表 5　紫斑病性腎炎の組織分類(ISKDC 分類)，臨床像と予後

ISKDC 分類	臨床像	予後 20 年後 末期腎不全
Ⅰ. 微小変化	血尿のみ	0 %
Ⅱ. メサンギウム細胞増殖のみ	血尿・蛋白尿	16 %
Ⅲ. 半月体・分節性病変を示す 糸球体が 50 %未満	血尿・蛋白尿, 急性腎炎症候群, ネフローゼ症候群	24 %
Ⅳ. 半月体・分節性病変を示す 糸球体が 50 %≦　<70 %	血尿・蛋白尿, 急性腎炎症候群, ネフローゼ症候群	55 %
Ⅴ. 半月体・分節性病変を示す 糸球体が 70 %以上	急速進行性腎炎症候群 血尿・蛋白尿, 急性腎炎症候群, ネフローゼ症候群，急速進行性 腎炎症候群	67 %
Ⅵ. 膜性増殖性腎炎様		

表 6　巣状分節性糸球体硬化症の組織分類

亜型	該当項目	除外項目
非特異型亜型 FSGS(NOS)variant	メサンギウム基質が増加し糸球体毛細血管係蹄を分節状に閉塞している糸球体が少なくとも 1 つある。 分節状に糸球体毛細血管係蹄が虚脱しているが，足細胞の増殖を合併していない。	門部周囲型，細胞型，糸球体尖型，虚脱型の亜型を除外
門部周囲型亜型 Perihilar variant	門部周囲に硝子化を伴う糸球体が少なくとも 1 つある(分節状硬化を伴う場合と伴わない場合)。 分節状病変を伴う糸球体の 50 %以上が門部周囲の硝子化・硬化を伴っている。	細胞型，糸球体尖型，虚脱型の亜型を除外
細胞型亜型 Cellular variant	分節状の管内型細胞増殖があり，糸球体毛細血管係蹄を閉塞している糸球体が少なくとも 1 つある。泡沫細胞や核破壊を伴うことがある。	糸球体尖型，虚脱型の亜型を除外
糸球体尖型亜型 Tip variant	糸球体尖部(近位尿細管に接する糸球体毛細血管係蹄の外側 25 %)に分節状病変を伴う糸球体が少なくとも 1 つある。 上記の病変を判定するときには尿管極の確認が必要であり，その病変は，尿管腔か尿管極の部位で，足細胞がボウマン嚢上皮か尿細管上皮と癒着しているか合流している。糸球体尖部病変は細胞性か硬化性である。	虚脱型の亜型を除外
虚脱型亜型 Collapsing variant	分節状あるいは球状に虚脱し，足細胞の肥大と増殖を伴っている糸球体が少なくとも 1 つある。	なし

第 1 回バンフ会議にて移植腎拒絶反応の病理組織学的診断基準が提案され，臨床的に有用な分類として国際的に広く使用されるようになった。1997 年の第 4 回会議で討議され 1999 年に発表された Banff 分類(1997)が現在の大きな骨組みとなっている[24]。2003 年には，抗ドナー抗体による抗体介入型拒絶反応(antibody-mediated rejection：AMR)の概念が追加された。続いて 2005 年の第 9 回会議において Banff 05 が発表され，Banff 97 以来，慢性拒絶反応(chronic/sclerosing allograft nephropathy：CAN)とされていた呼称を廃止し，免疫学的機序によらない間質線維化・尿細管萎縮(interstitial fibrosis and tubular atrophy：IF/TA)と，免疫学的機序によらないが，病因が形態学的に推定できるその他の急性・慢性病変が独立し，さらに，免疫学的機序による慢性病変を，慢性活動性抗体介入型拒絶と慢性活動性 T 細胞介入型拒絶に分類して新しい改訂がなされた[25]。さらに，2007 年の第 10 回会議において，抗体介入型拒絶の形態学的証拠となる C4d の沈着と傍尿細管毛細血管炎に対する客観的評価基準が提示された(**表 7**)。

表 7 移植拒絶腎における Banff 分類(2007)

カテゴリー 1：正常 Normal
カテゴリー 2：抗体介入型拒絶
1）ptc に C4d 陽性であるが，急性拒絶の形態的証拠がない。
2）急性抗体介入型拒絶
ptc に C4d が陽性で，循環する抗ドナー抗体が陽性，そして，以下の急性組織障害を伴う。
タイプ type(重症度 grade)
Ⅰ．急性尿細管壊死様，軽微な炎症所見
Ⅱ．毛細血管内への炎症細胞(好中球，単核球)集積または血栓
Ⅲ．v3 相当の動脈病変
3）慢性活動性抗体介入型拒絶
ptc に C4d が陽性で，循環する抗ドナー抗体陽性，そして，以下の慢性組織障害を伴う。
糸球体基底膜二重化，傍尿細管毛細血管基底膜の多層化，間質線維化/尿細管萎縮，動脈内膜の線維性肥厚の1つあるいは複数を認める。
カテゴリー 3：境界型病変
T リンパ球関連型急性拒絶反応が"疑わしい"状態
カテゴリー 4：T 細胞介入型拒絶
1）急性 T 細胞介入型拒絶
タイプ type(重症度 grade)
ⅠA：腎実質の 25 %以上を占める間質への炎症細胞浸潤(i2，i3)と中等度の尿細管炎(t2)
ⅠB：腎実質の 25 %以上を占める間質への炎症細胞浸潤(i2，i3)と高度な尿細管炎(t3)
ⅡA：間質細胞浸潤と，軽度から中等度の動脈内膜炎(v1)
ⅡB：血管腔の 25 %以上を占める中等度から高度な動脈内膜炎(v2)
Ⅲ：全層性の動脈炎あるいは中膜平滑筋細胞のフィブリノイド壊死や変性を認め，リンパ球浸潤を伴う(v3)。
2）慢性活動性 T 細胞介入型拒絶
慢性移植血管症(単核球の炎症細胞浸潤を伴う動脈内膜の線維性肥厚と新生内膜の形成)
カテゴリー 5：間質線維化と尿細管萎縮(特別の病因を持たない)
非特異的な血管や糸球体硬化を伴うが，傷害度は尿細管間質の程度で判断される。
程度 Grade
Ⅰ：皮質間質の 25 %以下を占める軽度の間質線維化と尿細管萎縮
Ⅱ：皮質間質の 26～50 %を占める中等度の間質線維化と尿細管萎縮
Ⅲ：皮質間質の 50 %以上を占める高度の間質線維化と尿細管萎縮
(急性あるいは慢性病変で，g あるいは cg あるいは cv を含むが，どのタイプの拒絶反応と混在してもよい。)

6）急速進行性糸球体腎炎(ANCA 関連腎症)

この疾患群は，小血管炎群に位置し，免疫複合体沈着が少量かあるいは沈着のない pauci-immune 型糸球体腎炎といわれ，Wegener 肉芽腫症，顕微鏡的多発血管炎，Churg-Strauss 症候群が含まれる。フィブリノイド壊死性動脈炎，びまん性壊死性半月体形成性糸球体腎炎，尿細管周囲毛細血管炎を特徴とする。腎機能に関する重症度分類には，腎生検による病理組織学的所見が有用である。急速進行性腎炎症候群診療指針(2002年)においては，半月体形成率，半月体病期，腎間質病変の程度をそれぞれスコア化し，そのスコアの総和から病理組織学的病期分類に従い，急速進行性糸球体腎炎を 3 群の病期に分類して腎生存率を比較している(**表 8**)[26]。しかし，この分類は予後を予測する病期分類であり，これに基づいて治療方針が選択できる分

表 8 ANCA 関連腎炎の病理組織所見スコアと病理組織学的病期

A)病理組織所見スコア

病理組織所見スコア	半月体形成率*	半月体病期	尿細管・間質病変
0			
1	<30 %	細胞性	なし
2	30～50	線維細胞性	軽度
3	50～80	線維性	中等度
4	>80 %		高度

*係蹄壊死・フィブリノイド壊死を含む。

B）病理組織学的病期分類

病理組織学的病期	総スコア	症例数	腎生存率(%)		
			1 年	2 年	3 年
Stage Ⅰ	2～6	207	83.5	81.7	77.8
Stage Ⅱ	7～8	214	67	63.3	58
Stage Ⅲ	9～10	73	54.3	54.3	50.7

類ではなかった。これまでにEUVAS分類[27]と重松分類[28]が発表され，それらを改良して病変の定量的把握のためのスコア・シートが提唱されている。これまでに治療方針の適正に関して明確なエビデンスに基づく組織分類がなく，今後の課題である[29]。

7）糖尿病性腎症

糖尿病性腎症の病理分類は古くから，結節性硬化型亜型(nodular sclerosis variant)とびまん性硬化型亜型(diffuse sclerosis variant)に分けられ，前者は，メサンギウム基質の結節状拡大，いわゆるKimmelstiel-Wilson nodule(KW結節)を特徴とし，後者は，メサンギウム基質のびまん性拡大とメサンギウム細胞の増生を特徴とする。滲出性病変はその両者に出現するが，結節性硬化型亜型のほうにその出現頻度が高い。近年，糖尿病性腎症に関する腎生検が増え，その糸球体病変の初期像から進行像までのスペクトラムが追跡できるようになった。さらに，小・細動脈病変の動脈硬化病変も予後や治療内容に大きく影響するといわれている。治療方針に役立つ腎組織分類の提唱が今後望まれる。

おわりに

腎病理診断標準化への取り組みについて，その必要性と標準化の実際，そして，組織分類に至る過程を概説し，組織分類がなされている腎疾患についてのup dateな紹介をした。標準化への重要な点は，再現性，互換性，実証性の出発点となることである。腎生検病理診断の標準化の実現により，治療の標準化と腎不全への進展の阻止に腎生検病理が役立つことを望む。

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ORIGINAL ARTICLE

Pathological influence of obesity on renal structural changes in chronic kidney disease

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Abstract

Background Role of obesity in renal pathological and structural changes remains poorly investigated, and this study was designed to examine the pathological effects of obesity on renal structural components in patients with chronic kidney diseases (CKD).

