 mg/dL ($p<0.001$). In the both the RAS inhibitor administration group (n = 50) and the non-RAS inhibitor administration group (n = 40), serum C3 levels did not exhibit a significant difference.

No significant correlation was observed between hematuria and corticosteroids or RAS inhibitor administration. And no correlation was observed between proteinuria and corticosteroid or RAS inhibitor administration.

Comparison of laboratory data among 3 serum C3 fluctuation patterns

Since the increase of serum C3 levels was observed in the resolved hematuria, turning-to-negative proteinuria and maintained renal function groups, we focused on the patients whose serum C3 levels were increased. All patients were divided into 3 groups based on serum C3 levels at the time of diagnosis, and we selected patients whose serum C3 levels increased or decreased.

At the time of diagnosis, the levels of BW, BMI, TC, TG, LDL-c, FPG and HbA1c in group I were lower than those in groups II and III. TC and TG levels in group I were significantly lower than those in group III ($p<0.05$ and $p<0.01$, respectively) (Tab. II). In group I, eGFR was decreased from 87.85 ± 27.52 ml/min per 1.73 m^2 to 84.73 ± 41.14 ml/min per 1.73 m^2, but did not exhibit a significant difference. In group II, eGFR was decreased from 88.24 ± 22.79 ml/min per 1.73 m^2 to 76.08 ± 28.37 ml/min per 1.73 m^2, but did not exhibit a significant difference. In group III, eGFR was significantly decreased ($p<0.05$) from 77.44 ± 12.12 ml/min per 1.73 m^2 to 62.74 ± 14.70 ml/min per 1.73 m^2 ($p<0.05$) (Tab. III).

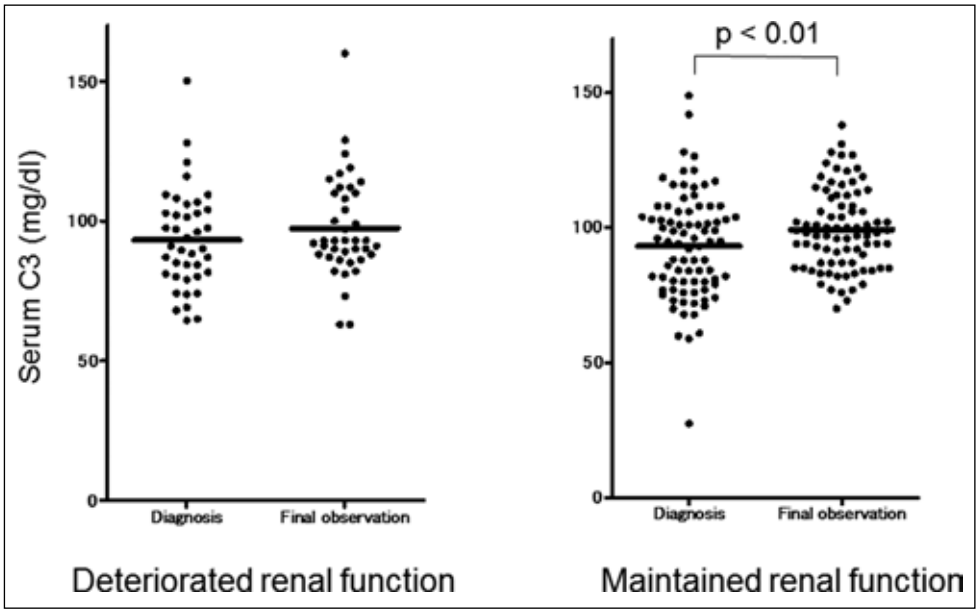

Fig. 2 - Fluctuations of serum C3 levels according to the changes of renal function during entire follow-up period (deteriorated renal function and maintained renal function).

TABLE II
COMPARISON OF LABORATORY DATA BETWEEN CHANGES OF SERUM C3 LEVELS AT TIME OF DIAGNOSIS

	Group I	Group II	Group III	p Value
Number	19	11	5	
Age (years)	32.37 ± 11.37	34.73 ± 12.69	51.20 ± 14.75	<0.05*, <0.01†
BW (kg)	58.45 ± 11.48	62.25± 6.73	65.50 ± 3.54	NS
BMI (kg/m^2)	21.81 ± 3.09	22.98 ± 1.65	23.86 ± 0.20	NS
Total cholesterol (mg/dL)	172.13 ± 31.32	192.36 ± 34.89	221.0 ± 48.46	<0.05†
HDL Cholesterol (mg/dL)	58.57 ± 18.85	46.82 ± 11.68	48.75 ± 8.62	NS
LDL cholesterol (mg/dL)	101.11 ± 30.71	116.09 ± 24.87	122.85 ± 80.11	NS
Triglycerides (mg/dL)	87.64 ±36.46	162.55 ± 106.24	247.00 ± 178.17	<0.05‡, <0.01†
Fasting plasma glucose (mg/dL)	99.67 ± 23.52	92.64 ± 6.71	109.3 ± 12.06	<0.01*
HbA1c (%)	4.85 ± 0.352	4.87 ± 0.20	5.08 ± 0.33	NS

Values are expressed as means ± SD, or number of patients. Group I includes patients with lower serum C3 levels whose levels increased; group II: patients with higher serum C3 levels whose levels decreased; Group III: patients with higher serum C3 levels whose levels increased.
BMI = body mass index; BW = body weight; HbAlc = hemoglobin A1c; HDL = high-density lipoprotein; LDL = low-density lipoprotein; NS = not significant.
*Group II vs. III.
†Group I vs. III.
‡Group I vs. II.

