た和田らの報告[13]によると，①suPAR濃度は疾患によらずにeGFRと負の相関を示し，もっとも強力な予測因子であったこと，②eGFRを層別化して検討すると，どのレベルのeGFRでもFSGS患者と非FSGS患者のsuPAR分布は類似しており，鑑別することは困難であったこと，③suPAR濃度高値はむしろ炎症と関連している可能性があること，が報告されており，現時点ではsuPARをFSGS診断のマーカーとしては有用とはいえず，今後の検討が必要と考えられる．

2. FSGSとポドサイト異常

miRNAは19～24塩基のRNAで，他の遺伝子の発現を調節する機能を有している．miRNAのひとつであるmiR-193aを過剰発現させたマウスでは，WT1の発現が抑制されることによりポドサイトの足突起の構造維持に必須の遺伝子であるpodocalyxinやnephrinの遺伝子発現が抑制され，ポドサイトの広範な足突起の消失が認められることが報告されている[14]．さらに，FSGSの患者の糸球体では健常人やほかの糸球体腎炎患者の糸球体と比較しもmiR-193aの発現が上昇しており，FSGSにおけるmiR-193aの関与が疑われている．

二次性FSGSをきたす遺伝子異常として，nephrin，podocin，CD2-ssociated protein(CD2A)，α-actinin 4，transient receptor potential cation 6(TRPC6)などが報告されている(図2)．NPHS1の遺伝子産物であるnephrinは足突起と足突起の間のスリット膜の構成蛋白であり，NPHS1の異常によりFinnish型先天性ネフローゼ症候群を発症する[15]．NPHS2の遺伝子産物であるpodocinもスリット膜の構成蛋白であり，その異常により難治性ネフローゼ症候群を呈する[16]．podocineはnephrinと結合し，スリット膜を構成する．podocineはC末端もN末端も細胞質内に存在するヘアピン構造をとっている．podocineはCD2APとも結合し，スリット膜の足場のような役割をもつ．ACTN4の遺伝子産物であるα-actinin 4は家族性FSGSに関連しており[17]，変異した蛋白によりポドサイトの細胞骨格が崩壊し，FSGSを発症すると考えられている．CD2APはT細胞のCD2の細胞内ドメインと結合するアダプタ蛋白として報告されたが，nephrinに結合し，細胞骨格であるアクチンに固定する働きをもつ．CD2AP欠損によりFSGSをきたした症例が報告されている[18]．TRPC6はホスホリパーゼCシグナルに応答してCaが流入するチャネルであるが，その異常によりFSGSをきたすことが報告されている[19]．そのほか，IFN2，MYO1Eなどの遺伝子異常もFSGSの発症に関与しているとされる．

河内らはシナプス小胞分子(SV2B)に注目している．CD2APは正常培養ポドサイトでは突起部に観察されるが，SV2Bが欠損するとCD2APは突起部での集積が認められず[20]，SV2Bノックアウトマウスは蛋白尿の増加を認めるとともに，スリット膜機能分子であるNephrin，NEpH1，CD2APの発現が低下することも観察している．

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ORIGINAL ARTICLE

Outcomes of primary nephrotic syndrome in elderly Japanese: retrospective analysis of the Japan Renal Biopsy Registry (J-RBR)

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Abstract

Background and objectives There are very little data available regarding nephrotic syndrome (NS) in elderly (aged ≥65 years) Japanese. The aim of this study was to examine the causes and outcomes of NS in elderly patients who underwent renal biopsies between 2007 and 2010.

Design, setting, participants, and measurements From July 2007 to June 2010, all of the elderly (aged ≥65 years) Japanese primary NS patients who underwent native renal biopsies and were registered in the Japan renal biopsy registry (J-RBR; 438 patients including 226 males and 212 females) were identified. From this cohort, 61 patients [28 males and 33 females including 29, 19, 6, 4, and 3 patients with membranous nephropathy (MN), minimal change nephrotic syndrome (MCNS), focal segmental glomerulosclerosis (FSGS), membranoproliferative glomerulonephritis (MPGN), and other conditions, respectively] were registered from the representative multi-centers over all districts of Japan, and analyzed retrospectively. The treatment outcome was assessed using proteinuria-based criteria; i.e., complete remission (CR) was defined as urinary protein level of <0.3 g/day or g/g Cr, and incomplete remission type I (ICR-I) was defined as urinary protein level of <1.0–0.3 g/day or g/g Cr, and renal dysfunction was defined as a serum creatinine (Cr) level of 1.5 times the baseline level.

Results In this elderly primary NS cohort, MN was the most common histological type of NS (54.8 %), followed

Special report from the Japan Renal Biopsy Registry (J-RBR).
On behalf of the Committee for the Standardization of Renal Pathological Diagnosis and Renal Biopsy and Disease Registry of the Japanese Society of Nephrology.
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by MCNS (19.4 %), FSGS (17.4 %), and MPGN (8.4 %). Of the patients with MN, MCNS, or FSGS, immunosuppressive therapy involving oral prednisolone was performed in 25 MN patients (86.2 %), 18 MCNS patients (94.7 %), and all 6 FSGS patients (100 %). CR was achieved in all 19 (100 %) MCNS patients. In addition, CR and ICR-I were achieved in 16 (55.2 %) and 18 (62.1 %) MN patients and 4 (66.7 %) and 5 (83.3 %) FSGS patients, respectively. There were significant differences in the median time to CR among the MCNS, FSGS, and MN patients (median: 26 vs. 271 vs. 461 days, respectively, $p < 0.001$), and between the elderly (65–74 years, $n = 7$) and very elderly (aged ≥75 years, $n = 12$) MCNS patients (7 vs. 22 days, $p = 0.037$). Relapse occurred in two (6.9 %) of the MN and nine (47.4 %) of the MCNS patients. Renal dysfunction was observed in five (7.2 %) of the MN patients. Serious complications developed in eight (14.8 %) patients, i.e., two (3.7 %) patients died, four (7.4 %, including three MCNS patients) were hospitalized due to infectious disease, and two (3.7 %) developed malignancies. The initiation of diabetic therapy was necessary in 14 of the 61 patients (23.0 %) with much higher initial steroid dosage.

Conclusion Renal biopsy is a valuable diagnostic tool for elderly Japanese NS patients. In this study, most of elderly primary NS patients respond to immunosuppressive therapy with favorable clinical outcomes. On the other hand, infectious disease is a harmful complication among elderly NS patients, especially those with MCNS. In future, modified clinical guidelines for elderly NS patients should be developed.

Keywords Nephrotic syndrome · Elderly · Japanese · Outcome · Immunosuppressive therapy · Complication

Introduction

In Japan, elderly individuals; i.e., those aged 65 and over, accounted for 25.8 % of the total population in October 2010, and this will increase to 30.5 % by 2025 [1]. As life expectancy increases, more elderly patients with chronic renal diseases are surviving longer. In addition, the progressive decline in the glomerular filtration rate that occurs with age and age-related systemic diseases, such as anti-neutrophil cytoplasmic antibody (ANCA)-positive vasculitis, are expected to contribute to an increased incidence of renal disease in the elderly population [2].

As for nephrotic syndrome (NS), a previous study demonstrated that the elderly accounted for 1160 of the 2753 NS patients (42.4 %) registered in Japan. In addition, NS was found to be the most common indication for renal biopsy among both the elderly (aged ≥65 years, 36.3 %) and very elderly (aged ≥75 years, 50.7 %). Furthermore, membranous nephropathy (MN) was the most common pathological type of NS among the elderly (*n* 365, 31.5 %) and very elderly (*n* 45, 28.1 %), followed by minimal change nephrotic syndrome (MCNS; *n* 146, 12.6 %; *n* 19, 11.9 %) and focal segmental glomerulosclerosis (FSGS; *n* 68, 5.9 %; *n* 12, 7.5 %) [2].

Several studies involving limited numbers of elderly NS Japanese patients have reported that renal biopsy can provide significant diagnostic and prognostic information [3–7]. However, regarding the available therapies for and outcomes of elderly NS patients (and analyses of these factors in patients aged over 75 years) only single-center studies from Japan and Hong Kong and a study based on the Spanish Registry of Glomerulonephritis have been reported [7–9].

In 2007, the Committee for the Standardization of Renal Pathological Diagnosis and the Working Group for the Renal

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Table 1 Background data of the elderly nephrotic syndrome cohort in the J-RBR (2007–2010)

Primary nephrotic diseases	Cases (%)	Age at renal biopsy [median (range)]
Subjects (male: female = 226: 212)	438	73 (65–88)
Membranous nephropathy	240 (54.8)	73 (65–88)
Minimal change nephrotic syndrome	85 (19.4)	74 (65–85)
Focal segmental glomerulosclerosis	45 (10.3)	74 (65–83)
Membranoproliferative glomerulonephritis (type I or III)	37 (8.4)	73 (65–84)
Mesangial proliferative glomerulonephritis	12 (2.7)	75 (65–87)
Crescentic glomerulonephritis	9 (2.1)	73 (65–84)
Endocapillary proliferative glomerulonephritis	6 (1.4)	73 (65–87)
Sclerosing glomerulonephritis	1 (0.2)	77
Others	3 (0.7)	71 (66–77)

J-RBR Japan Renal Biopsy Registry

Biopsy Database of the Japanese Society of Nephrology established the first nationwide, web-based, prospective registry system, the Japan Renal Biopsy Registry (J-RBR), to record pathological, clinical, and laboratory data about the renal biopsies performed in Japan [10]. This nationwide registry system can be used to facilitate national epidemiological studies of renal diseases such as NS.

The aim of this study was to retrospectively examine the outcomes of NS patients using a large group of elderly (65–74 years) and very elderly (75 years old or older) patients who had undergone native renal biopsy and were scheduled to be followed up for 5 years (median follow-up period: approx. 2 years).