Methods The study subjects were obese (body mass index, BMI $\geq$ 25 kg/m^2) patients with nonglomerulonephritis (non-GN, $n = 26$), IgA nephropathy (IgAN, $n = 19$), benign nephrosclerosis (BNS, $n = 15$), and thin basement membrane disease (TMD, $n = 6$), and 65 nonobese controls ($n = 20$, 20, 10, and 15, respectively). Patients were evaluated for glomerular lesions (mesangial proliferation and focal segmental/global glomerulosclerosis), glomerular size, and thickness of glomerular basement membrane (GBM).

Results Urinary protein was higher in obese non-GN, IgAN, and BNS groups than in the respective controls. Focal segmental glomerulosclerosis (FSGS) lesions were noted in all obesity groups. The glomeruli were larger in size in obese than in nonobese patients of the non-GN and IgAN groups. The glomeruli of nonobese TMD and BNS patients were significantly larger in size than those of nonobese non-GN patients. GBM were thicker in obese than in nonobese patients irrespective of types of glomerular diseases, but only significantly so in non-GN and BNS groups.

Conclusion In non-GN, IgAN, and BNS, obesity worsens proteinuria and is associated with structural changes such as glomerulomegaly and GBM thickening, similar to changes observed in obesity-related nephropathy. Obesity seems to worsen the renopathological state in CKD.

Keywords Obesity · Chronic kidney disease · IgA nephropathy · Pathology · Electron microscopy · Glomerular basement membrane

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Introduction

Several studies have reported recently about the association between obesity and renal dysfunction [1–5]. Obesity should be placed high on the list of potentially preventable causes of chronic kidney disease (CKD) [6]. Clinical features of obese subjects without systemic disorders or apparent renal disorders, so-called obesity-related glomerulopathy (ORG), include slowly progressive proteinuria. Various structural changes, including glomerulomegaly, focal segmental glomerulosclerosis (FSGS), and thickening of the glomerular basement membrane (GBM) can be seen in biopsy sections of ORG [2, 3, 7].

Glomerulomegaly is also observed in the kidneys of patients with diabetic nephropathy and hypertensive nephropathies [8–10]. The increase in glomerular volume is usually the consequence of glomerular hyperfiltration, and can be associated with expansion of the capillary loops [1, 11]. Obesity can accelerate renal dysfunction in patients with glomerulonephritis such as IgA nephropathy (IgAN). In fact, obese patients with IgAN exhibit more severe pathological changes and proteinuria [4]. However, there is only little information on the histopathological findings, especially ultrastructural changes, in obese patients with CKD.

The aim of this study was to examine the clinical and pathological effects of obesity in three types of CKD: IgAN, benign nephrosclerosis (BNS), and thin basement membrane disease (TMD), and to compare them with those seen in ORG.

Methods

Patients and clinical parameters

Clinical and pathological information available for 3,908 renal biopsy samples collected from 1997 to 2007 at the Department of Pathology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan, was reviewed. The common feature was samples from patients aged older than 15 years of age at time of tissue harvest. The renal biopsies of all patients were examined by light microscopy (LM), electron microscopy (EM), and immunofluorescence (IF). The intended cases were selected from four patient groups: nonglomerulonephritis (non-GN), IgAN, BNS, and TMD. Patients in the non-GN group had no evidence of glomerulonephritis confirmed by LM, EM, and IF, and no systemic diseases. We regarded obese patients among the non-GN as ORG. IgAN represented mild mesangial proliferation as determined by LM. BNS was defined as renal changes associated with essential hypertension. TMD patients were those who had no clinical evidence of renal diseases except for micro/macrohematuria and histopathologically showed thin GBM (<250 nm) involving at least in 50% of GBM [12]. Patients with edema (e.g., nephrotic syndrome) and systemic disorders, such as diabetes mellitus, lupus nephritis, were excluded. The exclusion criteria of diabetes mellitus were titer of fasting blood glucose (FBG) lower than 120 mg/dL and no glucosuria. Obesity was defined as body mass index (BMI) $\geq$25 kg/m^2, calculated as body weight (kg)/height^2 (m^2). According to the definition by the Japan Society for the Study of Obesity [13], classification was assigned as follows; class 1 obesity, BMI $\geq$ 25 but <30 kg/m^2; class 2 obesity, BMI $\geq$ 30 but <35 kg/m^2; class 3 obesity, BMI $\geq$ 35 but <40 kg/m^2; class 4 obesity, BMI $\geq$ 40 kg/m^2. In this study, obese patients were divided into two obesity groups; mild obesity (class 1 obesity) and severe obesity (class 2, 3 and 4 obesity). Age-matched nonobese (BMI < 25 kg/m^2) patients were also examined as controls in each group. Laboratory data were selected at time of renal biopsy. The study was approved by the Ethics Review Committee of Nagasaki University Graduate School of Biomedical Sciences.

Histological analysis

Histopathological lesions of the glomeruli were evaluated on LM sections stained with periodic acid-Schiff (PAS) and periodic acid silver-methenamin (PAM). Histopathological evaluation was performed on the index of glomerular lesion (IGL), which was modified by the methods of Stahl et al. [14]. IGL was evaluated by both proliferative and sclerotic changes. In addition, glomerular sclerosis was also scored as follows. Score of focal segmental glomerulosclerotic lesion (FSGS lesion score, %) was calculated as percentage of FSGS lesion. Global sclerotic glomeruli score (SG score, %) was calculated as percentage of global sclerotic glomeruli.

Measurement of glomerular diameter was conducted under LM and measured by WinRoof version 5.03 (Mitani Corp, Tokyo, Japan). Mean glomerular size was calculated from average of largest five glomerular diameters (μm) per case to approximate glomerular equatorial section^2. The size (μm^2) was calculated as [(diameter/2)^2 × 3.14].

EM photographs at original magnification of 3,000× were used to determine the thickness of the GBM using the technique described by Osawa et al. [15].

Statistical analysis

All data were expressed as mean ± standard deviation (SD). Differences were performed by one-way analysis of variance (ANOVA), unpaired Student's t test, and Fisher's exact test. Statistical significance was defined as $P < 0.05$. All statistical analyses were performed using SPSS 16.0J software for Windows (SPSS Inc., Chicago, IL).

Results

Clinical features

Table 1 summarizes the clinical and laboratory findings of the patients. Urinary protein was greater in obese patients of the non-GN, IgAN and BNS groups than in nonobese group, respectively, but severity of proteinuria did not correlate with extent of obesity. None of the TMD patients had severe

Table 1 Clinical and laboratory findings in obese and nonobese patients

	Non-GN			IgAN			BNS			TMD	
	Nonobese	Mild obesity	Severe obesity	Nonobese	Mild obesity	Severe obesity	Nonobese	Mild obesity	Severe obesity	Nonobese	Mild obesity
Male/female	14/6	10/6	7/3	8/12	7/4	5/3	5/5	7/2	4/2	8/7	3/3
Age (years)	22.5 ± 8.5	44.5 ± 14.9[a]	32.0 ± 12.3[d]	29.0 ± 12.4	33.8 ± 5.5	34.5 ± 7.8	55.0 ± 7.1	50.7 ± 13.3	46.3 ± 15.6	37.9 ± 11.6	44.8 ± 13.3
BMI (kg/m^2)	20.2 ± 01.8	27.3 ± 1.4[a]	35.3 ± 5.4[a,c]	21.6 ± 1.5	26.4 ± 1.4[a]	36.9 ± 3.9[a,c]	23.3 ± 1.2	27.6 ± 1.0[a]	33.4 ± 2.6[a,c]	19.9 ± 2.2	27.4 ± 1.9[a]
SBP (mmHg)	113 ± 11	122 ± 13	129 ± 14[a]	114 ± 9	124 ± 16	128 ± 18	140 ± 22	142 ± 22	136 ± 12	114 ± 12	126 ± 9[b]
DBP (mmHg)	61 ± 10	79 ± 7[a]	75 ± 11[a]	68 ± 11	74 ± 13	80 ± 11	86 ± 11	81 ± 15	86 ± 17	68 ± 9	79 ± 6[b]
UP (g/24-h)	0.2 ± 0.2	0.9 ± 1.2[b]	0.3 ± 0.2	0.5 ± 0.7	0.3 ± 0.2	1.5 ± 0.9[a,c]	0.3 ± 0.2	1.8 ± 1.3[a]	0.8 ± 0.7	0.1 ± 0.1	0.3 ± 0.3
SCr (mg/dL)	0.8 ± 0.2	0.8 ± 0.2	0.7 ± 0.2	0.8 ± 0.2	0.8 ± 0.2	0.8 ± 0.1	0.9 ± 0.4	0.9 ± 0.1	1.0 ± 0.2	0.7 ± 0.1	0.7 ± 0.2
BUN (mg/dL)	12.7 ± 2.2	14.6 ± 4.1	11.0 ± 3.2[d]	12.7 ± 2.9	13.5 ± 3.2	13.2 ± 4.5	16.1 ± 4.9	15.4 ± 3.2	17.7 ± 6.6	13.3 ± 2.6	14.0 ± 4.8
TP (g/dL)	7.1 ± 0.5	7.1 ± 0.6	7.2 ± 0.4	7.0 ± 0.6	7.1 ± 0.5	7.0 ± 0.4	7.2 ± 0.5	6.9 ± 0.6	7.4 ± 0.5	7.0 ± 0.4	6.7 ± 0.4
Alb (g/dL)	4.7 ± 0.4	4.4 ± 0.5	4.5 ± 0.2	4.2 ± 0.4	4.3 ± 0.2	4.0 ± 0.4	4.8 ± 1.1	4.3 ± 0.4	4.3 ± 0.5	4.4 ± 0.3	4.3 ± 0.4
TG (mg/dL)	83 ± 50	187 ± 117[b]	269 ± 151[a]	112 ± 66	146 ± 64	245 ± 125[a]	156 ± 80	173 ± 81	206 ± 69	95 ± 33	155 ± 52[b]
TC (mg/dL)	158 ± 32	219 ± 32[a]	215 ± 42[a]	198 ± 39	203 ± 26	205 ± 27	226 ± 40	215 ± 40	182 ± 21	187 ± 37	201 ± 25
FBG (mg/dL)	86 ± 7	93 ± 12	94 ± 11	88 ± 6	99 ± 27	94 ± 13	100 ± 9	102 ± 3	95 ± 10	89 ± 8	96 ± 12
eGFR (mL/min/1.73 m^2)	93 ± 20	79 ± 18[b]	87 ± 18	78 ± 15	77 ± 23	73 ± 16	67 ± 26	70 ± 31	60 ± 20	90 ± 16	83 ± 14
No. of eGFR <60 (%)	0	2 (11.1)	1(10)	2 (10)	2 (22.2)	2 (25)	4 (40)	5 (55.6)	3 (50)	0	0

