Progress of the study

Prior to the study, we selected 15 management facilities and 49 local medical associations, registered 491 family physicians (between April and June 2008), and registered 2,494 study participants on a provisional basis (between April and October 15, 2008), 2,413 of whom were randomly divided into intervention groups A (1,211) and B (1,202) in units of medical associations (or clusters) in September 2008. We started the intervention study on October 20, 2008.

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References

1. Nakai S, Masakane I, Akiba T, Iseki K, Watanabe Y, Itami N, et al. Overview of regular dialysis treatment in Japan (as of 31 December 2005). Ther Apher Dial. 2007;11:411–41.
2. Sarnak MJ, Levey AS, Schoolwerth AC, Coresh J, Culleton B, Hamm LL, et al. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. Circulation. 2003;108:2154–69.
3. Foley RN, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. Am J Kidney Dis. 1998;32:S112–9.
4. Imai E, Horio M, Watanabe T, Iseki K, Yamagata K, Hara S, et al. Prevalence of chronic kidney disease (CKD) in Japanese general population. Clin Exp Nephrol, 2009.
5. Mann JF, Gerstein HC, Pogue J, Bosch J, Yusuf S. Renal insufficiency as a predictor of cardiovascular outcomes and the impact of ramipril: the HOPE randomized trial. Ann Intern Med. 2001;134:629–36.
6. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med. 2004;351:1296–305.
7. Hillege HL, Girbes AR, de Kam PJ, Boomsma F, de Zeeuw D, Charlesworth A, et al. Renal function, neurohormonal activation, and survival in patients with chronic heart failure. Circulation. 2000;102:203–10.
8. Brugts JJ, Knetsch AM, Mattace-Raso FU, Hofman A, Witteman JC. Renal function and risk of myocardial infarction in an elderly population: the Rotterdam Study. Arch Intern Med. 2005;165: 2659–65.
9. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis. 2002; 39:S1–266.
10. Levey AS, Eckardt KU, Tsukamoto Y, Levin A, Coresh J, Rossert J, et al. Definition and classification of chronic kidney disease: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int. 2005;67:2089–100.
11. Yamagata K, Takahashi H, Suzuki S, Mase K, Hagiwara M, Shimizu Y, et al. Age distribution and yearly changes in the incidence of end-stage renal disease in Japan. Am J Kidney Dis. 2004;43:433–43.
12. Sorensen VR, Hansen PM, Heaf J, Feldt-Rasmussen B. Stabilized incidence of diabetic patients referred for renal replacement therapy in Denmark. Kidney Int. 2006;70:187–91.
13. Yamagata K, Ishida K, Sairenchi T, Takahashi H, Ohba S, Shiigai T, et al. Risk factors for chronic kidney disease in a community-based population: a 10-year follow-up study. Kidney Int. 2007;71: 159–66.
14. Heagerty A. Optimizing hypertension management in clinical practice. J Hum Hypertens. 2006;20:841–9.
15. Usami T, Nakao N, Fukuda M, Takeuchi O, Kamiya Y, Yoshida A, et al. Maps of end-stage renal disease and amounts of angiotensin-converting enzyme inhibitors prescribed in Japan. Kidney Int. 2003;64:1445–9.
16. CKD Clinical Practice Guidelines: Japanese Society of Nephrology (written and edited), First edition, Tokyo Igakusha, 2007.
17. Usami T, Koyama K, Takeuchi O, Morozumi K, Kimura G. Regional variations in the incidence of end-stage renal failure in Japan. JAMA. 2000;284:2622–4.
18. Imai E, Horio M, Yamagata K, Iseki K, Hara S, Ura N, et al. Slower decline of glomerular filtration rate in the Japanese general population: a longitudinal 10-year follow-up study. Hypertens Res. 2008;31:433–41.
19. Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med. 2001;345:851–60.
20. Churchill DN, Blake PG, Jindal KK, Toffelmire EB, Goldstein MB. Clinical practice guidelines for initiation of dialysis. Canadian Society of Nephrology. J Am Soc Nephrol. 1999;10(Suppl 13): S289–91.
21. Burden R, Tomson C. Identification, management and referral of adults with chronic kidney disease: concise guidelines. Clin Med. 2005;5:635–42.
22. Nicholls K. Prevention of progression of kidney disease: diabetic nephropathy—CARI guidelines. Aust Fam Physician. 2007;36: 137–8.
23. IV. NKF-K/DOQI Clinical practice guidelines for anemia of chronic kidney disease: update 2000. Am J Kidney Dis. 2001; 37:S182–238.
24. Neumann ME. Results in KEEP's first report show progress in early identification of CKD patients. Nephrol News Issues. 2003;17:84–7.
25. Yamagata K, Takahashi H, Tomida C, Yamagata Y, Koyama A. Prognosis of asymptomatic hematuria and/or proteinuria in men. Nephron. 2002;91:34–42.
26. Ishida K, Ishida H, Narita M, Sairenchi T, Saito Y, Fukutomi H, et al. Factors affecting renal function in 119 985 adults over three years. QJM. 2001;94:541–50.
27. Ninomiya T, Kiyohara Y, Kubo M, Yonemoto K, Tanizaki Y, Doi Y, et al. Metabolic syndrome and CKD in a general Japanese population: the Hisayama Study. Am J Kidney Dis. 2006;48: 383–91.
28. Orth SR, Hallan SI. Smoking: a risk factor for progression of chronic kidney disease and for cardiovascular morbidity and mortality in renal patients—absence of evidence or evidence of absence?. Clin J Am Soc Nephrol. 2008;3:226–36.
29. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. N Engl J Med. 1993; 329: 977–86.