Materials and methods

J-RBR system and subjects

The researchers of the Committee for the Standardization of Renal Pathological Diagnosis and the Working Group for the Renal Biopsy Database of the Japanese Society of Nephrology set up the J-RBR [10]. From July 2007 to June 2010, all of the elderly (aged ≥65 years) and very elderly (aged ≥75 years) primary NS patients who had undergone native renal biopsy and been registered in the J-RBR (438 patients including 226 males and 212 females) were identified (Table 1). From this cohort, 61 patients [28 males and 33 females including 29, 19, 6, 4, and 3 patients with MN, MCNS, FSGS, membranoproliferative glomerulonephritis (MPGN), and other conditions, respectively] were registered from the representative multi-centers over all districts of Japan, and their data were analyzed retrospectively (Table 2, Chi-square value for background cohort vs. selected cohort: 4.497, $p = 0.4803$). The patients in this study showed the nephrotic range proteinuria at least once before renal biopsy. Patient data including information regarding each patient's age, gender, and laboratory findings as well as the clinical category and pathological diagnosis of their condition were electronically recorded at each institution and registered on the J-RBR webpage via the Internet Data and Information Center for Medical Research (INDICE) system, which is part of the University Hospital Medical Information Network (UMIN). Clinical data, including urinalysis data; daily proteinuria values;

Table 2 Data for the 61 subjects from 10 centers selected for this retrospective study

Primary nephrotic diseases	Cases (%)	Gender (male:female)	Age at renal biopsy [Median (range)]
Subjects	61	28:33	73 (65–86)
Membranous nephropathy	29 (47.5)	12:17	72 (66–82)
Minimal change nephrotic syndrome	19 (31.1)	7:12	76 (65–86)
Focal segmental glomerulosclerosis	6 (9.8)	4:2	75 (70–81)
Membranoproliferative glomerulonephritis (type I or III)	4 (6.6)	2:2	73 (66–76)
Crescentic glomerulonephritis	2 (3.3)	2:0	71 (66–76)
Endocapillary proliferative glomerulonephritis	1 (1.6)	1:0	65 (65)

There was no significant difference between the data for the background cohort and those for the selected subjects (Chi-square 4.497, $p = 0.4803$)

Registered centers and cases: Okayama Univ.: 17 cases; Niigata Univ.: 9 cases; Fukuoka Univ.: 7 cases, Tsukuba Univ.: 6 cases; Kanazawa Med Univ.: 5 cases; Miyazaki Univ. & Hokkaido Univ.: 4 cases each; Fujita Health Univ., Kurume Univ., & Shizuoka Prefectural Hospital: 3 cases each

and laboratory data such as serum creatinine (Cr), total protein (TP), albumin, total cholesterol (TC), low-density lipid cholesterol (LDL-C), high-density lipid cholesterol (HDL-C), glycated hemoglobin (HbA1c), and hemoglobin levels were also recorded on a check sheet at the time of the renal biopsy and at 1, 3, 6, 12, and 24 months after J-RBR registration.

The ethical committee of the Japanese Society of Nephrology comprehensively examined and approved the study protocol, and the local committees of the participating centers and their affiliate hospitals individually approved the study. The J-RBR is registered at the Clinical Trial Registry of UMIN (UMIN000000618).

Clinical categories and pathological diagnoses

Glomerular disease was classified into the following clinical categories: NS, chronic nephritic syndrome, recurrent or persistent hematuria, acute nephritic syndrome, and rapidly progressive nephritic syndrome, based on the criteria developed by the WHO [11]. NS was defined as proteinuria of $\geq$3.5 g/day and/or a urinary protein/creatinine ratio (UPCR) of $\geq$3.5 g/g Cr combined with hypoalbuminemia (serum albumin <3.0 g/dl) and/or hypoproteinemia (total protein <6.0 g/dl), as defined by the Progressive Renal Diseases Research (2011) criteria [12].

The patients' renal histological diagnoses were classified according to their pathogeneses (group A) or histopathological findings (group B): group A: primary glomerular disease (except IgA nephropathy, IgAN), IgAN, purpura nephritis, lupus nephritis, myeloperoxidase- antineutrophil cytoplasmic antibody (ANCA)-positive nephritis, protein 3-ANCA-positive nephritis, anti-glomerular basement membrane antibody nephritis, hypertensive nephrosclerosis, thrombotic microangiopathy, diabetic nephropathy, amyloid nephropathy, Alport syndrome, thin basement membrane disease, infection-related nephropathy, kidney transplantation, and others; group B: minor glomerular abnormalities, FSGS, MN, endocapillary proliferative glomerulonephritis, MPGN (types I and III), and crescentic and necrotizing glomerulonephritis [11].

Therapy for nephrotic syndrome and treatment response

Due to the retrospective nature of this study, the immunosuppressive or supportive therapy protocols varied between individual centers. The use of immunosuppressant or supportive drugs was checked on the record sheet and registered in the web-based folder for this study.

The response of NS to treatment was assessed according to the definition outlined by the Japanese Society of Nephrology [12], i.e., a urinary protein level of <0.3 /day or a UPCR of <0.3 g/g Cr, a urinary protein level of between 0.3 and <1.0 g/day or a UPCR of between 0.3 and <1.0 g/g Cr, a urinary protein level of between 1.0 and <3.5 g/day or a UPCR of between 1.0 and <3.5 g/g Cr, and a urinary protein level of $\geq$3.5 g/day or a UPCR of $\geq$5 g/g Cr were defined as complete remission (CR), incomplete remission (ICR)-I, ICR-II, and ineffective, respectively. The clinical significance to achieve ICR-I in nephrotic Japanese was previously reported [19, 20].

The responses of CR, ICR-I and ICR-II were judged by the recorded time from the initiation of immunosuppressive therapy or biopsied time, if patients were not treated by immunosuppressive therapy, to the first remission of proteinuria. When the patient's urinary protein level did not decrease to <1 g/day and/or their UPCR did not fall to <1.0 g/g Cr after 6 months' treatment, e.g., with steroids and/or immunosuppressive drugs, their condition was defined as intractable NS.

Relapse was defined as daily proteinuria of >1.0 g, a UPCR of >1.0 g/g Cr, and/or a dipstick urinary protein value of $\geq$1+ after CR had been achieved.

Renal dysfunction was defined as a serum Cr level of 1.5 times the initial baseline level.

Statistical analyses

Continuous variables are reported as mean values (standard deviation, SD). Statistical analyses were performed using SPSS version 18.0 (SPSS, Tokyo, Japan). Comparisons of categorical variables among groups of different indications or diagnoses were performed using Fischer's exact test. Continuous variables were compared using the Student's *t* test or the ANOVA test for parametric data and Wilcoxon signed-rank test or the Kruskal–Wallis test for non-parametric data. The cumulative probability of a first remission was calculated using the Kaplan–Meier method. The effectiveness of immunosuppressive therapy and the influence of age on the treatment outcome were compared using the log-rank test and multivariate Cox regression analysis. *P* values of <0.05 (obtained by two-tailed testing) were considered to indicate statistical significance.

Results

The baseline background data of the patients with the 3 major pathological types of primary NS (MCNS, MN, and FSGS) are shown in Table 3. The MCNS patients exhibited significantly lower systolic blood pressure (mean: 118.9 $\pm$ SD 16.0, 133.2 $\pm$ 19.6 for MN, 136.5 $\pm$ 11.7 for FSGS mmHg, $p = 0.010$) and significantly higher serum TC levels than the MN and FSGS patients (394.4 $\pm$ 104.3 for MCNS, 293.8 $\pm$ 113.7 for MN, 295.7 $\pm$ 112.5 for FSGS mg/dL, $p = 0.027$). On the other hand, the FSGS

Table 3 Demographics of the elderly patients with the 3 major pathological types of NS

Cases Elderly/very elderly (n)	MN (29 cases) (17:12)		MCNS (19 cases) (7:13)		FSGS (6 cases) (2:4)		*P* value
	Mean	SD	Mean	SD	Mean	SD	
Height (cm)	153.7	9.2	154.4	8.2	153.3	7.5	0.938
Weight (kg)	58.4	7.8	62.9	10.6	61.2	10.9	0.286
Systolic BP (mmHg)	133.2	19.6	118.9[a]	16.0	136.5	11.7	0.010
Diastolic BP (mmHg)	77.6	14.2	72.2	6.8	67.2	7.5	0.104
Edema (%)	26 cases (89.7 %)		18 cases (94.7 %)		6 cases (100 %)		0.615
Daily proteinuria (g)	4.56	2.16	5.47	3.56	8.90[b]	3.50	0.032
uPCR (g/g Cr)	6.86	3.96	7.20	4.19	7.56	3.55	0.792
Hematuria (> 1 +)	20 cases (69.0 %)		9 cases (47.4 %)		4 cases (66.7 %)		0.310
Serum Cr (mg/dL)	0.94	0.44	1.17	0.67	2.37[b]	1.34	0.004
Serum BUN (mg/dL)	14.7	6.9	20.4	12.3	30.2[b]	7.8	0.004
Serum TP (g/dL)	4.79	0.86	4.64	0.40	4.97	0.74	0.762
Serum Alb (g/dL)	1.97	0.56	1.65	0.38	2.05	0.48	0.063
Serum TC (mg/dL)	293.8	113.7	394.4[a]	104.3	295.7	112.5	0.027
Serum LDL-C (mg/dL)	208.0	54.2	270.8	83.9	263.0	158.4	0.140
Serum HDL-C (mg/dL)	58.8	16.4	66.1	19.2	63.8	15.3	0.427
TG (mg/dL)	252.8	107.7	222.7	93.8	204.3	151.7	0.267
HbA1c (%)	5.28	0.54	5.68	0.31	5.40	0.25	0.076
Hb (g/dL)	12.55	1.46	12.54	1.85	10.88	1.48	0.082
IgG levels (mg/dL) (*n*: 26/16/4)	705	254	741	318	953	180	0.196

P values are for comparisons among the three histological types, i.e., MN, MCNS, and FSGS

MN membranous nephropathy, *MCNS* minimal change nephrotic syndrome, *FSGS* focal segmental glomerulosclerosis, *BP* blood pressure, *uPCR* urinary protein to creatinine ratio, *Cr* creatinine, *BUN* blood urea nitrogen, *TP* total protein, *Alb* albumin, *TC* total cholesterol, *LDL-C* low-density lipid cholesterol, *HDL-C* high-density lipid cholesterol, *TG* triglycerides, *HbA1c* glycated hemoglobin, *Hb* hemoglobin

[a] the value for MCNS was significantly different from those for MN and FSGS

[b] the value for FSGS was significantly different from those for MN and MCNS

patients exhibited significantly increased daily proteinuria (8.90 ± 3.50 for FSGS, 4.56 ± 2.16 for MN, 5.47 ± 3.56 for MCNS g/day, $p = 0.032$), serum creatinine levels (2.37 ± 1.34 for FSGS, 0.94 ± 0.44 for MN, 1.17 ± 0.67 for MCNS mg/dL, $p = 0.004$), and serum blood urea nitrogen levels (30.2 ± 7.8 for FSGS, 14.7 ± 6.9 for MN, 20.4 ± 12.3 for MCNS mg/dL, $p = 0.004$) compared with the other groups. No significant difference in the serum TP level or serum albumin level was detected among the various forms of NS. In addition, there was no difference in the frequency of hematuria (>1+) among the various types of NS because about half of the MCNS patients (47.4 %) had hematuria.