Data are mean ± SD

Non-GN nonglomerulonephritis, *IgAN* IgA nephropathy, *BNS* benign nephrosclerosis, *TMD* thin basement membrane disease, *BMI* body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *UP* 24-h urine protein, *SCr* serum creatinine, *BUN* blood urea nitrogen, *TP* total protein, *Alb* serum albumin, *TG* triglyceride, *TC* total cholesterol, *FBG* fasting blood glucose, *eGFR* estimated glomerular filtration rate

[a] $P < 0.01$ versus nonobese in each group

[b] $P < 0.05$ versus nonobese in each group

[c] $P < 0.01$ severe obesity versus mild obesity in each group

[d] $P < 0.05$ severe-obesity non-GN versus mild-obesity non-GN

Table 2 Renal histopathological findings in non-GN and IgAN

	Non-GN			IgAN		
	Nonobese	Mild obesity	Severe obesity	Nonobese	Mild obesity	Severe obesity
n	20	16	10	20	11	8
No. of glomeruli	26 ± 15	12 ± 9[a]	22 ± 12	24 ± 16	19 ± 12	16 ± 9
Index of glomerular lesion (IGL)	1.2 ± 0.1	1.3 ± 0.4	1.6 ± 0.6[b]	2.0 ± 0.4	1.9 ± 0.5	2.8 ± 0.8[a,c]
Focal segmental glomerulosclerosis lesion						
Patients with FSGS lesion	0 (0%)*	0 (0%)*	2 (20%)*	5 (25%)	3 (27%)	3 (38%)
No. of glomeruli with FSGS lesion	0	0	1.5 ± 0.5[a,c]	1.2 ± 0.4	2.3 ± 1.5	3.0 ± 1.2
Score of FSGS lesion	0	0	6.6 ± 1.1[a,c]	11.6 ± 12.8	10.2 ± 7.2	24.3 ± 17.7
Sclerotic glomeruli						
Patients with sclerotic glomeruli	2 (10%)*	3 (19%)*	5 (50%)*	10 (50%)	4 (36%)	8 (100%)
No. of sclerotic glomeruli	1.0 ± 0.0	2.0 ± 2.0	2.0 ± 1.7	2.4 ± 2.1	1.5 ± 0.6	3.1 ± 3.0
SG score	3.9 ± 2.8	10.4 ± 9.1	12.9 ± 12.4	11.9 ± 12.2	10.6 ± 5.8	23.5 ± 21.3

Data are mean ± SD

Non-GN nonglomerulonephritis, *IgAN* IgA nephropathy, *Score of FSGS lesion* focal segmental glomerulosclerosis lesion scores, *SG score* global sclerotic glomeruli and/or hyalinized glomeruli score, score of FSGS lesion, and SG score were calculated in specimens with lesions

* $P < 0.05$ by Fisher's exact test

[a] $P < 0.01$ versus nonobese in each group

[b] $P < 0.05$ versus nonobese in each group

[c] $P < 0.01$ severe obesity versus mild obesity in each group

Table 3 Renal histopathological findings in BNS and TMD

	BNS			TMD	
	Nonobese	Mild obesity	Severe obesity	Nonobese	Mild obesity
n	10	9	6	15	6
No. of glomeruli	14 ± 7	10 ± 4	19 ± 11	21 ± 13	18 ± 14
Index of glomerular lesion (IGL)	2.4 ± 0.9	2.8 ± 0.9	2.0 ± 0.6	1.4 ± 0.4	1.5 ± 0.4
Focal segmental glomerulosclerosis lesion					
Patients with FSGS lesion	1 (10%)	0 (0%)	1 (17%)	0 (0%)	1 (17%)
No. of glomeruli with FSGS lesion	1	0	1	0	1
Score of FSGS lesion	33.3	0	2.6	0	5.3
Sclerotic glomeruli					
Patients with sclerotic glomeruli	10 (100%)	8 (89%)	5 (83%)	6 (40%)	2 (33%)
No. of sclerotic glomeruli	2.8 ± 3.0	2.9 ± 2.5	4.0 ± 4.5	2.2 ± 1.2	2.0 ± 0.0
SG score	21.7 ± 16.4	33.2 ± 18.0	16.6 ± 10.4	10.7 ± 7.6	20.2 ± 6.8

Data are mean ± SD

BNS benign nephrosclerosis, *TMD* thin basement membrane disease, *Score of FSGS lesion* focal segmental glomerulosclerosis lesion scores, *SG score* global sclerotic glomeruli and/or hyalinized glomeruli score, score of FSGS lesion, and SG score were calculated in specimens with lesions

obesity (BMI $\geq$ 30 kg/m^2). Titers of serum creatinine and blood urea nitrogen (BUN) were not significantly different between obese and nonobese groups. In non-GN group, blood pressure, triglyceride, and total cholesterol were significantly higher in obese groups than nonobese group. In IgAN and TMD, triglyceride was also significantly higher in obese patients. In TMD, blood pressure was higher in obese group than in nonobese group. Estimated glomerular filtration rate (eGFR) was lower in obese than in nonobese patients in non-GN group, but statistically significant difference was present only between nonobese and mildly obese patients. No difference was noted in eGFR level among nonobese and obese patients in IgAN, BNS or TMD groups. Percentage of cases with eGFR level lower than 60 mL/min/1.73 m^2 was higher in obese than in nonobese patients in IgAN and BNS, but not statistically significantly so.