TABLE III
FLUCTUATIONS OF SERUM C3 LEVELS, eGFR AND PROTEINURIA IN GROUPS

	Group I			Group II			Group III		
	At time of diagnosis	At end of observation period	p Value	At time of diagnosis	At end of observation period	p Value	At time of diagnosis	At end of observation period	p Value
Serum C3 (mg/dL)	65.56 ± 10.64	113.58 ± 72.35		125.31 ± 11.23	104.82 ± 15.63		124.65 ± 14.45	131.60 ± 16.16	
eGFR (ml/min per 1.73 m^2)	87.85 ± 27.52	84.73 ± 41.14	NS	88.24 ± 22.79	76.08 ± 28.37	NS	77.44 ± 12.12	62.74 ± 14.70	<0.05
Proteinuria (g/g cre)	0.53 ± 0.66	0.94 ± 2.60	NS	0.63 ± 0.67	0.00 ± 0.00	<0.05	1.28 ± 1.64	0.36 ± 0.80	NS

Values are expressed as means ± SD, or number of patients. Group I includes patients with lower serum C3 levels whose levels increased; group II: patients with higher serum C3 levels whose levels decreased; Group III: patients with higher serum C3 levels whose levels increased.
cre = creatinine; eGFR; estimated glomerular filtration rate; NS = not significant.

Discussion

The immune system is markedly involved in the mechanisms of onset and progression of various kidney diseases. IgAN is the most frequently occurring form of CGN and is characterized by mesangial deposition of IgA. Complement component C3 deposits were observed by immunostaining in the renal biopsy specimens of IgAN patients. Because C1q deposits were not observed, it appeared that complement activation through the alternative pathway was involved in the progression of IgAN (11). However, in recent years, it has been discovered that mannose-binding lectin (MBL) and MBL-associated serine protease 1 are deposited in the glomerular mesangial areas, and it was confirmed that lectin pathway complement activation is involved in IgAN (4, 5, 12-14).

Although it is understood that some local glomerular complement activation occurs, most serum complement levels and complement components stay within the normal clinical range, though only a few reports have been released regarding this (3, 11). According to one report, low levels of serum C3 at the time of renal biopsy are associated with deterioration of renal function in IgAN (15). We have reported that both serum C4 and CH50 levels in IgAN patients were higher than those in healthy subjects (7). Most patients with IgAN showed a chronic clinical course, and the production of complements might be stimulated by persistent inflammation. It was considered that IgAN patients tended to present hypercomplementemia as compared with healthy subjects. However, the fact that no increase was observed in serum C3 levels suggests that C3 might be more strongly consumed than other components by AP and LP activation in IgAN. Then, we focused on the fluctuations of serum C3 levels in this disease.

In this study, variations in serum C3 levels were observed within the normal range, and it was shown that they increased in the groups that had improved urinary findings (hematuria and proteinuria) and maintained renal function. Regarding complement activation, it appears that serum C3 levels were consumed by AP and LP activation, and their activation might decrease the improvement of disease activity. Thus, it also appeared that the continuous consumption of serum C3 was observed in IgAN patients whose disease activity did not improve. C3 might have been associated with immune-complex formation in the fluid phase or in situ.

In the corticosteroid administration group, serum C3 levels were increased but did not exhibit a significant difference. On the other hand, serum C3 levels were significantly increased in the non-corticosteroid administration group. That there were only 24 patients in the corticosteroid administration group or that the antiinflammatory effect of the corticosteroid might not affect the LP and AP, could have affected the results. In other words, LP and AP might bind to the sites of tissue damage, and they might have to be activated (16).

Recently, investigators have identified obesity as an independent risk factor for the onset, aggravated course and

poor outcome of chronic kidney disease (17), and they have found associations between the levels of BMI, FPG and hyperinsulinemia and those of serum C3 (8, 18). Serum C3 is produced by liver, adipocytes and activated macrophages at the inflammation sites. Serum C3 has been shown to be associated with metabolic disorders including obesity, dyslipidemia, insulin resistance, type 2 diabetes and cardiovascular diseases. A possible explanation for this might be enhanced production of C3 by abdominal adipose tissues. We have demonstrated previously that the serum C3 levels showed a strongly positive association with markers of metabolic syndrome such as BMI, TC, TG, LDL and homeostasis model assessment of insulin resistance (9). Furthermore, the patients with IgAN who had extraglomerular deposits of C3 showed the worse prognoses with high BMI and high TG (19). Since a complement cascade is activated within the sites of connective tissues and atherosclerotic lesions, a metabolic factor might impact the deposition of C3 into vascular wall components. In this subsequent study of IgAN, the patients with high serum C3 levels at the time of renal biopsy presented higher TC and TG. Furthermore, eGFR was deteriorated along with an increase of serum C3 levels. However, this group consisted of older patients as compared with other groups. In contrast to them, patients with low serum C3 levels at the time of renal biopsy presented with maintained eGFR. Resolved hematuria, turning-to-negative proteinuria and maintained hematuria groups were increased C3 levels. These fluctuations of C3 level increased from low C3 level may reflect improvement of disease activity. On the other hand, Group III presented higher TC and TG at the time of diagnosis, furthermore eGFR was deteriorated. These reflects metabolic backgrounds. It is considered that treatment of obesity, insulin resistance and dyslipidemia should be an important target in the supportive approach to patients with IgAN with high levels of serum C3. In conclusion, it appears that fluctuations of serum C3 levels exhibited a correlation with disease activity and metabolic background in IgAN patients. We need to give attention not only to the changes of hematuria, proteinuria and renal function but also those of serum C3 levels, in IgAN patients.

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Institutional Review Board (IRB)/Ethics Committee approval was obtained on April 7, 2009.

This research was conducted in accordance with the protocol and in compliance with the moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki (1975).

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