Initial immunosuppressive therapy for elderly NS patients in Japan

Among the three major pathological types of primary NS (MN, MCNS, and FSGS), oral prednisolone (PSL) was administered as an immunosuppressive therapy to 25 MN (86.2 %) patients, 18 MCNS (94.7 %) patients, and all 6 FSGS (100 %) patients, as shown in Table 4. In total, 49 patients (90.7 %) received oral PSL. In addition, intravenous methylprednisolone (mPSL) therapy, cyclosporine (CyA), oral cyclophosphamide, mizoribine, and mycophenolate mofetil were administered to 6 (11.1 %), 23 (42.6 %), 2 (3.7 %), 1 (1.9 %), and 1 (1.9 %) patient(s), respectively. Regarding the immunosuppressive drugs used to treat each pathological type of NS, intravenous mPSL therapy was most frequently used to treat FSGS (50 %), whereas CyA was most commonly used to treat MN and FSGS (58.6 and 50.0 %, respectively).

Among the MPGN patients, three (75 %) were treated with oral PSL and intravenous mPSL, and cyclophosphamide and mizoribine were used in one case each. The remaining MPGN patient dropped out after undergoing a renal biopsy and so did not receive immunosuppressive therapy. The two patients with crescentic glomerulonephritis (CrGN) were treated with oral PSL with or without intravenous mPSL, and the patient with endocapillary

Table 4 Clinical outcome of elderly patients with the 3 major pathological types of NS

Subjects [Elderly/very elderly]	MN (*n*:29) [17/12]		MCNS (*n*:19) [7/12]		FSGS (*n*:6) [2/4]		Total (*n*:54) [26/28]	
Follow-up period (days)	578		701		767		718	
Median [interquartile range]	[404–970]		[318–701]		[423–839]		[395–916]	
Outcomes	n	%	n	%	n	%	n	%
ICR type II (UP 1.0 to < 3.5 g/day)	27	93.1	19	100	5	83.3	51	94.4
Elderly	16	94.1	7	100	2	100	25	96.2
Very elderly	11	91.7	12	100	3	75.0	26	92.9
ICR type I (UP 0.3 to < 1.0 g/day)	18	62.1	19	100	5	83.3	42	77.8
Elderly	10	58.8	7	100	2	100	19	73.1
Very elderly	8	66.7	12	100	3	75.0	23	82.1
Complete remission (UP < 0.3 g/day)	16	55.2	19	100	4	66.7	39	72.2
Elderly	9	52.9	7	100	1	50.0	17	65.4
Very elderly	7	58.3	12	100	3	75.0	22	78.6
Relapse (UP ≥ 1.0 g/day)	2	6.9	9	47.4	0	0.0	11	20.4
Cr × 1.5 times	5[a]	17.2	0	0.0	0	0.0	5	9.3
Cr × 2 times	1	3.4	0	0.0	0	0.0	1	1.9
ESRD	0	0.0	0	0.0	0	0.0	0	0.0
Death	0	0.0	2[b]	10.5	0	0.0	2	3.7
Hospitalization due to infection	2	6.9	2	10.5	0	0.0	4	7.4
Use of anti-diabetic drugs	5	17.2	3	15.8	2	33.3	10	18.5
Malignancy	1	3.4	1	5.3	0	0.0	2	3.7
Immunosuppressive therapy	n	%	n	%	n	%	n	%
Oral prednisolone	25	86.2	18	94.7	6	100.0	49	90.7
IV methylprednisolone	1	3.4	2	10.5	3	50.0	6	11.1
Oral cyclophosphamide	2	6.9	0	0.0	0	0.0	2	3.7
Cyclosporine	17	58.6	3	15.8	3	50.0	23	42.6
Mizoribine	1	3.4	0	0.0	0	0.0	1	1.9
MMF	1	3.4	0	0.0	0	0.0	1	1.9

UP urinary protein, *Cr* creatinine, *ESRD* end-stage renal disease, *IV* intravenous, *MMF* mycophenolate mofetil

[a] One NS patient who was treated with supportive therapy involving renin–angiotensin system inhibitors (RAS-I), two patients with refractory NS (ICR-II) who were treated with PSL+CyA+RAS-I therapy, and two patients who achieved CR after PSL+CyA+RAS-I therapy

[b] One patient who died suddenly at 4 months after achieving CR, and another patient who died of infectious disease at the first relapse (at 6 months after achieving CR)

proliferative glomerulonephritis was treated with supportive therapy alone.

Clinical outcomes and complications of the elderly Japanese primary NS patients

All 19 (100 %) MCNS patients, including one patient who achieved spontaneous remission without immunosuppressive therapy, achieved CR. In addition, CR and ICR-I were achieved in 16 (55.2 %) and 18 (62.1 %) MN patients, 4 (66.7 %) and 5 (83.3 %) FSGS patients, 2 (66.7 %) and 3 (100 %) MPGN patients, and 1 (50 %) and 2 (100 %) CrGN patients, respectively. Relapse occurred in two (6.9 %) of the MN patients and nine (47.4 %) of the MCNS patients. As for renal dysfunction, it was observed in five (7.2 %) MN patients, including one patient who received supportive therapy with renin–angiotensin system inhibitors (RAS-I), two patients with refractory NS who were treated with PSL + CyA + RAS-I therapy, and two patients who achieved CR after PSL + CyA + RAS-I therapy (Table 4).

Among the three major pathological types of NS, serious complications were observed in eight (14.8 %) patients, i.e., two (3.7 %) patients died including one patient who died suddenly at 4 months after achieving CR and another patient who died of infectious disease at the first relapse, which occurred 6 months after achieving CR; four patients (7.4 %, two MCNS patients and two MN patients) who were hospitalized due to infectious disease; and two (3.7 %) patients who developed malignancies (Table 4). In addition, the initiation of anti-diabetic drug treatment was necessary in 14 of the 61 patients (23.0 %), and all 14 of these patients were treated with immunosuppressive drugs including PSL (25.0 %). In addition, the initial dosage of prednisolone was much higher in the group of the initiation of anti-diabetic drug treatment as compared with others (mean 39.3 ± 7.3 vs. 23.6 ± 14.3 mg/day, $p < 0.001$).

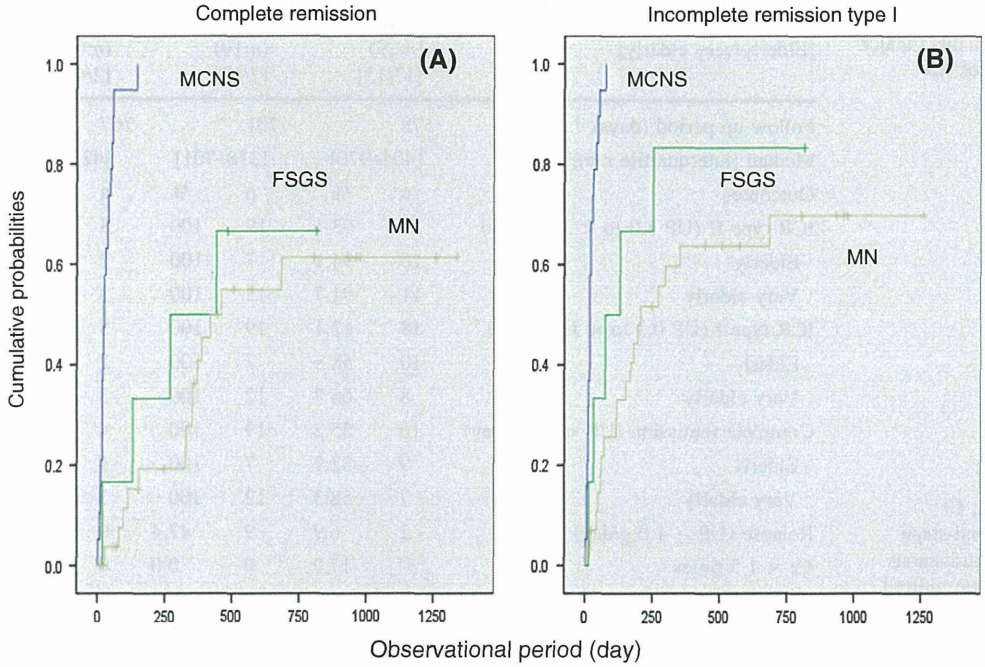

Fig. 1 Kaplan–Meier curves of remission among the elderly NS patients. There were significant differences in the median time to complete remission (a) or ICR-I (b) among the MCNS, FSGS, and MN patients (median: 26 days vs. 271 days vs. 461 days, respectively, log-rank test, Chi-square: 56.606, $p < 0.001$ for CR; 18 days vs. 76 days vs. 207 days, respectively, log-rank test, Chi-square: 44.655, $p < 0.001$ for ICR-I)

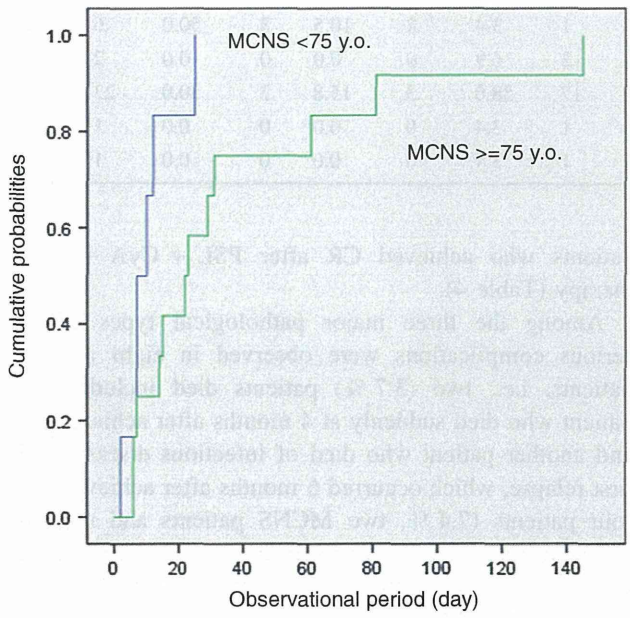

Fig. 2 Kaplan–Meier curves of complete remission among the elderly and very elderly MCNS patients. A significant difference in the median time to complete remission was detected between the elderly (65–74 years, $n = 7$) and very elderly (≥75 years old, $n = 12$) MCNS patients (median: 7 vs. 22 days, respectively, log-rank test, Chi-square: 4.333, $p = 0.037$)

Remission of primary NS in elderly and very elderly MN, MCNS, and FSGS patients

There was a significant difference in the median time to remission; i.e., CR (Kaplan–Meier analysis: 26 vs. 271 vs. 461 days, $p < 0.001$, Fig. 1a) or ICR-I (Kaplan–Meier analysis: 18 vs. 76 vs. 207 days, $p < 0.001$, Fig. 1b), among the patients with MCNS, FSGS, and MN.