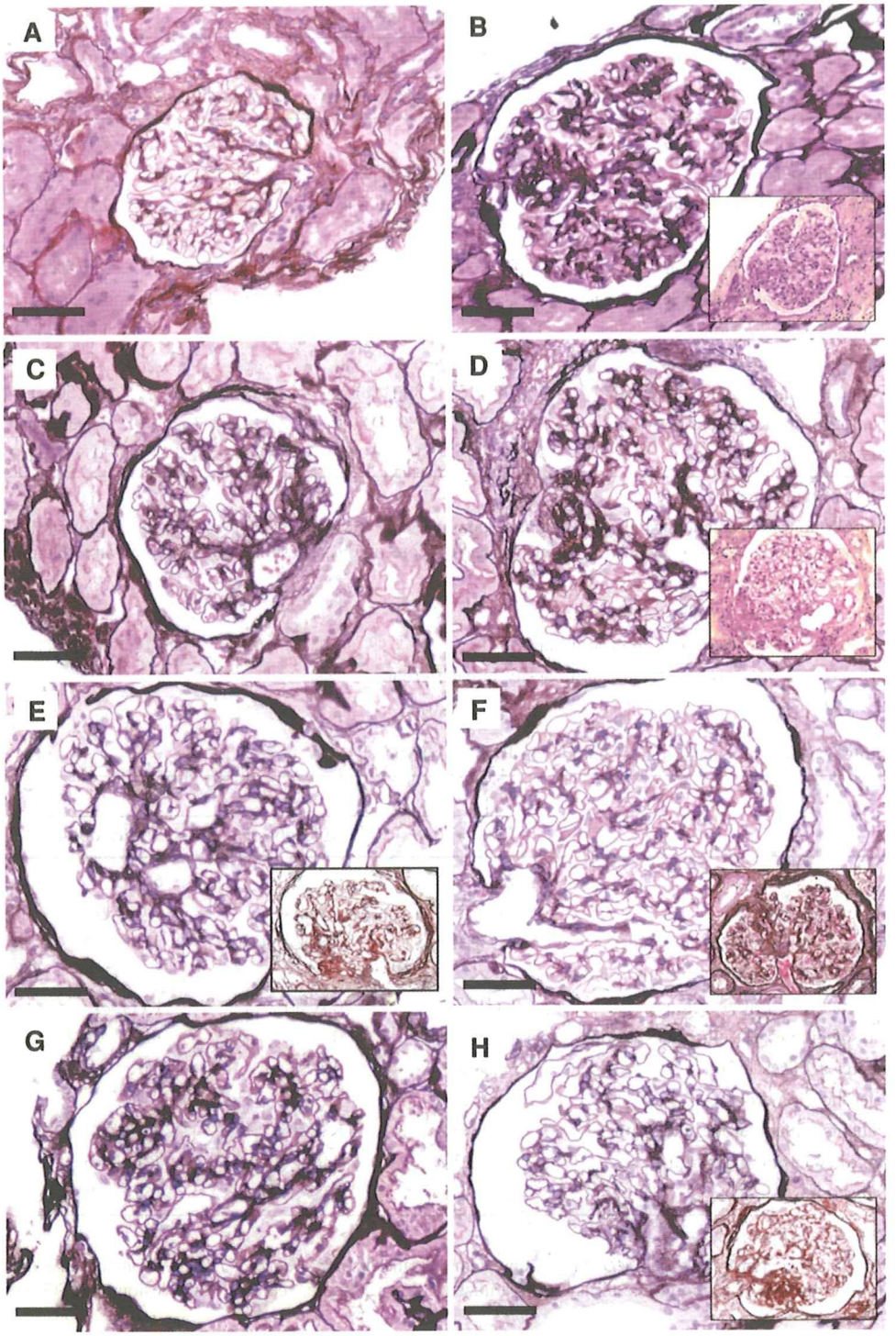

Fig. 1 Representative examples of histopathological findings in nonobese (**a**, **c**, **e**, **g**) and obese (**b**, **d**, **f**, **h**) patients. **a**, **b** Nonglomerulonephritis, **c**, **d** IgA nephropathy, **e**, **f** benign nephrosclerosis, **g**, **h** thin basement membrane disease. Inset of pictures **b** and **d**, showing FSGS lesions, were each serial section stained with PAS. FSGS lesions are also shown in **e**, **f**, and **h** in inset of each group; PAM stain. *Scale bars* 50 μm

Histopathological findings

Tables 2 and 3 show the scores assigned to histological features of nonobese and obese groups.

Non-GN group: FSGS lesions were not seen in nonobese (Fig. 1a) or mild obesity groups. Two (20%) patients of the severe obesity group showed FSGS lesion (Fig. 1b). Scores of IGL and FSGS lesion were higher in severe-obesity group than in nonobese and mild-obesity groups (Table 2).

IgAN group: The IGL was significantly higher in severe-obesity group than nonobese and mild-obesity group. There were no differences in score of FSGS lesion and SG scores among nonobese and obese groups. FSGS lesion and SG were observed in IgAN (Fig. 1d; Table 2).

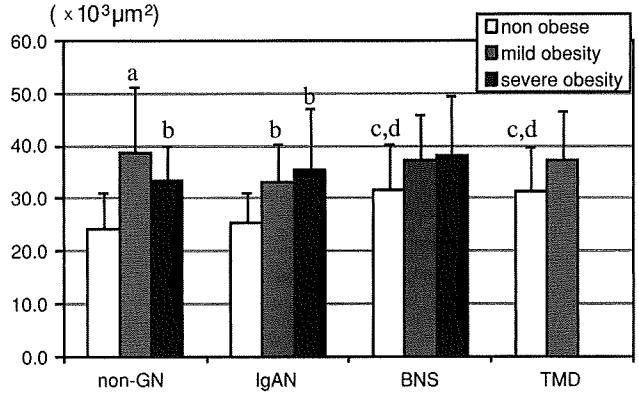

Fig. 2 Glomerular size in nonobese, mild-, and severe-obesity groups with nonglomerulonephritis (non-GN), IgA nephropathy (IgAN), benign nephrosclerosis (BNS), and thin basement membrane disease (TMD). *Bars* are mean ± SD, *a* $P < 0.01$ versus nonobese non-GN group; *b* $P < 0.05$ versus nonobese patients in each group; *c* $P < 0.01$ nonobese BNS or nonobese TMD versus nonobese non-GN group; *d* $P < 0.05$ nonobese BNS or nonobese TMD versus nonobese IgAN group

This result might reflect the characteristic pathological feature of IgAN.

BNS group: The IGL, score of FSGS lesion, and SG scores were not different between obese and nonobese groups. Although incidence of SG was high in patients with BNS, FSGS lesion was noted in only one nonobese patient and one severely obese patient (Fig. 1e, f; Table 3).

TMD group: None of the patients of the TMD group had severe obesity. In TMD group, there were no significant differences in IGL, score of FSGS lesion or SG scores between obese and nonobese groups (Table 3). Only one obese patient had FSGS lesion and another one had two sclerotic glomeruli.

Glomerular size

Glomerular sizes of all groups are shown in Fig. 2. In non-GN, the glomerular size of mild and severe obesity groups was significantly larger than that of the nonobese group. The proportion of cases with large glomeruli tended to be higher in mild-obesity than severe-obesity group, although the difference was not statistically significant. In IgAN, glomerular size was significantly greater in obese patients than in nonobese patients, and correlated with severity of obesity (Fig. 1c, d). In BNS group, glomerular size was larger in obese than in nonobese groups, but the difference was not statistically significant. On the other hand, glomerular size was significantly greater in nonobese BNS than nonobese non-GN subjects (Fig. 2; Table 3). Obesity was categorized as mild in all patients of the TMD group. Glomerular size of TMD was slightly, but not statistically significantly, larger in obese than in nonobese patients. Comparison of nonobese patients showed that glomerular size was significantly greater in TMD than in non-GN subjects, in spite of compatible blood pressure levels (Figs. 1g, h, 2).

Thickness of glomerular basement membrane

The results of measurement of GBM by EM observation are shown in Fig. 4. GBM was thicker in obese patients than non-GN, and varied proportionately with severity of obesity (Figs. 3a, 4) ($P < 0.05$, nonobese versus severe obesity). In IgAN, the GBM was slightly thicker in mild-obesity group than nonobese group, though the difference was not statistically significant. Basement membrane in patients with IgAN was thin in some areas, in association with thick GBM (Fig. 3c, d). In BNS, GBM was significantly ticker in mild-obesity group than in nonobese group ($P < 0.05$) (Fig. 3g, h). In TMD, there was no significant difference in GBM thickness between obese and nonobese groups (Fig. 3g, h).

Discussion

In the present study, to observe the influence of obesity in patients with CKD, we selected patients with mild structural changes: mild forms of IgAN, BNS, and TMD. The obese patients of the nonglomerulonephritis group in our study had ORG. To our knowledge, this is the first report of the pathological influence of obesity on CKD, focusing on GBM thickness and obesity level.

Histopathological analysis identified glomerulomegaly and FSGS lesion in ORG patients, thus confirming previous findings [4]. In particular, FSGS lesion was observed in patients with severe obesity, and IGL score varied according to severity of obesity. Thickness of GBM was proportionate to severity of obesity in ORG. Kambham et al. [2] reported focal GBM thickening in ORG patients. A recent ultrastructural study of ORG showed widening of the foot processes and enlargement of podocytes in extremely obese patients, in addition to marked thickening of GBM [11]. The mechanisms of obesity-induced glomerulomegaly and GBM thickening are not completely understood. Obesity-associated humoral factors such as hyperinsulinemia and hyperleptinemia might increase transforming growth factor-β, vascular endothelial growth factor, and angiotensin II [1, 2], stimulating overproduction of extracellular matrix. Therefore, glomerulomegaly [2] and GBM thickening [1, 16] were consequently developed. Wu et al. [17] showed that these factors were increased in ORG patients. Based on the above reports and the present study, it is concluded that obesity seems to influence GBM thickness in ORG with subsequent development of abnormalities,