30. Ohkubo Y, Kishikawa H, Araki E, Miyata T, Isami S, Motoyoshi S, et al. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. Diabetes Res Clin Pract. 1995;28:103–17.
31. Bakris GL, Williams M, Dworkin L, Elliott WJ, Epstein M, Toto R, et al. Preserving renal function in adults with hypertension and diabetes: a consensus approach. National Kidney Foundation Hypertension and Diabetes Executive Committees Working Group. Am J Kidney Dis. 2000;36:646–61.
32. Schaeffner ES, Kurth T, Curhan GC, Glynn RJ, Rexrode KM, Baigent C, et al. Cholesterol and the risk of renal dysfunction in apparently healthy men. J Am Soc Nephrol. 2003;14:2084–91.
33. Iseki K, Ikemiya Y, Iseki C, Takishita S. Proteinuria and the risk of developing end-stage renal disease. Kidney Int. 2003;63:1468–74.
34. Maschio G, Alberti D, Janin G, Locatelli F, Mann JF, Motolese M, et al. Effect of the angiotensin-converting-enzyme inhibitor benazepril on the progression of chronic renal insufficiency. The angiotensin-converting-enzyme inhibition in Progressive Renal Insufficiency Study Group. N Engl J Med. 1996;334:939–45.
35. Lewis JB, Berl T, Bain RP, Rohde RD, Lewis EJ. Effect of intensive blood pressure control on the course of type 1 diabetic nephropathy. Collaborative Study Group. Am J Kidney Dis. 1999;34:809–17.
36. Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med. 2001;345:861–9.
37. Halbesma N, Kuiken DS, Brantsma AH, Bakker SJ, Wetzels JF, De Zeeuw D, et al. Macroalbuminuria is a better risk marker than low estimated GFR to identify individuals at risk for accelerated GFR loss in population screening. J Am Soc Nephrol. 2006;17:2582–90.

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CASE REPORT

Renal involvement of monoclonal immunoglobulin deposition disease associated with an unusual monoclonal immunoglobulin A glycan profile

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Abstract A 38-year-old man was admitted to the hospital for the evaluation of proteinuria, microscopic hematuria, and monoclonal IgA-κ gammopathy. The initial renal pathological findings showed mesangial proliferative glomerulonephritis with endocapillary proliferation, a necrotizing lesion, and cellular crescent formation accompanied by IgA1-κ deposition in the mesangium. Neither typical immune-complex deposits nor organized-structure deposits were detected. We diagnosed the patient with monoclonal immunoglobulin deposition disease (MIDD) associated with monoclonal IgA (mIgA). After the initiation of a monthly treatment with melphalan and predonisolone (MP therapy), the patient's serum IgA levels declined, and clinical remission was ultimately achieved. The follow-up renal biopsy showed reduced IgA-κ staining, and both the endocapillary proliferation and the necrotizing lesion had disappeared. To elucidate the mechanism of IgA deposition, we investigated the glycan profile of the patient's serum mIgA using a mass spectrometry technique. The results revealed an unusual *N*-glycan profile compared to that of another patient with circulating mIgA lacking renal involvement and that of a healthy control. mIgA deposition in the mesangial area is a rare disease, and the glycan profiling of MIDD with renal involvement has not been reported previously. Thus, the present case suggests that any variation in Ig glycosylation may be a step in the pathogenesis of MIDD with renal involvement and/or contribute to some cases of IgA nephropathy.

Keywords Glycan profiling · IgA · Mesangial proliferative glomerulonephritis · Monoclonal immunoglobulin deposition disease

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Introduction

Monoclonal immunoglobulin (mIg) deposition disease (MIDD) with renal involvement is classified based on the origin of the mIg, pathohistological features, and the structure of the deposits. AL amyloidosis, light and/or heavy chain deposition disease (i.e., LCDD, LHCDD, HCDD, respectively) and organized type MIDD (i.e., immunotactoid glomerulopathy, fibrillary glomerulonephritis, and type-1 cryoglobulinemia) have been widely recognized. Recently, other types of MIDD glomerulopathy (i.e., non-AL amyloid and non-LCDD/LHCDD/HCDD, nonorganized) have been reported in the literature [1–6]. However, circulating mIg is not typically associated with renal involvement, and all forms of MIDD are related to the expansion of a B cell clone-producing mIg. Cases of monoclonal IgA (mIgA) MIDD are rare, and to date there has been no report of the glycan profiling of mIg in cases of non-AL amyloid, non-LCDD/LHCDD/HCDD, or in non-organized type MIDD. Here, we describe a case of mIgA

MIDD associated with mIgA in which we detected an unusual *N*-glycan profile.