In addition, the elderly (65–74 years, $n = 7$) MCNS patients exhibited a significantly shorter time to first remission than the very elderly (aged ≥ 75 years, $n = 12$) MCNS patients (median 7 vs. 22 days, $p = 0.037$, Fig. 2). However, there was no difference in the doses of prednisolone between elderly group (age <75 years, mean dose at 36.7 ± 9.6 mg/day) and very elderly group (age ≥75 years, mean dose at 37.0 ± 10.3 mg/day). After adjusting for clinically relevant factors such as gender, age, serum creatinine levels, serum albumin levels, initial prednisolone doses, and proteinuria using a Cox regression model, age (≥75 years) was identified as a significant predictor of later remission (Chi-square 4.094, $p = 0.043$). On the other hand, no significant difference in the time to first remission was detected between the elderly (17 MN and 2 FSGS patients) and very elderly patients in the MN or FSGS group (12 MN and 4 FSGS patients).

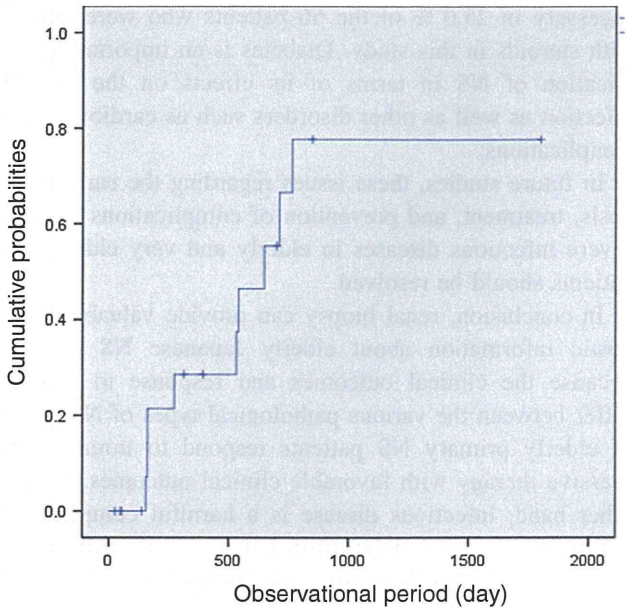

Fig. 3 Kaplan–Meier curves of the first relapse among the elderly MCNS patients. The estimated median time to relapse and the cumulative probability of a first relapse were 647 (95 % confidence interval, 466–828) days and 0.77, respectively

Age did not influence the relapse rate of the elderly or very elderly MCNS patients

Relapses occurred in nine (47.4 %) of the MCNS patients. However, there was no difference in the frequency of relapses between the elderly (65–74 years, $n = 3$, 50 %, one patient dropped out after achieving CR) and the very elderly MCNS patients (aged ≥75 years, $n = 6$, 50 %).

The median time to relapse was 402 days [interquartile range: 159–663]. According to Kaplan–Meier analysis, the estimated median time to relapse and the cumulative probability of a first relapse were 647 days (95 % confidence interval (CI), 466–828) and 0.77, respectively (Fig. 3).

Discussion and comments

The J-RBR represents the largest renal biopsy series of elderly (aged over 65 years) or very elderly (over 75 years) patients in the world [2]. While we cannot exclude the possibility that the J-RBR is subject to sampling bias, it is likely to be reasonably representative of the nationwide situation in Japan. In addition, it allows investigators to analyze the registered data in real time and to select patients with pathologically diagnosed renal conditions such as NS. Using the J-RBR, a previous study demonstrated that among elderly and very elderly Japanese renal biopsies are most commonly performed for NS (36.3 % and 50.7 % of the renal biopsies performed in the elderly and very elderly, respectively) [2]. Similarly, NS was reported to be the most common indication (37–64 %) for renal biopsy in elderly patients of over 60 years old in South Korea, India, Italy, and Spain [13–16].

As for the pathogenesis of NS, a previous study of the J-RBR found that one-third of elderly NS patients displayed primary MN, whereas MCNS exhibited a much lower frequency of about 12–13 % among the elderly and very elderly [2]. Although the difference was not significant, the frequency of MCNS (31.1 %) among the patients selected for the present retrospective study was higher than that observed among the background cohort (19.4 %). The MCNS patients might have been referred to appropriate regional medical centers because MCNS and some cases of FSGS developed so severe generalized edema, and diagnosing MCNS is useful as it allows the patient to be switched to steroid treatment, as shown in this study.

In this study, we detected a difference in the remission rates of elderly Japanese NS patients between the various pathological types of primary NS such as MCNS, FSGS, and MN. The response to immunosuppressive therapy was favorable (100 % of the MCNS patients achieved CR, and 83.3 % of the FSGS patients and 62.1 % of the MN patients achieved an ICR-I or CR) compared with those described in previous reports from Japan [4, 7] and other countries [17, 18]. However, we found the delayed response to steroid in the very elderly MCNS, but not in other pathological types such as MN and FSGS. Moreover, there was no difference in the dosage of prednisolone between the elderly and very elderly MCNS patients. Then, our findings may reflect the delayed recovery of podocyte injury by aging on early response to steroid as shown in MCNS. On the other hand, the ICR-I + CR remission rate of the elderly MN patients (62.1 %, 18 out of 29 patients with a median age of 72 years) was similar to those described in previous reports involving much younger MN patients (66.7 %, 633 out of 949 patients with a mean age of 50.5 years in a nationwide retrospective Japanese survey [19]; 61.4 %, 62 out of 101 patients with a mean age of 46.7 years, in a study of patients treated at Kanazawa University Hospital, Japan [20]). One of the interesting features of the present elderly MN cohort was the fact that 58.6 % of them were administered CyA. Kalliakmani et al. reported that administering low doses of CyA in combination with PSL resulted in the remission of NS in most patients with idiopathic MN [21]. As for FSGS, the ICR-I + CR remission rate observed in the present study (83.3 %, 5 out of 6 patients with a median age of 75 years) was better than that obtained in a nationwide retrospective Japanese survey performed in 2002 (51.8 %, 144 out of

278 patients with a mean age of 38.0 years) [22]. These findings have important implications for the assessment of immunosuppressive therapy in elderly Japanese NS patients. In future, an ongoing prospective study of NS (Japan Nephrotic Syndrome Cohort Study, J-NSCS) as mentioned in the annual report of J-RBR will provide more accurate data on the outcomes of NS patients in Japan [23].

As for the relapse rate of MCNS, the frequency and cumulative probability of a first relapse were 47.4 % and 0.77, respectively, among the elderly patients in the present study, and the median time to the first relapse was quite long (647 days, 95 %CI: 466–823 days). A recent Japanese report about a non-elderly MCNS patient cohort demonstrated that the relapse rates differed between the patients treated with oral PSL combined with intravenous mPSL therapy (mPSL + PSL, 46.2 %, 30 out of 65 patients; median time to relapse: 1-year [0.6–1.5]) and those administered oral PSL alone (66.7 %, 40 out of 60 patients; median time to relapse: 8 months [0.4–1.6]) [24]. Although intravenous mPSL therapy was only administered to two MCNS patients in the present study, their relapse rate was similar to that of the abovementioned mPSL+PSL group, which was derived from a much younger population. In addition, elderly MCNS patients displayed a much longer interval until the first relapse. Therefore, immunosuppressive therapy including corticosteroids might be effective for elderly Japanese MCNS patients.

On the contrary, renal dysfunction developed in five MN patients; i.e., one patient with prolonged NS who was treated with supportive therapy involving RAS-I, two patients with refractory NS who were treated with PSL+CyA+RAS-I therapy, and two patients who achieved CR after PSL+CyA+RAS-I therapy. These findings suggest that prolonged proteinuria, as was shown in previous studies [19, 20], and/or long-term combination treatment with RAS-I and CyA influence the risk of renal dysfunction, even after CR has been achieved. Similarly, it was reported that significant deterioration of histological lesions occurs with time even in MN patients who achieve remission, although MN patients do not display the typical features of CyA nephrotoxicity [21]. In this notion, CyA-related renal injury after remission in the elderly nephrotic syndrome was a future issue to answer by more large case studies.

In this study, two of the MCNS patients died, and two MCNS patients were hospitalized due to infectious disease. Thus, about 20 % of the elderly MCNS patients suffered serious complications. Infectious diseases are a life-threatening complication of NS. A previous report suggested that intravenous immunoglobulin injections might be useful for maintaining serum IgG levels of >600 mg/dL and for preventing infectious complications of NS [25]. In addition, the initiation of anti-diabetic drug treatment was necessary in 25.0 % of the 56 patients who were treated with steroids in this study. Diabetes is an important complication of NS in terms of its effects on the risk of infection as well as other disorders such as cardiovascular complications.

In future studies, these issues regarding the early diagnosis, treatment, and prevention of complications such as severe infectious diseases in elderly and very elderly NS patients should be resolved.

In conclusion, renal biopsy can provide valuable diagnostic information about elderly Japanese NS patients because the clinical outcomes and response to therapy differ between the various pathological types of NS. Most of elderly primary NS patients respond to immunosuppressive therapy with favorable clinical outcomes. On the other hand, infectious disease is a harmful complication among elderly NS patients, especially those with MCNS. In future, modified clinical guidelines for elderly NS patients should be developed.

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Conflict of interest None of authors have any conflicts of interest to disclose for this paper.

Appendix

The following investigators and institutions have participated in the development of the J-RBR since 2007: Hirofumi Makino and Hitoshi Sugiyama (Okayama University), Takashi Taguchi (Nagasaki University; present institution: Nagasaki City Hospital), Hitoshi Yokoyama (Kanazawa Medical University), Hiroshi Sato (Tohoku University), Takao Saito and Yoshie Sasatomi (Fukuoka University), Yukimasa Kohda (Kumamoto University; present institution: Hikarinomori Clinic), Shinichi Nishi (Niigata University; present institution: Kobe University), Kazuhiko Tsuruya and Yutaka Kiyohara (Kyushu University), Hideyasu Kiyomoto (Kagawa University; present institution: Tohoku University), Hiroyuki Iida (Toyama Prefectural Central Hospital; present institution, Saiseikai Takaoka Hospital), Tamaki Sasaki (Kawasaki Medical School), Makoto Higuchi (Shinshu University), Motoshi Hattori (Tokyo Women's Medical University), Kazumasa

Oka (Osaka Kaisei Hospital; present institution: Hyogo Prefectural Nishinomiya Hospital), Shoji Kagami (The University of Tokushima Graduate School), Michio Nagata (University of Tsukuba), Tetsuya Kawamura (Jikei University School of Medicine), Masataka Honda (Tokyo Metropolitan Children's Medical Center), Yuichiro Fukasawa (KKR Sapporo Medical Center; present institution: Sapporo City Hospital), Atsushi Fukatsu (Kyoto University Graduate School of Medicine), Kunio Morozumi (Japanese Red Cross Nagoya Daini Hospital), Norishige Yoshikawa (Wakayama Medical University), Yukio Yuzawa (present institution: Fujita Health University), Seiichi Matsuo (Nagoya University Graduate School of Medicine) and Kensuke Joh (Chiba-East National Hospital; present institution: Sendai Shakai Hoken Hospital).