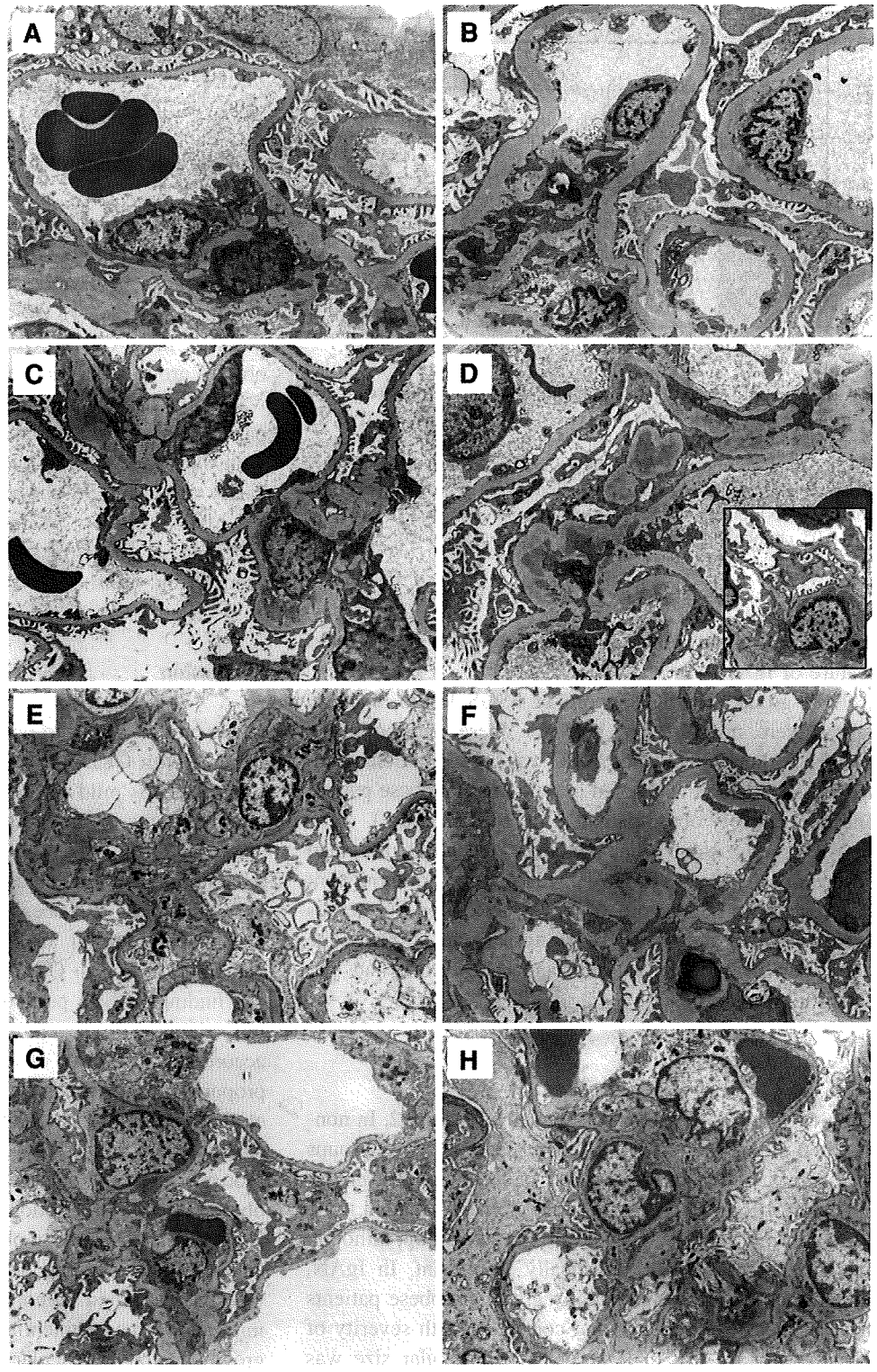

Fig. 3 Features of electron microscopy in nonobese (**a**, **c**, **e**, **g**) and obese (**b**, **d**, **f**, **h**) patients of each disease group. **a**, **b** Nonglomerulonephritis, **c**, **d** IgA nephropathy, **e**, **f** benign nephrosclerosis, **g**, **h** thin basement membrane disease. *Inset* of picture **d** shows focal thinning of GBM. ×3,000

which probably depends on severity and duration of obese state. Hypertension is thought to be an important factor for progression of renal disease in ORG [1]. The effects of mild obesity were not present in IGL and FSGS lesion in mild-obesity groups. However, some clinical parameters, such as eGFR, proteinuria and diastolic blood pressure (DBP), were worse in mild-obesity than in nonobese group in non-GN. This may reflect glomerular enlargement and GBM thickening. In our study, systemic blood pressure and thickness of GBM worsened with severity of obesity. It is possible

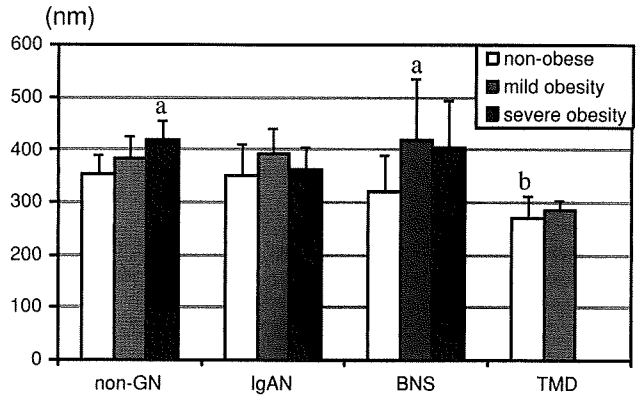

Fig. 4 Thickness of GBM in nonglomerulonephritis (non-GN), IgA nephropathy (IgAN), benign nephrosclerosis (BNS), and thin basement membrane disease (TMD). *Bars* are mean ± SD, *a* $P < 0.05$ versus nonobese patients in each group; *b* $P < 0.01$ versus nonobese non-GN group

that thickening of GBM is related to increased intraglomerular pressure in such patients [1, 18].

A few studies on obesity in IgAN have been reported [4, 19]. When obesity accompanies IgAN, pathological changes were more severe and proteinuria was grater [4]. However, there are only a few ultrastructural studies on the effect of obesity in IgAN; for example, Tanaka et al. [19] reported greater GBM thickening and larger total glomerular tuft areas in obese IgAN than in lean IgAN patients. Our data also showed significantly larger glomeruli in obese IgAN than in nonobese IgAN. Although the thickness of GBM in obese patients was slightly larger than that in nonobese patients, no significant difference was noted. EM showed areas of thin GBM in most patients with IgAN. This could explain the lack of statistical significance in terms of GBM thickness. IGL was higher in patients with severe obesity. Considered together, these results indicate that glomerular changes seem to be enhanced in IgAN obese patients, similar to in ORG patients.

Many studies have analyzed the relationships among BMI and blood pressure with glomerular lesions in ORG patients [5, 6, 20, 21]. In hypertensive patients, increased renal tubular sodium reabsorption and glomerular hyperfiltration may cause glomerulomegaly [1]. Fewer and larger glomeruli were described in hypertensive patients than in nonhypertensives [22, 23]. In our study, the glomeruli were larger in size in nonobese BNS group than in nonobese non-GN and IgAN groups. This change may be caused by intraglomerular hypertension and compensatory hypertrophy of the few glomeruli present in the kidney. Furthermore, the GBM was significantly thicker in obese BNS group than in nonobese group. Although glomerular injury was caused by hemodynamic abnormalities in BNS, obesity per se could accelerate glomerular lesions.

TMD is known to be associated with excellent prognosis, and is clinically called benign familial hematuria [12]. Many reports are available on ultrastructural changes in TMD, as well as the mechanism of the thin GBM. These studies emphasized that the only significant change in TMD is mild glomerulopathy, including thinning of GBM [24]. Interestingly, the glomeruli were significantly larger in size in obese TMD group than in nonobese non-GN and IgAN groups. The cause of glomerulomegaly in TMD is not clear at present; however, the lumen of glomerular capillaries may easily expand in presence of high intraglomerular pressure and abnormally thin GBM. None of the patients in the TMD group were severely obese. However, GBM may be thicker in severely obese TMD patients. Further studies are necessary to examine the effects of GBM thickening in obese TMD patients, including immunohistochemical examination of subunits of collagen type IV [12].

In conclusion, the results of the present study indicate that obesity worsens urinary protein excretion and glomerular damage in patients with IgAN, BNS, and TMD. In addition, hypertension might be an important factor that precipitates renal disease in obesity-related nephropathy. In patients with CKD, obesity might worsen proteinuria and renal structural changes, similar to obesity-related nephropathy. In other words, obesity might promote progression of CKD.

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REVIEW ARTICLE

Current status and issues of C1q nephropathy

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Abstract C1q nephropathy, first proposed by Jennette and Hipp [Am J Clin Pathol 83:415-420, 1985; Am J Kidney Dis 6:103-110, 1985], was described as a distinct glomerular disease entity characterized by extensive mesangial deposition of C1q, with associated mesangial immune complexes, and the absence of any clinical and laboratory evidence of systemic lupus erythematosus. Now, 20 years since the first report, the disease entity is gradually attaining recognition, particularly in the field of pediatrics. C1q is the subcomponent of C1 in the classical pathway of complement activation. Generally, C1q deposition is caused by the activation of C1 by immunoglobulin G (IgG) and IgM; therefore, C1q nephropathy is considered as an immune complex glomerulonephritis. However, in C1q nephropathy, it remains unclear whether the deposition of C1q in the glomeruli is in response to the deposition of immunoglobulin or immune complex, or whether deposition is non-specific trapping that accompanies increased glomerular protein trafficking associated with proteinuria. Since not only the pathogenesis of C1q deposition in glomeruli but also its significance are still uncertain, it has not yet been established as an independent disease. From recent publications of the clinical and pathological characterizations, C1q nephropathy has been thought to be a subgroup of primary focal segmental glomerular sclerosis. However, many reports describe different symptoms, histopathologies, therapeutic responses and prognoses, suggesting that C1q nephropathy is not a single disease entity, but that it may be a combination of several disease groups. There are many uncertain areas requiring further investigation, though it is hoped that a detailed examination of future cases will clarify the subgroups making up C1q nephropathy and their clinicopathological characteristics, and will lead to the establishment of C1q nephropathy as an independent disease entity.

Keywords C1q nephropathy · Complement · C1q

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Introduction

The term "C1q nephropathy" was first proposed by Jennette and Hipp [1, 2] in 1985 for biopsies exhibiting dominant or co-dominant staining for C1q, confirmation of mesangial deposits by electron microscopy, and the absence of clinical or serologic evidence of systemic lupus erythematosus (SLE). It is now 20 years since the first report of C1q nephropathy. With the recent increase in the number of reports, mainly in the field of pediatrics, C1q nephropathy is gradually becoming established as an independent disease. In clinico-pathological studies, C1q nephropathy is characterized by its onset in older children and young adults with severe proteinuria or nephrotic syndrome, with resistance to steroid treatment, frequent recurrence and a poor long-term prognosis. Serological examination reveals no antinuclear antibodies or complement abnormalities. In renal biopsies, C1q nephropathy is characterized by various

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histopathological findings ranging from minimal change disease (MCD) to diffuse proliferative glomerulonephritis (GN). However, C1q nephropathy is still a controversial entity and is poorly understood. There are also many uncertain points concerning C1q nephropathy. This review provides a summary of the major reports regarding C1q nephropathy with conjectures on possible pathogenesis of C1q deposition in glomeruli and a discussion of problems surrounding the disease.