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ORIGINAL ARTICLE

The influences of larger physical constitutions including obesity on the amount of urine protein excretion in primary glomerulonephritis: research of the Japan Renal Biopsy Registry

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Abstract
Background This study aimed to describe the influences of larger physical constitutions including obesity on the amount of urine protein excretion (AUPE) in primary glomerulonephritis. The distinct effects on the AUPE in various types of glomerulonephritis were evaluated.
Methods Using the database of the Japan Renal Biopsy Registry (J-RBR) from 2007 to 2010, 4060 cases with primary glomerulonephritis including MCNS, FSGS, MN, MPGN, IgAN, and non-IgA were reviewed. The AUPEs were compared between high and low Body Mass Index (BMI) groups, and larger and smaller body surface area (BSA) groups using the indexes of BMI 25.0 kg/m^2 and BSA 1.73 m^2 in all cases and in each histological group. Multivariable analysis was performed to evaluate the predominant contributors to the AUPE.
Results The larger physical constitution groups (BMI $\geq$25.0 kg/m^2 or BSA $\geq$1.73 m^2) had significantly higher AUPEs in all cases with primary glomerulonephritis. When compared in each histological group, the mean AUPEs were significantly higher in the larger physical constitution groups, excluding the FSGS and non-IgA groups. Multiple regression analysis revealed that the significant contributors to the AUPE were BMI and BSA in MCNS and MN, whereas BMI and BSA were not significant and mean blood pressure and serum creatinine were significant in FSGS and non-IgA.
Conclusion Larger physical constitutions including obesity had a significant impact on the increase in the AUPE in primary glomerulonephritis, especially in MCNS and MN. However, FSGS and non-IgA were distinct for having blood pressure and renal dysfunction as possibly the major causes of proteinuria.

Keywords Obesity · Urine protein · Glomerulonephritis · Body mass index · Body surface area

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Introduction

Multiple mechanisms, such as hyperfiltration, increased glomerular capillary wall tension, and podocyte stress, have been postulated as affecting the amount of urine protein of obese person [1]. Ohashi et al. [2] used bioelectrical impedance analysis to evaluate the correlation between BMI, ambulatory blood pressure, and total body water. These investigators found significant relationships between BMI, proteinuria and hypertension. In glomerulonephritis, Tanaka et al. [3] proved that increased proteinuria is associated with glomerular enlargement and glomerular basement membrane thickening in obese

patients with IgA nephropathy. Woo et al. [4] suspected that the dramatic increase in focal segmental glomerulosclerosis in Asian countries might be related to the increase of the obesity population worldwide. It is thought that larger physical constitutions including obesity affect the glomeruli both physiologically and pathologically, as well as the amount of urine protein excretion (AUPE) in glomerulonephritis. Recently, the average age of patients with glomerulonephritis has been increasing in Japan. Data from the Japan Renal Biopsy Registry (J-RBR) showed that the mean ages of patients with chronic nephritic syndrome and nephrotic syndrome were 42.5 and 51.5 years, respectively [5]. In the middle-aged population, the rate of complications from obesity rises [6]; therefore, attention should be given to the extent of the affect this non-histological factor has on the AUPE. However, unfortunately edematous condition is not perfectly excluded in nephrotic patients. Thus, we determined that the goal of the study was to evaluate the relationships between larger physical constitution including obesity and the AUPE in each histological type of glomerulonephritis.

Materials and methods

Subjects

This was a cross sectional study of a cohort of patients who were registered in the J-RBR from 31 July 2007 to 31 October 2010. During that time period, 10,550 patients ≥18 years were registered in the J-RBR. From the data on these patients, information was extracted on pathologically and clinically diagnosed primary glomerulonephritis including minimal change nephrotic syndrome (MCNS), focal segmental glomerulosclerosis (FSGS), membranous nephropathy (MN), membranoproliferative glomerulonephritis (MPGN), IgA nephropathy (IgAN), and non-IgA type mesangial proliferative glomerulonephritis (non-IgA). Exclusion criteria were: patients with secondary glomerulonephritis, body weight under 30 kg or over 150 kg, height under 140 cm or over 200 cm, serum creatinine (S–Cr) under 0.1 mg/dL or over 20 mg/dL, serum total protein under 1 g/dL or over 12 g/dL, serum albumin over 6 g/dL, and the AUPE over 30 g/day. The AUPE was measured from a 24-h urine collection. Nephrotic syndrome was defined as low albumin (<3.0 g/dL) and AUPE more than 3.5 g/day.

The ethics committee of the Japanese Society of Nephrology comprehensively approved the study, and a local committee of participating centers and their affiliated hospitals individually approved the study. Written informed consent was obtained from the patients at the time of biopsy and at the time they were registered to participate in the study. The J-RBR/J-KDR is registered in the Clinical Trial Registry of UMIN (Registered Number UMIN000000618).

Physical constitutions

BMI and BSA were used to evaluate a patient's body constitutions. According to the definition of obesity by the Japan Society for the Study of Obesity (JASSO), the patients were divided into two groups: BMI ≥25 as the high BMI group, and BMI <25 as the low BMI group. The DuBoi's formula ($Wt^{0.425}$(kg) × $Ht^{0.725}$(cm) × 0.007184) was used to calculate BSA. The subjects were divided into two groups: BSA ≥1.73 m^2 as the high BSA group, and BSA <1.73 m^2 as the low BSA group.

Analysis between AUPE and physical constitution

The mean ± standard deviation (SD) of the AUPE for each type of glomerulonephritis was calculated. The AUPE was compared between the high and low BMI groups, and between the high and low BSA groups in all patients and in each type of glomerulonephritis. Additionally, the AUPE was compared between patients with or without nephrotic syndrome.

Multivariable analyses were performed to extract significant factors contributing to AUPE. BMI, BSA, age, S–Cr, and mean arterial pressure (MAP = [(2 × diastolic BP) + systolic BP]/3), were selected as independent variables.

Statistical analyses

Statistical analyses were performed using Dr. SPSS II for Windows (SPSS, Tokyo, Japan). Data were compared using Kruskal–Wallis analysis and Mann–Whitney *U* test. *p* values <0.05 were considered to indicate statistical significance. Multiple linear regression analysis was performed as a multivariable analysis in this study.

Results

Patient profiles

Among the 10,550 cases registered in the J-RBR, 4060 cases with primary glomerulonephritis were extracted (MCNS, 454 cases; FSGS, 279 cases; MN, 696 cases; MPGN, 105 cases; IgAN, 2354 cases; and non-IgA, 172 cases). The mean age was 47.3 years. The mean BMI and mean BSA were 23.2 kg/m^2 and 1.65 m^2, respectively. Among the 4060 patients with primary glomerulonephritis, 27.6 % of the patients had BMI ≥25.0 kg/m^2 and 35.2 %

had BSA ≥1.73 m^2. The mean AUPE was 2.50 g/day. A quarter of all cases had proteinuria at the nephrotic level of ≥3.5 g/day (Table 1).

In the MN and MPGN groups, the mean ages tend to be older, >60 years. In the IgAN group, the ages tend to be younger, about 40 years. The mean AUPE exceeded the nephrotic level, 3.5/day, in the MCNS, MN, and MPGN groups. The average AUPE in the MCNS group was 7.00 g/day, but 22.5 % of the patients in this group showed the sub-nephrotic range of AUPE at the time of registration. In the IgAN and non-IgA groups, the rates of nephrotic syndrome were lower, <10 %. In the FSGS, MN, and MPGN groups, MAP averages were higher and exceeded 95.0 mmHg (Table 2).

Table 1 Characteristics of all patients ($n = 4060$)

Age (years)	47.3 ± 17.9
Male (%)	54.4
Body weight (kg)	61.6 ± 12.5
Height (m)	1.63 ± 0.09
BMI (kg/m^2)	23.2 ± 3.80
Rate of BMI ≥25 (%)	27.6
BSA (m^2)	1.65 ± 0.19
Rate of BSA ≥1.73 (%)	35.2
Proteinuria (g/day)	2.50 ± 3.34
Rate of nephrotic syndrome (%)	25.0
Serum creatinine (mg/dL)	1.04 ± 0.78
Serum albumin (g/dL)	3.40 ± 1.01
Mean arterial pressure (mmHg)	92.5 ± 13.5

Data are shown as mean ± S.D

BMI body mass index, *BSA* body surface area

Comparison between larger and smaller physical constitution groups

In the evaluation of all subjects, the mean AUPE was significantly higher in the high BMI and high BSA groups, respectively (low vs. high BMI 2.21 ± 3.03 vs. 3.27 ± 3.93, $p < 0.001$; low vs. high BSA 2.28 ± 2.99 vs. 2.89 ± 3.88, $p < 0.001$) (Fig. 1). When compared with each histological group, the averages of the AUPE were significantly higher in the high BMI groups than in the low BMI groups, excluding the FSGS and non-IgA groups (Fig. 2). The averages of the AUPE were also significantly higher in the high BSA groups compared with the low BSA groups, excluding the FSGS, MPGN and non-IgA groups (Fig. 3).

Comparison of nephrotic and non-nephrotic cases

Comparison of the AUPE in the nephrotic patients of each histological group showed significant differences between the MCNS, MN, MPGN, and IgAN groups. The averages of the AUPE were significantly higher in the high BMIgroups (low vs. high BMI, MCNS 8.23 ± 4.18 vs. 9.31 ± 4.64, $p = 0.021$; MN 6.08 ± 3.19 vs. 7.23 ± 3.97, $p = 0.003$; MPGN 5.69 ± 2.18 vs. 8.30 ± 3.27, $p = 0.007$; IgAN 5.00 ± 1.95 vs. 5.94 ± 2.43, $p = 0.015$). However, the FSGS and non-IgA groups did not show significant differences between the high and low BMI groups with nephrotic syndrome (Fig. 4). Comparing the

Table 2 Basic characteristics of patients in each primary histological group

Histological diagnosis	MCNS	FSGS	MN	MPGN	IgAN	Non-IgA	*p*
Number of Patients	454	279	696	105	2354	172	–
Age (years)	46.5 ± 19.6	49.3 ± 18.2	64.0 ± 11.4	61.6 ± 17.0	41.5 ± 15.5	50.2 ± 16.9	<0.01
Male (%)	57.9	64.2	57.8	56.2	51.9	47.7	–
Body Weight (kg)	63.6 ± 13.1	64.4 ± 14.3	60.6 ± 11.6	58.3 ± 10.8	61.4 ± 12.5	61.0 ± 12.4	<0.01
Height (m)	1.63 ± 0.09	1.63 ± 0.09	1.60 ± 0.09	1.59 ± 0.09	1.63 ± 0.088	1.62 ± 0.09	<0.01
BMI (kg/m^2)	23.8 ± 4.10	24.1 ± 4.57	23.7 ± 3.55	23.1 ± 3.50	22.88 ± 3.68	23.3 ± 3.78	<0.01
Rate of BMI ≥25 (%)	31.7	35.8	31.8	21.9	24.7	29.1	–
BSA (m^2)	1.68 ± 0.19	1.69 ± 0.20	1.62 ± 0.18	1.59 ± 0.17	1.66 ± 0.19	1.64 ± 0.18	<0.01
Rate of BSA ≥1.73 (%)	40.1	44.4	28.3	21.9	36	33.1	–
AUPE (g/day)	7.00 ± 4.89	3.41 ± 3.13	4.08 ± 3.54	4.10 ± 3.39	1.06 ± 1.38	1.43 ± 2.27	<0.01
Rate of nephrotic syndrome (%)	77.5	38.7	49.3	51.4	5.90	11.0	–
Serum creatinine (mg/dL)	1.06 ± 0.77	1.24 ± 0.96	0.90 ± 0.47	1.45 ± 1.05	1.02 ± 0.74	1.12 ± 1.44	<0.01
Serum albumin (g/dL)	1.92 ± 0.77	3.10 ± 1.06	2.63 ± 0.81	2.87 ± 0.73	3.94 ± 0.55	3.87 ± 0.78	<0.01
Mean arterial pressure (mmHg)	89.6 ± 12.2	95.9 ± 13.7	95.2 ± 13.8	99.6 ± 14.2	91.4 ± 13.3	94.1 ± 13.8	<0.01

Data are shown as mean ± SD

MCNS minimal change nephrotic syndrome, *FSGS* focal segmental glomerulosclerosis, *MN* membranous nephropathy, *MPGN* membranoproliferative glomerulonephritis, *IgAN* IgA nephropathy, *non–IgA* non-IgA glomerulonephritis, *AUPE* amount of urinary protein excretion

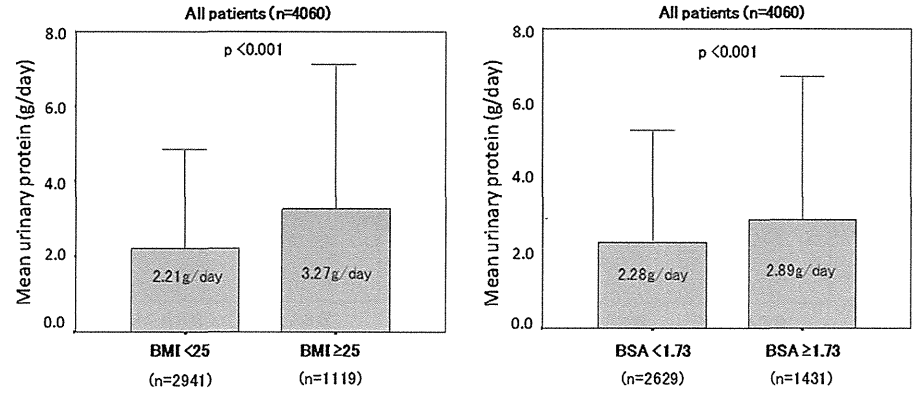

Fig. 1 The comparison amount of urine protein between high and low BMI/BSA groups in all patients. Data are shown as mean ± SD, *BMI* body mass index, *BSA* body surface area

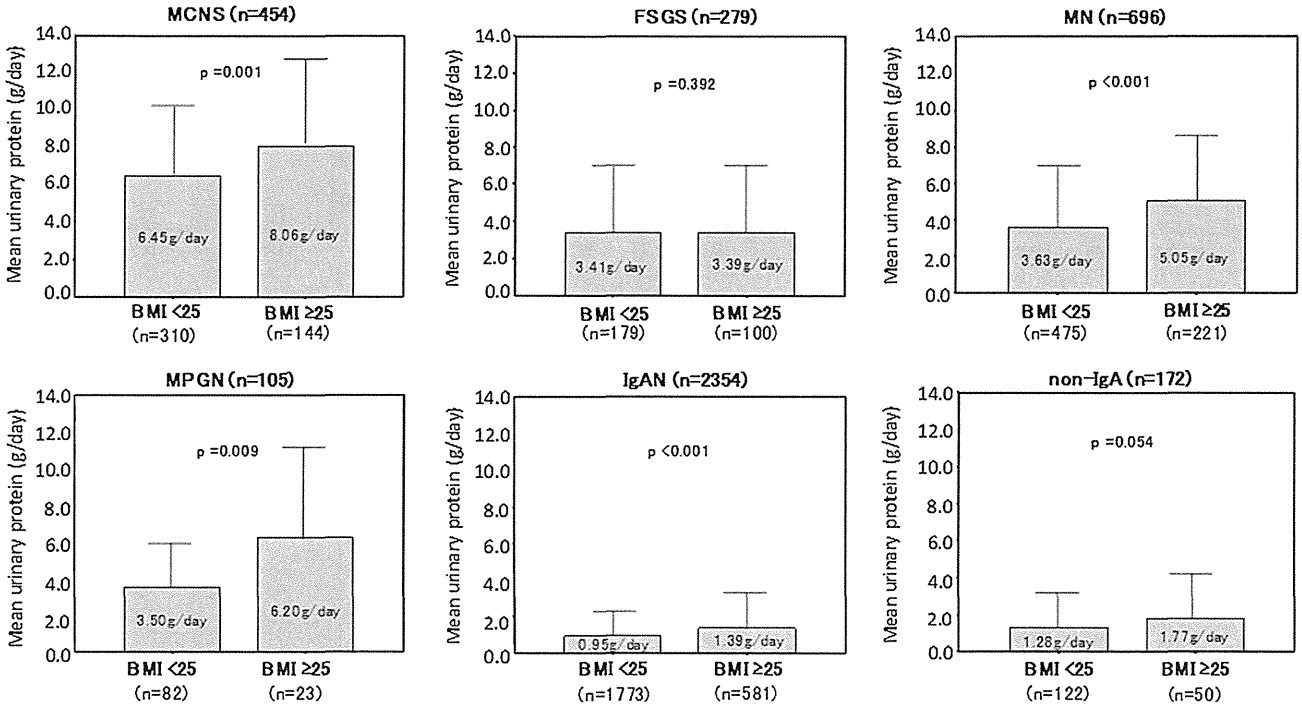

Fig. 2 The comparison amount of urine protein between high and low BMI groups in all patients of each histological group. Data are shown as mean ± SD, *BMI* body mass index, *BSA* body surface area

high and low BSA groups with nephrotic syndrome, significant differences were noted only in the MCNS and MN groups (low vs. high BSA, MCNS 7.62 ± 3.59 vs. 9.94 ± 4.96, $p < 0.001$; MN 6.17 ± 3.19 vs. 7.31 ± 4.13, $p = 0.004$) (Fig. 5).

Comparison of the AUPE in non-nephrotic patients of each histological group showed significant differences in the FSGS and IgAN groups between the high and low BMI groups (low vs. high BMI, FSGS 1.24 ± 0.93 vs. 1.60 ± 0.99, $p = 0.016$; IgAN 0.74 ± 0.72 vs. 0.96 ± 0.77, $p < 0.001$) (Fig. 6). Comparison of the high and low BSA groups with non-nephrotic syndrome, significant differences were noted only in the IgA and non-IgA groups (low vs. high BSA, IgAN 0.75 ± 0.73 vs. 0.87 ± 0.75, $p < 0.001$; non-IgA 0.71 ± 0.86 vs. 0.82 ± 0.71, $p = 0.039$) (Fig. 7).

Multivariable analysis

To evaluate the contributing factors for the AUPE, multiple regression analysis was performed in all, nephrotic and non-nephrotic patients. BMI and BSA were found to be the significant independent contributing factors for the AUPE in all cases, all nephrotic and all non-nephrotic patients, respectively. Nevertheless, in the restricted FSGS group, BMI and BSA were not the significant independent contributing factors for the AUPE even in nephrotic and non-nephrotic cases. Rather, S–Cr and MAP were the

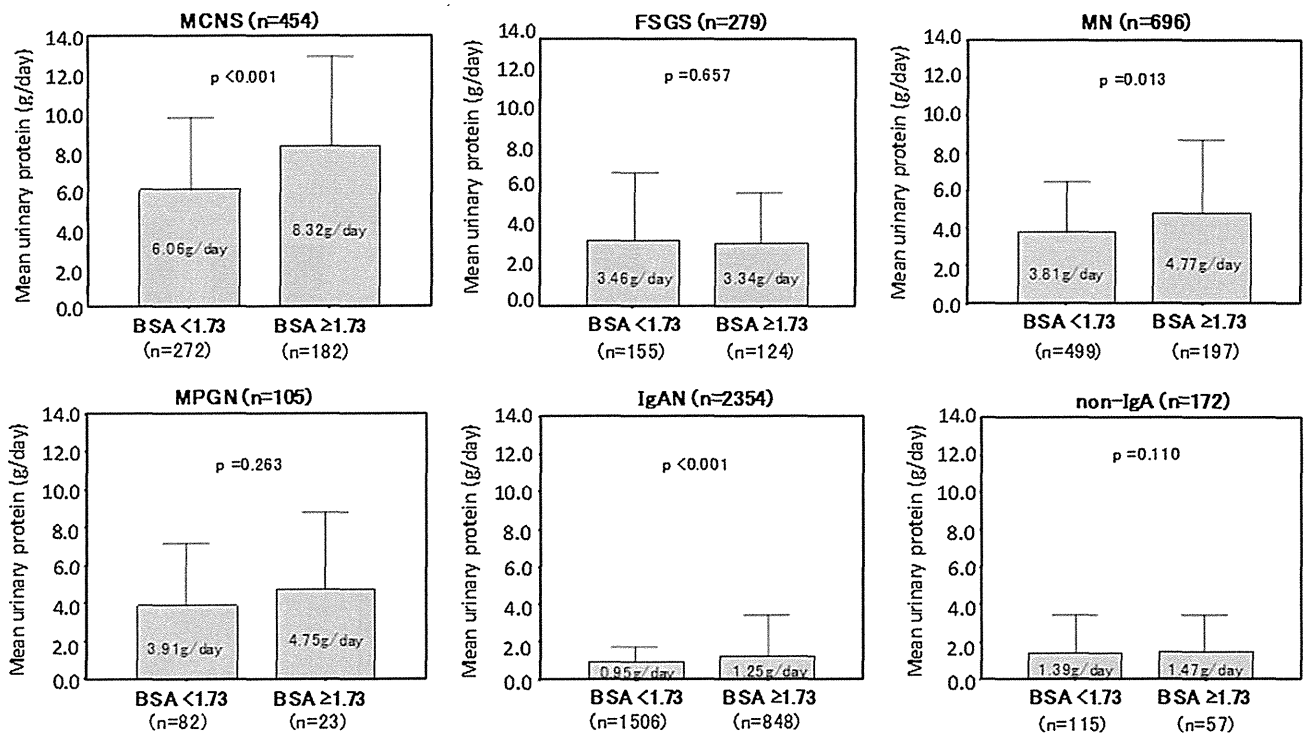

Fig. 3 The comparison amount of urine protein between high and low BSA groups in all patients of each histological group. Data are shown as mean ± SD, *BMI* body mass index, *BSA* body surface area