The "C1q" in C1q nephropathy

The "C1q" in C1q nephropathy is the key subcomponent of the C1 complex of the classical pathway, one of the three pathways of complement activation: the classical pathway, the alternative pathway and the lectin pathway, and a major connecting link between classical pathway-driven innate immunity and IgG- or IgM-mediated acquired immunity (Fig. 1) [3–7]. C1 is a pentamer composed of five molecules: a single C1q, two each of the C1r and C1s. C1q is a large, calcium-dependent glycoprotein that contains six discrete globular heads (globular domain of C1q, gC1q) and triple helical collagen-like domains (Fig. 2). The classical complement cascade begins when C1q binds to the immunoglobulin, specifically to the CH2 domain of the Fc portion of IgG and to the CH3 domain of IgM. C1q binds strongly to IgM, IgG1 and IgG3, but binds weakly to other immunoglobulins, such as IgG2, and does not bind at all to IgG4, IgA, IgD and IgE.

Binding of C1q to IgG- or IgM-containing immune complexes via the ligand-recognition gC1q domain induces a conformational change in the collagen region, leading to the autoactivation of C1r, which, in turn, activates C1s, leading to a series of enzymatic reactions that results in the initiation of the complement activation pathway. The activation of the C1 complex subsequently leads to the activation of the following complement components and formation of the terminal membrane attack complex.

In addition to being a key component of the classical pathway, C1q is involved in several other immunological processes. C1q binds to a variety of different cell types and triggers various cellular responses, including phagocytosis of bacteria, neutralization of retroviruses and maintenance of immune tolerance via the clearance of apoptotic cells [7]. Its ability to carry out such diverse functions is supported by a wide range of its ligands, binding proteins and receptors. The expression of C1q receptors have been confirmed on monocytes, macrophages, polymorphonuclear cells, fibroblasts, platelets, lymphocytes, endothelial cells and mesangial cells. Therefore, C1q can bind directly to mesangial cells through C1q receptor [3, 8, 9].

Major reports on C1q nephropathy (Table 1)

C1q nephropathy associated with immune complex GN

In 1985, the first report by Jannette and Hipp [1, 2] described 15 cases of C1q nephropathy in patients who had

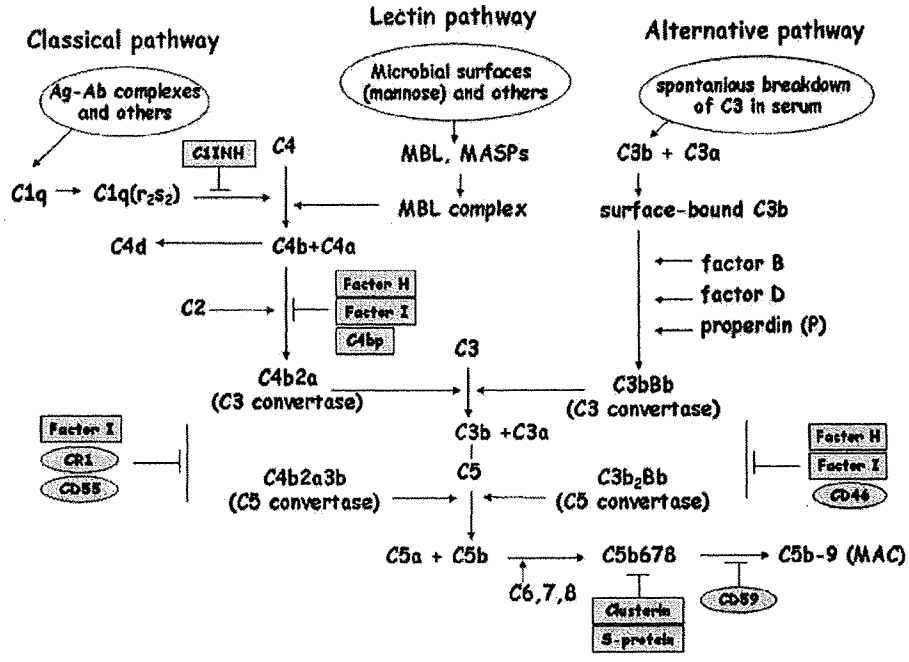

Fig. 1 Complement activation pathways and serum and cell-surface inhibitors. The complement system can be activated in three different ways, the classical pathway, the alternative pathway and the mannose-binding lectin (MBL) pathway. All three pathways lead to the generation of an enzymatically active C3 convertase, which cleaves the central complement C3 and subsequent formation of membrane attack complex (C5b-9). To prevent continuous activation of the complex system, regulatory (inhibitory) proteins are present as serum (indicate as dark square) and cell-surface (indicate as dark circle) inhibitory factors

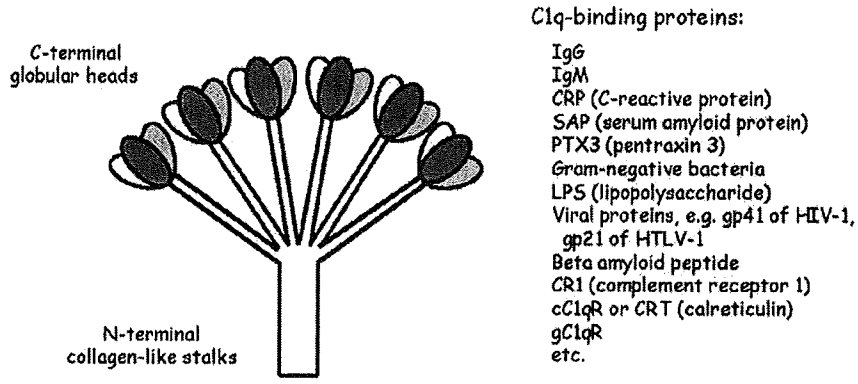

Fig. 2 Structure of C1q and its binding molecules. The C1q molecule is a 460,000-D glycoprotein composed of six globular heads and held together by six collagen-like stalks. Each head is composed of the C-terminal halves of three distinct polypeptide A, B and C chains, and these heads are connected to a collagen-like neck. Dimers of the C1r and C1s subcomponents contain the enzymatic activities associated with the C1 complex and form a tetrameric proenzyme structure around the collagen-like neck of C1q. Globular heads of C1q bind CH2 domain of IgG and CH3 domain of IgM and mediate subsequent activation of classical pathway of complement. On the other hand, several molecules also can bind C1q and induce several immunologic reactions

intense (greater than or equal to 2+ on a scale of 0 to 4+), predominantly mesangial, glomerular C1q deposition by immunofluorescence, but who had no clinical evidence of SLE. By electron microscopy, all cases had mesangial electron dense deposits. Endothelial tubuloreticular inclusions, usually seen in SLE, were not detected in any cases. Light microscopic appearance varied from case to case, such as MCD, mesangial hypercellularity and proliferative GN. Patients with C1q nephropathy may present with nephrotic syndrome, nephrotic range proteinuria, or low-grade proteinuria with or without hematuria. None of the patients had a serum creatinine above 1.5 mg/dl.

Similar cases were subsequently reported by Davenport et al. [10]. Four patients with C1q nephropathy were characterized with various GN features, including diffuse proliferative GN, proliferative GN with segmental sclerosis, membranoproliferative GN (MPGN) and membranous nephropathy (MN). They proposed that C1q dominance in patients with nephrotic syndrome may reflect a better clinical prognosis.

In addition, 3 years before the first report by Jennette and Hipp, a group of five patients with similar clinical and morphologic features was already presented by Jones and Magil [11] under the designation of nonsystemic mesangiopathic GN with "full house" immunofluorescence. All cases had proteinuria, two with nephrotic-range proteinuria, and four had microhematuria. Renal function deteriorated with reduction of creatinine clearance.

Similar GN with "full house" immunofluorescence, so-called "seronegative lupus nephritis" cases, were proposed to fulfill the criteria for C1q nephropathy by Sharman et al. [12]. They described nine cases presenting with massive proteinuria, nephrotic syndrome and hematuria. Histological findings varied widely, including focal or diffuse proliferative GN, crescentic GN and membranous and mesangial proliferative GN with "full house" immunofluorescence. A patient with crescentic GN died of renal failure, and another patient with mesangial proliferative GN progressed to end-stage renal failure after 4 years despite steroid treatment. Among the other seven cases, there was no exacerbation of proteinuria, even in four patients who did not receive immunosuppressive therapy, and all these patients maintained good renal function.

Most of the cases classified as C1q nephropathy in the above reports were characterized by an immune complex-mediated GN, across the spectrum of proliferative GN to MPGN-like GN and MN, usually with nephrotic-range proteinuria with or without hematuria.

C1q nephropathy associated with MCD and FSGS

In contrast, the recent reports also suggest that C1q nephropathy may be more closely associated with the continuum of MCD and FSGS.

The pediatric series by Iskander et al. [13] reported 15 cases of C1q nephropathy with proteinuria, at the nephrotic level in the majority of cases, who had MCD (8 cases), FSGS (4 cases) and proliferative GN with segmental sclerosis (3 cases). Among ten patients with nephrotic syndrome, nine received oral steroids and showed remission in two cases, resistance in six cases, and frequent recurrence in one case. Iskandar et al. described that C1q nephropathy was an immune-complex-mediated glomerulopathy and was clearly distinguished from either usual cases of MCD or of FSGS, because a group of cases with the presence of immune deposits including C1q identified poor response to steroids.

In a retrospective study of C1q nephropathy, Markowitz et al. [14] concluded that C1q nephropathy was a variant of FSGS, and C1q in the glomeruli may only be deposited nonspecifically and that its presence does not necessarily suggest an ongoing immune-mediated process. In this series, 19 patients presenting with nephrotic-range proteinuria or nephrotic syndrome included FSGS in 17 and MCD in 2. MCD patients and two-thirds of FSGS patients had a good prognosis, while another third of FSGS patients had a poor outcome.

In recent studies of C1q nephropathy by Lau et al. [15] (20 cases) or Levart et al. [16] (12 cases), light microscopic findings indicated FSGS in 40–50%, MCD in 30% and proliferative GN in 15–17%. In the 20 cases reported by Lau et al. [15], 14 had proteinuria, with 8 cases of nephrotic syndrome. No reduction of renal function was observed in the 12 patients that did not present with nephrotic syndrome. Two of the FSGS and two of the global sclerosis cases showed resistance to treatment with ARB, ACE inhibitors and steroid, and progressed to end-stage renal failure. In the 12 cases reported by Levart et al. [16], proteinuria was observed in all, with 9 cases of nephrotic syndrome. All four MCD patients with nephrotic syndrome responded to steroid and immunosuppressive therapy. Among the six patients with FSGS, five had nephrotic syndrome, and even with steroid and immunosuppressive therapy they tended to have a poor outcome.

C1q nephropathy with asymptomatic urine abnormalities

In the three studies from Japan, many cases of C1q nephropathy in mainly children showed asymptomatic urine abnormalities, unlike previous reports in which many cases had severe proteinuria or nephrotic syndrome.

A report by Nishida et al. [17] described four cases of C1q nephropathy. Three of these patients had asymptomatic urine abnormalities (detected by the school urinary screening program), and showed histologic features of MPGN and a relatively good clinical course without steroid therapy.

In another report by Fukuma et al. [18], 30 cases of C1q nephropathy in children were divided into two groups, one of patients with asymptomatic proteinuria and hematuria ($n = 18$), and the other of patients with nephrotic syndrome ($n = 12$). Among the asymptomatic group, histological findings indicated MCD (11 cases), mesangial proliferative GN (6 cases) and FSGS (1 case). The prognosis tended to be favorable for all of the patients, except for one with FSGS that progressed to end-stage renal failure. The nephrotic syndrome group showed histological findings of MCD (11 cases) and FSGS (1 case), with resistance to treatment and frequent recurrence of nephrotic syndrome. Subsequently, the other report by Hisano et al. [19] examined a large number of patients ($n = 61$), including adults, who were divided into those with asymptomatic urinary abnormalities and those with nephrotic syndrome. A second biopsy was performed in eight patients because of poor clinical course, and three of them showed disappearance of mesangial C1q deposits.

Various cases of C1q nephropathy

Since the first report of C1q nephropathy by Jennette and Hipp, various case reports have also appeared [20–33]. Among the cases included are rare cases featuring unusual clinical course, atypical pathological findings, involvement of genetic diseases and viral infection. Because of different symptoms, histological findings, response to treatment and prognosis, C1q nephropathy may not be a uniform entity.

By their pathological characteristics, C1q nephropathy in previous publications seems to be divided into two major pathological variants, which we termed in this review (1) MCD/FSGS variant and (2) immune complex GN variant. IgA nephropathy, in a manner similar to C1q nephropathy, is defined by immunofluorescence staining for IgA and is thought to be composed of several disease groups. Indeed, various cases with glomerular IgA deposition are observed except for typical IgA nephropathy case, such as simple IgA deposition without any renal disease, MCD with nephrotic syndrome, marked IgA deposition without prominent proliferative GN, endocapillary proliferative GN with obvious deposits on GBM and crescentic GN. However, IgA nephropathy is now accepted as a discrete type of glomerular disease. As with the acceptance of IgA nephropathy, clinicopathological characterization of C1q nephropathy needs to be consolidated for the establishment of C1q nephropathy as an independent entity of glomerular disease.

Etiology and pathogenesis of C1q nephropathy

Although the etiology and pathogenesis of C1q nephropathy are still not clear, the following are conjectured.

(1) C1q is the first component of the classical pathway of complement activation (Fig. 1) [3–7]. Together with the deposition of C1q, deposition of immunoglobulin is often detected in the glomeruli in C1q nephropathy. This suggests complement activation by the formation of antigen–antibody complexes in the glomeruli and is probably the reason that C1q nephropathy is categorized as immune complex type GN. At present, however, the antigen involved in C1q nephropathy has not been determined. In addition to the classical

pathway of complement activation, the alternative and lectin pathways are also involved in C1q nephropathy [34].

(2) The C1q molecule has a strong affinity and binds to various poly-anionic substances, such as DNA, RNA, polynucleotides, gram-negative bacterial protein, lipopolysaccharides and virus proteins (Fig. 2). In addition, C1q can bind to monocytes, macrophages, neutrophils, B lymphocytes, platelets, endothelial cells, smooth muscle cells and mesangial cells through C1q receptors [3, 8, 9]. It is possible that the binding of C1q to poly-anionic substances or through C1q receptors is directly involved in the onset of C1q nephropathy without being mediated by immunoglobulin.

(3) Macrophages and monocyte-derived dendritic cells (DCs) synthesize C1q and can provide sufficient local tissue complement for opsonization without recruiting plasma complement [35]. Regulatory mechanisms of C1q production by macrophages and DCs have been reported, and several inflammatory cytokines induce the up-regulation of C1q production. It is probable that the macrophages and/or DCs in glomeruli synthesize C1q and mediate C1q nephropathy in inflammatory milieu.

(4) Anti-C1q antibodies are often observed in SLE patients, and are also associated with the severity and activity of GN in SLE [36, 37]. Anti-C1q antibodies mediate IgG and C1q deposition in the glomeruli. However, there have been no detailed reports on the causal relation between anti-C1q antibodies and C1q nephropathy. Jennette and Hipp [2] expressed skepticism about the involvement of anti-C1q antibodies since the presence of anti-C1q antibodies is usually accompanied by evidence of intense activation of the classical pathway with hypocomplementemia, but C1q nephropathy cases do not display hypocomplementemia. In the report by Sharman et al. [12], there is mention of a personal communication with Jennette indicating that anti-C1q antibodies were not observed in C1q nephropathy cases. Further examination of anti-C1q antibody in patients of C1q nephropathy will need to clarify the correlation between the anti-C1q antibody and C1q nephropathy.

(5) The complement system has a series of serum and cell-surface inhibitors against complement activation that prevent inappropriate or excessive production of complement and subsequent tissue injury (Fig. 1). Serum inhibitor against C1 is also present, termed C1 inhibitor that can bind to activated C1r and C1s, removing them from C1q, and can inhibit activation of C1. Abnormalities of C1 inhibitor may induce C1q deposition in glomeruli. The pathogenesis of C1q deposition should also be considered to be from inadequate regulation of complement inhibitor protein.

(6) Since hypocomplementemia and systemic immune complex diseases (autoimmune disease or systemic infection) are not observed in C1q nephropathy, it is possible that C1q is deposited in the mesangial region as a response to nonspecific accumulation of immunoglobulin due to increased flow of protein into the mesangial pathway and decreased clearance of plasma protein [14]. This is thought to be the same phenomenon as IgM and C3 deposition in the mesangial sclerotic region observed in FSGS. Indeed, C1q deposition is sometimes combined with deposition of IgM and C3 in sclerotic area in FSGS [38].

(7) C1q binds directly to the many viruses, enveloped and non-enveloped, which might result in virus neutralization [3–7]. The relationship between C1q nephropathy and viral infection has also been considered. Several cases were reported, including a case of recurrent MPGN type I with C1q deposition in a transplant patient with systemic CMV infection [39], and de novo C1q nephropathy in the setting of BK polyomavirus interstitial nephritis in a kidney and pancreas transplant patient [26]. With regard to nephropathy related to hepatitis B and hepatitis C viruses [40–45], MN and MPGN-like GN developed with C1q deposition in glomeruli as an immune complex type GN. In addition, HIV-related immune complex type GN [42, 46], so-called "lupus-like GN," has histological findings that closely resemble lupus nephritis and may be included in similar morphological categories, such as immune complex GN variant of C1q nephropathy.

The pathogenesis of C1q deposition in the glomeruli remains a matter of speculation. Additional studies are needed to determine the specificity and inciting factors leading to C1q deposition as well as the etiology and pathogenesis of C1q nephropathy.

Characteristics of C1q nephropathy in our cases

Among a total of 4,600 renal biopsies examined by immunofluorescence staining for C1q at the Department of Pathology, Nippon Medical School, Tokyo, Japan, 342 cpatient (7.4%) showed more than (1+) C1q immunostaining in glomeruli. These cases included SLE (77 cases with C1q+, 55% in total 140 SLE cases), MCD (58 cases with C1q+, 7.2% in total 802 MCD cases), FSGS (2 cases with C1q+, 6.1% in total 33 FSGS cases), non-SLE and non IgA nephropathy proliferative GN (37 cases with

C1q+, 11.9% in total 311 cases), MN (80 cases with C1q+, 17.2% in total 466 MN cases), MPGN (12 cases with C1q+, 22.6% in total 53 MPGN cases), PSAGN (13 cases with C1q+, 24.5% in total 53 PSAGN cases), IgA nephropathy (7 cases with C1q+, 0.4% in total 1,743 IgA nephropathy cases), and purpura nephritis (1 case with C1q+, 0.5% in total 189 purpura nephritis cases). In addition, 43 cases (0.9%) fulfilled the diagnostic criteria of C1q nephropathy when we used the criteria proposed by Jannette and Hipp. Based on the glomerular histopathology, our cases also could be divided into two major variants: MCD/FSGS and immune complex GN variants. Furthermore, these two variants consisted of five subgroups: MCD and FSGS groups in MCD/FSGS variant, and mesangial proliferative GN, MN or focal segmental MN, and MPGN-like GN groups in immune complex GN variant (Figs. 3, 4, 5).