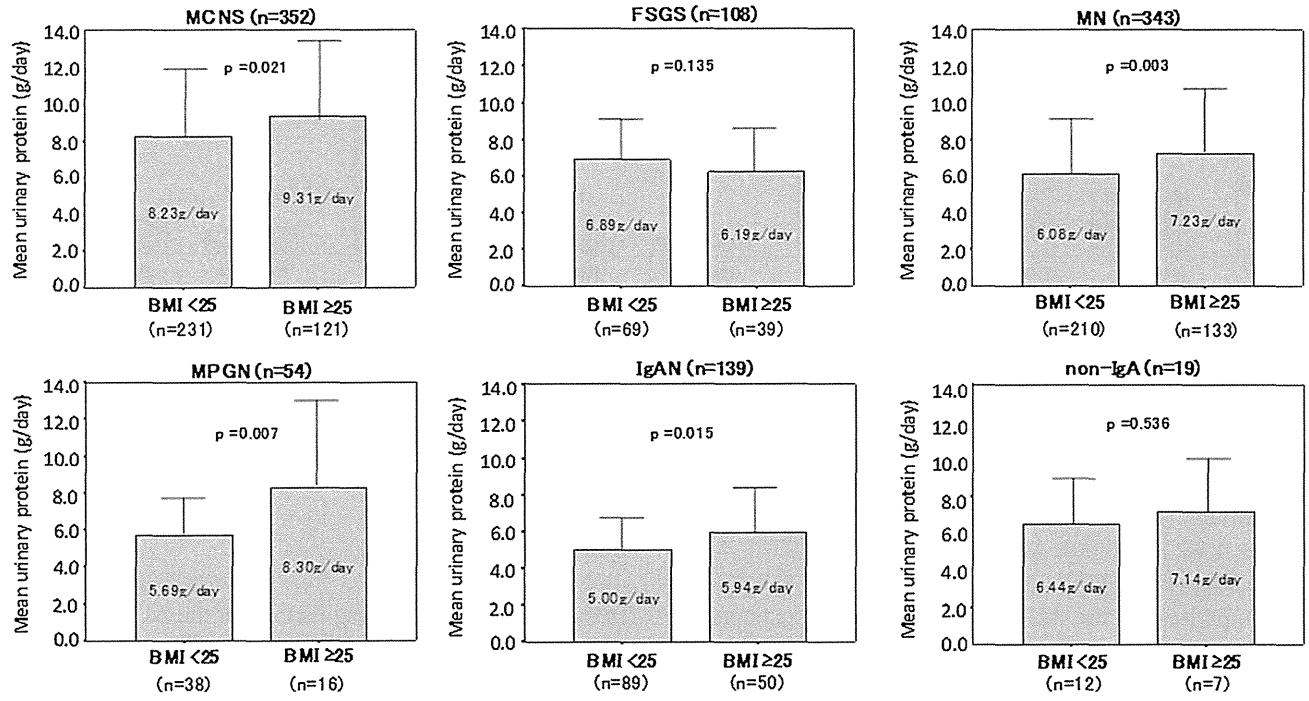

Fig. 4 The comparison amount of urine protein between high and low BMI groups in nephrotic patients of each histological group. Data are shown as mean ± SD, *BMI* body mass index, *BSA* body surface area

significant contributing factors for the AUPE in the FSGS group. Similarly in the analysis of the non-IgAN group, BMI and BSA were not the significant independent contributing factors for the AUPE even in nephrotic and non-nephrotic cases. Only S–Cr was a significant independent factor contributing to the AUPE (Table 3). In other

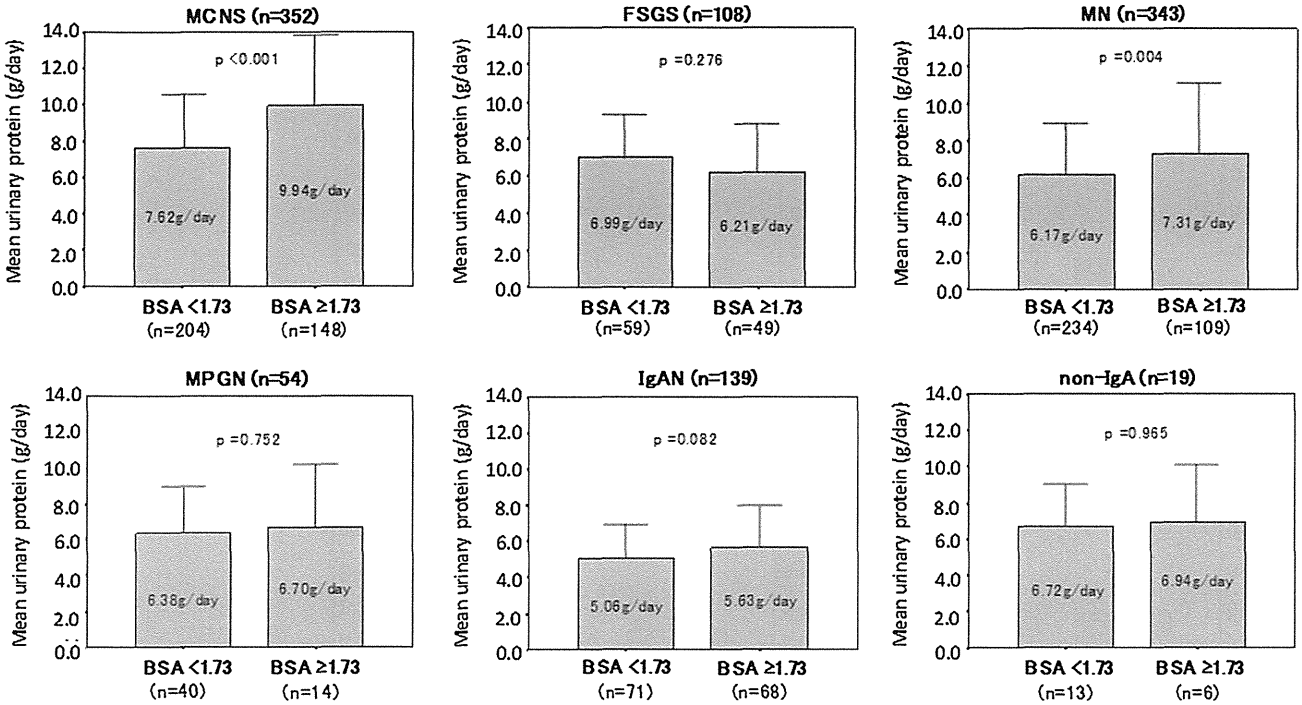

Fig. 5 The comparison amount of urine protein between high and low BSA groups in nephrotic patients of each histological group. Data are shown as mean ± SD, *BMI* body mass index, *BSA* body surface area

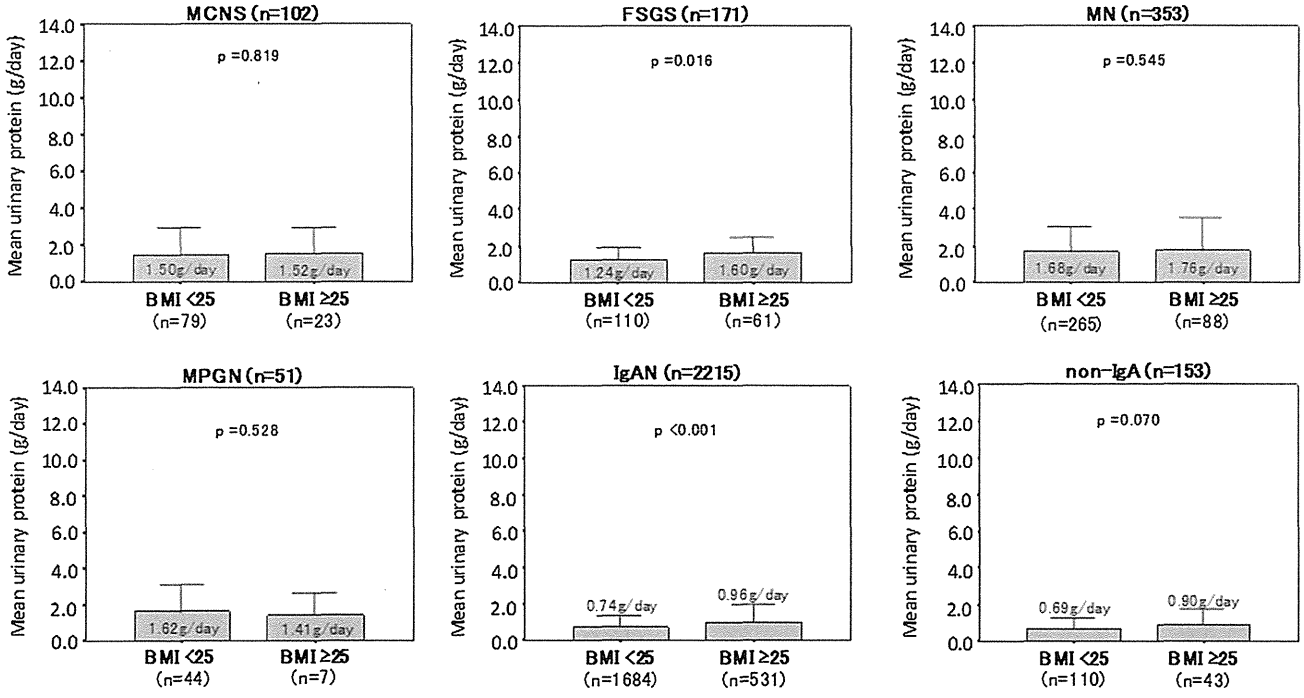

Fig. 6 The comparison amount of urine protein between high and low BMI groups in non-nephrotic patients of each histological group. Data are shown as mean ± SD, *BMI* body mass index, *BSA* body surface area

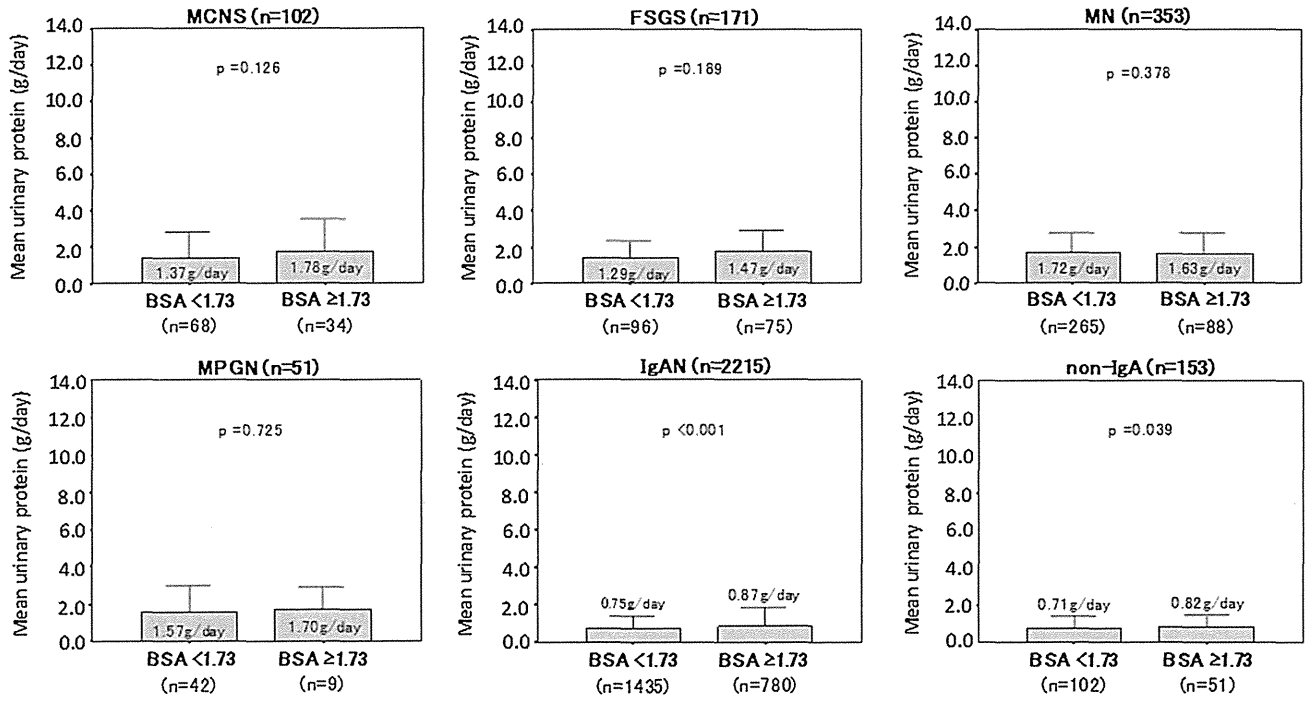

Fig. 7 The comparison amount of urine protein between high and low BSA groups in non-nephrotic patients of each histological group. Data are shown as mean ± SD, *BMI* body mass index, *BSA* body surface area

way BMI and BSA showed the significant impacts on the AUPE in only nephrotic MCNS and MN. Interestingly BMI and BSA of IgAN were significant contributors to the AUPE in nephrotic and non-nephrotic groups.

Discussion

Consistent with the tendency toward an aging society, the average age of patients with primary glomerulonephritis has been rising in recent years. The latest J-RBR report revealed that the average ages of patients with chronic nephritic syndrome and nephrotic syndrome were 42.5 and 51.5 years, respectively [5]. When limited to patients with membranous nephropathy, the average was 62.2 years in another J-RBR data report [7].

In the present study, the mean age of all patients with primary glomerulonephritis was 47.3 years (Table 1). The mean age of each histological group exceeded 40 years (Table 2). The rates of obesity (BMI $\geq$25 kg/m^2) ranged from 21.0 to 35.5 % in the histological groups.

The prevalence of obesity has been increasing in many countries. According to the international definition of obesity, the prevalence of obesity (BMI $\geq$30 kg/m^2) in Japanese adults has been said to be approximately 1–3 % [6], which is quite low compared with other countries. On the other hand, the recent prevalence of being overweight (BMI $\geq$25 kg/m$^{2)}$ that corresponds to the Japanese definition of obesity, was discovered to be approximately 20–30 %, especially in middle-aged people [6].

There has been a focus on obesity as a risk factor for impairment due to chronic kidney disease (CKD) and cardiovascular disease because obesity is an inducer of massive proteinuria [8]. Additionally, in the progression of CKD in obese patients, the pathogenic mechanisms are considered to be hypertension, dysregulated production of adipokines, and inflammation derived from fat accumulation [8, 9]. Therefore, reduction of BMI is the preferential strategy for preventing the progress of CKD [10, 11]. However, the influences of larger physical constitutions including obesity on the AUPE have not been sufficiently evaluated in various types of primary glomerulonephritis.

Obesity-related glomerulopathy has received attention as an independent glomerulopathy characterized by dominant proteinuria with glomerular hypertrophy alone or focal segmental glomerulosclerosis lesions with glomerular hypertrophy [12–14]. Its etiologies have been conjectured to be associated with activation of the renin-angiotensin system, inflammation, and oxidative stress that develops in obese patients [15, 16]. In particular, glomerular hyperfiltration is believed to lead to the characteristic proteinuira [12, 17]. Thus, it is important to consider that proteinuria is produced not only by glomerular damage, but also through the disproportional physical constitution that is found particularly in obese patients.

Table 3 Multiple linear regression analysis for the amount of urine protein

All cases				
	β	Coefficient	95 % CI	*p*
All cases				
Model 1				
Age	0.030	0.163	0.024 to 0.037	<0.01
BMI	0.123	0.142	0.093 to 0.153	<0.01
S–Cr	0.395	0.090	0.245 to 0.546	<0.01
MAP	0.008	0.031	–0.001 to 0.017	0.089
Model 2				
Age	0.036	0.196	0.030–0.043	<0.01
BSA	2.056	0.117	1.447–2.666	<0.01
S–Cr	0.351	0.080	0.198–0.503	<0.01
MAP	0.010	0.039	0.001–0.0019	<0.05
Non–nephrotic cases				
Model 1				
Age	0.011	0.215	0.009–0.013	<0.01
BMI	0.011	0.045	0.002–0.020	<0.05
S–Cr	0.151	0.024	0.104–0.199	<0.01
MAP	0.011	0.162	0.008–0.014	<0.01
Model 2				
Age	0.011	0.218	0.009 to 0.013	<0.01
BSA	–0.031	–0.007	–0.215 to 0.153	0.74
S–Cr	0.153	0.123	0.105 to 0.210	<0.01
MAP	0.012	0.174	0.009 to 0.014	<0.01
Nephrotic cases				
Model 1				
Age	–0.031	–0.152	–0.044 to 0.017	<0.01
BMI	0.106	0.120	0.045 to 0.167	<0.01
S–Cr	0.205	0.048	–0.089 to 0.500	0.171
MAP	–0.021	–0.080	–0.039 to 0.02	<0.05
Model 2				
Age	–0.020	–0.102	–0.035 to 0.006	<0.01
BSA	3.008	0.164	1.675 to 4.341	<0.01
S–Cr	0.152	0.036	–0.143 to 0.447	0.312
MAP	–0.022	–0.085	–0.040 to 0.004	<0.05
FSGS cases				
	β	Coefficient	95 % CI	*p*
All cases				
Model 1				
Age	0.014	0.081	–0.009 to 0.038	0.236
BMI	–0.028	–0.042	–0.119 to 0.062	0.539
S–Cr	0.426	0.140	0.026 to 0.826	<0.05
MAP	0.054	0.231	0.022 to 0.086	<0.01
Model 2				
Age	0.015	0.086	–0.009 to 0.040	0.223
BSA	–0.058	–0.004	–2.178 to 2.062	0.957
S–Cr	0.420	0.138	0.018 to 0.822	<0.05
MAP	0.052	0.223	0.021 to 0.084	<0.01
Non–nephrotic cases				
Model 1				
Age	0.008	0.138	–0.002 to 0.018	0.126
BMI	0.016	0.075	–0.020 to 0.051	0.386
S–Cr	0.159	0.192	0.019 to 0.299	<0.05
MAP	0.015	0.209	0.002 to 0.028	<0.05
Model 2				
Age	0.007	0.132	–0.003 to 0.018	0.158
BSA	0.097	0.020	–0.764 to 0.957	0.824
S–Cr	0.158	0.191	0.017 to 0.299	<0.05
MAP	0.016	0.220	0.003 to 0.029	<0.05
Nephrotic cases				
Model 1				
Age	0.008	0.057	–0.022 to 0.038	0.6
BMI	–0.090	–0.166	–0.210 to 0.031	0.142
S–Cr	0.574	0.192	–0.077 to 1.226	0.083
MAP	0.021	0.110	–0.021 to 0.063	0.324
Model 2				
Age	0.006	0.047	–0.024 to 0.037	0.678
BSA	–1.431	–0.119	–4.134 to 1.272	0.295
S–Cr	0.555	0.185	–0.100 to 1.210	0.095
MAP	0.017	0.089	–0.025 to 0.059	0.419
Non–IgAN cases				
	β	Coefficient	95 % CI	*p*
All cases				
Model 1				
Age	0.024	0.189	0.002 to 0.046	<0.05
BMI	0.051	0.086	–0.053 to 0.155	0.332
S–Cr	0.535	0.181	0.029 to 1.041	<0.05
MAP	0.005	0.035	–0.022 to 0.033	0.699
Model 2				
Age	0.027	0.212	0.004 to 0.050	<0.05
BSA	1.142	0.094	–0.993 to 3.277	0.292
S–Cr	0.513	0.174	0.003 to 1.023	<0.05
MAP	0.007	0.046	–0.020 to 0.034	0.601
Non–nephrotic cases				
Model 1				
Age	–0.005	–0.095	–0.014 to 0.004	0.321