MCD/FSGS variant

MCD group Ten cases (23.3%) showed histopathological findings of MCD. In immunofluorescence studies, together with C1q, IgG deposition was noted in all cases, but four cases (40%), one case (10%), and eight cases (80%) lacked the deposition of IgM, C3, and C4, respectively. "Full house" immunostaining was evident in two cases. Mean age was 15.6 years (range, 1–44 years). At the time of biopsy, patients had massive proteinuria and nephrotic syndrome, and showed resistance to steroid treatment or frequent recurrence of nephrotic syndrome.

FSGS group Two cases (4.7%) had histopathological findings of FSGS. In immunofluorescence studies, although C1q, IgG and C3 were present in both cases, IgM deposition was evident in one case, and C4 was not detected in both cases. Renal biopsies of two cases were performed at the age of 15 years. These cases showed frequent recurrence of nephrotic syndrome or persistent proteinuria despite steroid therapy.

Immune complex GN variant

Proliferative GN group This group included 19 patients (44.2%) and showed histopathological findings of proliferative GN. In our cases, this group was most common. Immunofluorescence studies showed three cases (15.8%)

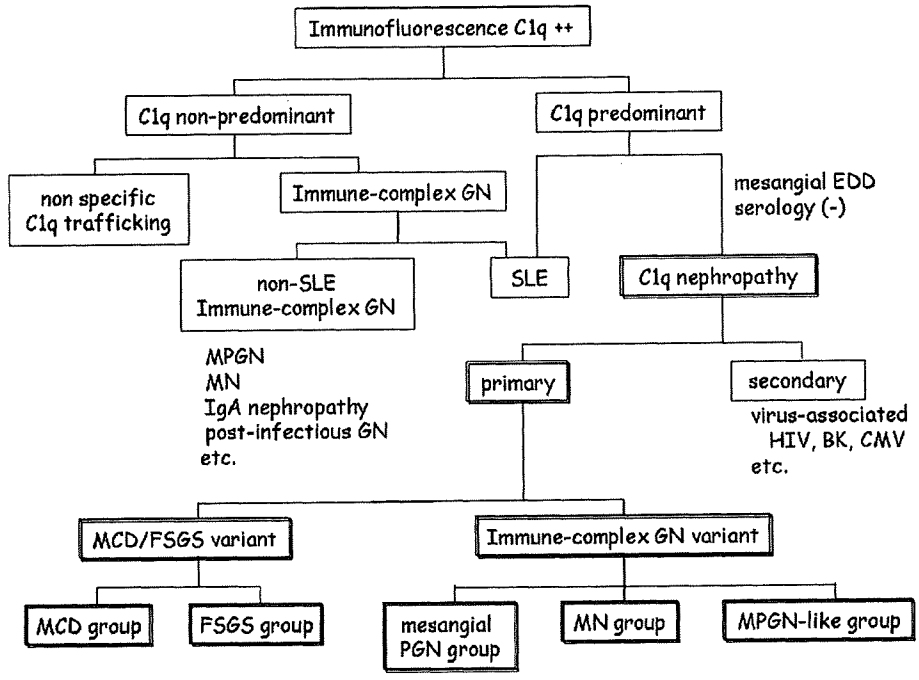

Fig. 3 Diagnostic approach in C1q nephropathy. C1q nephropathy is diagnosed by (1) dominant or co-dominant immunostaining for C1q, (2) confirmation of mesangial electron dense deposits and (3) the exclusion of various types of immune complex-mediated glomerulonephritis, including systemic lupus erythematosus (SLE). C1q nephropathy may consist of primary type and secondary type. Primary C1q nephropathy is divided into two variants, such as MCD/FSGS variant and immune-complex GN variant. These two variants are composed of five subgroups: MCD (minimal change disease), FSGS (focal segmental glomerular sclerosis), mesangial PGN (proliferative glomerulonephritis), MN (membranous nephropathy) and MPGN-like (membranoproliferative GN-like). Secondary C1q nephropathy may be seen in patients with viral infection. The diagnosis of secondary C1q nephropathy is based on the clinical history and serological data

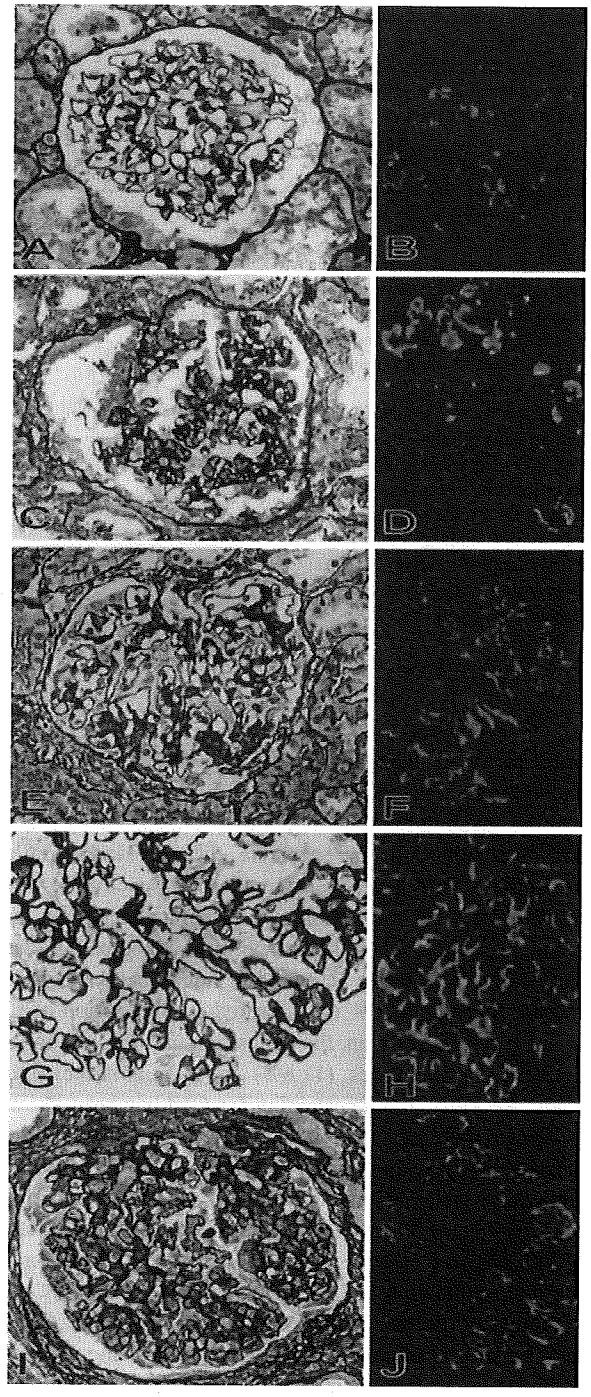

Fig. 4 Light microscopic findings (**a**, **c**, **e**, **g**, **i**: PAM stain) and C1q deposition (**b**, **d**, **f**, **h**, **i**) in C1q nephropathy in our cases. C1q nephropathy in our cases could be divided into five groups: (1) group with light microscopy findings indicating minimal-change disease (**a**, **b**), (2) focal segmental glomerular sclerosis (**c**, **d**), (3) mesangial proliferative glomerulonephritis (**e**, **f**), (4) membranous nephropathy or segmental membranous glomerulonephritis (**g**, **h**) and (5) membranoproliferative glomerulonephritis-like glomerulonephritis (**i**, **j**). C1q deposition was detected in a mesangial pattern (**b**, **d**, **f**) and a mesangial and peripheral pattern (**h**, **j**)

with "full house" immunostaining. C1q and IgG were deposited in all cases; however, 7 cases (36.8%), 4 case (21.1%), and 14 cases (73.7%) lacked the deposition of IgM, C3 and C4, respectively. All cases showed glomerular mesangial proliferative lesions, together with focal and irregular subepithelial and subendothelial deposition in six cases (31.6%). Patient ages ranged from 3 to 24 years (mean, 13.4 years). Fifteen percent of patients had nephrotic syndrome, but most patients showed persistent proteinuria and hematuria.

MN or focal segmental MN group Only one case at age 15 years (2.3%) showed morphological features of focal segmental MN with clinically persistent proteinuria. Immunofluorescence showed IgG, IgM, C1q and C3, but no C4 deposition, in the mesangial region and focal segmental capillaries. Electron microscopic findings also indicated mesangial and focal segmental subepithelial electron dense deposits. Obana et al. [47] reported that 91% cases of idiopathic segmental membranous GN had positive C1q staining and mesangial electron dense deposits, although Obana et al. did not include these cases in C1q nephropathy in this article.

MPGN-like GN group Eleven cases (25.6%) showed morphological findings similar to those of MPGN. Glomerular IgG, C1q and C3 deposition was seen in all cases, with "full house" deposition in four cases (36.4%). C4 was not detected in six cases (54.5%). Electron microscopic findings indicated widespread mesangial, subendothelial and subepithelial deposits in the glomeruli. Patient ages ranged from 19 to 68 years (mean, 51.4 years). None of the patients had clinical or serologic evidence of SLE. At the time of biopsy, patients had large proteinuria and nephrotic syndrome (71.4%), and showed the deterioration of renal function and resistance to steroid therapy.

Our findings also suggest that C1q nephropathy may be made up of several disease groups. Like previous publications, we assume that C1q nephropathy in our cases could be divided histopathologically into two major pathological variants: MCD/FSGS and immune complex GN variants. These two variants included five subgroups: MCD and FSGS groups in MCD/FSGS variant, mesangial PGN, MN or focal segmental MN, and MPGN-like GN groups in immune complex GN variant. Many cases of publications from other laboratories could also be divided histopathologically into the same two major variants and these five subgroups (Fig. 3). Markowitz et al. [14] recommended that the absence of hypocomplementemia and the absence of a membranoproliferative pattern of glomerular disease be added to the defining criteria for C1q nephropathy in