Case report

A 38-year-old man with no past medical history had been well until February 2002, when proteinuria and microscopic hematuria were detected at an annual medical checkup that revealed a serum IgA level of 1650 mg/dL (primarily monoclonal IgA-κ detected by serum immunoelectrophoresis). By March 2005, the patient's proteinuria levels had increased to over 1 g/24 h, despite the administration of 300 mg of dilazep, an anti-platelet drug, and 80 mg of valsartan, an angiotensin type 2 receptor blocker.

In December 2005, an initial renal biopsy was performed. At that time, no abnormalities were found upon physical examination, and the following laboratory test results were obtained: blood urea nitrogen, 18 mg/dL; serum creatinine, 1.06 mg/dL; high serum IgA at 1203 mg/dL; and a second detection of monoclonal IgA-κ. Levels of IgG and IgM were low at 669 and 19 mg/dL, respectively. Complements were all within normal limits, and all of the following were negative: antinuclear antigen, HBs-antigen, anti-HCV antibody, and anti-HIV antibody tests. Urinalysis revealed proteinuria (2+) and microscopic hematuria (3+), and urine sedimentation showed a red blood cell (RBC) count of 5–9/HPF, a granular cast of 1 to 4/WF, and an RBC cast of 1–4/WF. The creatinine clearance test yielded a ratio of 98.6 mL/min, and the urinary protein excretion rate was

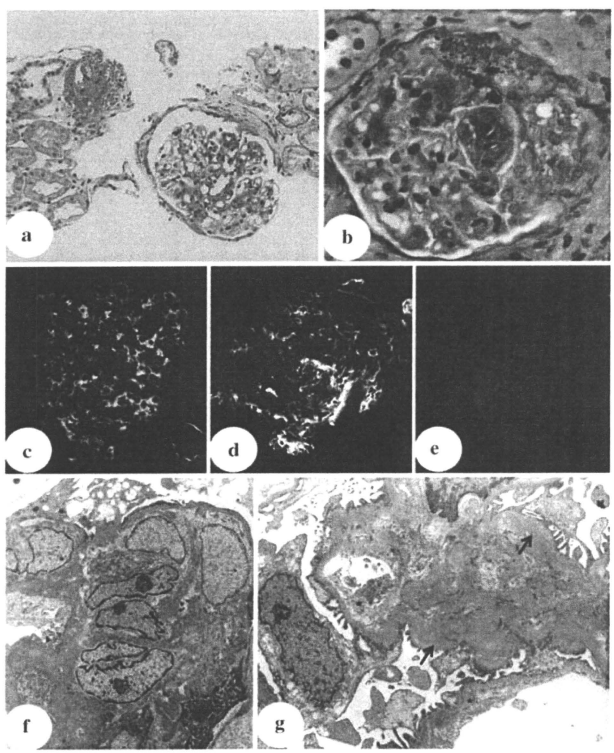


Fig. 1 Findings of the first renal biopsy. **a** The right glomerulus shows mild mesangial proliferation of both matrix and cells accompanying fibrous crescents (light microscopy, PAS staining, ×200). **b** The glomerulus shows endocapillary proliferation accompanying a necrotizing lesion and cellular crescent formation (light microscopy, PAS staining, ×400). **c** The glomerulus shows strongly positive, mesangial-dominant staining for anti-IgA (immunofluorescence staining, ×200). **d** The glomerulus shows strongly positive, mesangial-dominant staining for anti-κ (immunofluorescence staining, ×200). **e** The glomerulus is negative for anti-λ (immunofluorescence staining, ×200). **f** Segmental mesangial cell proliferation and an increase in mesangial matrix are shown (electron microscopy, ×3000). **g** Deposits are amorphous in mesangial and paramesangial areas (*arrow*). Neither electron-dense deposits (typically observed in immune-complex type glomerulonephritis) nor organized-structure deposits are observed. Subendothelial edema (*asterisk*) is observed (electron microscopy, ×5000)

1.2 g/24 h. Urine protein electrophoresis analysis showed no monoclonal protein peak. Bone marrow puncture yielded 0.5% plasma cells. Neither computed tomography from the head to the neck nor ultrasonography from the abdomen to the pelvis revealed any tumors. The first renal biopsy was studied by light microscopy (Fig. 1), and focal mesangial proliferation of both matrix and cells was observed (Fig. 1a). Endocapillary proliferation accompanying a necrotizing lesion and cellular crescent formation were detected at a single location (Fig. 1b). No tubulointerstitial damage nor vascular injuries were identified. Immunofluorescence staining revealed mesangial-dominant staining for anti-IgA (IgA1 subclass) and anti-light-chain κ, but no anti-light-chain λ was seen (Fig. 1c–e). No tubular basement membrane staining was observed. Anti-C3 staining was slightly positive in the mesangium. No significant staining was noted for anti-IgG, IgM, C4, fibrinogen, or IgA2. The electron microscopy sample was obtained from a paraffin embedding block. Focal and segmental mesangial cell proliferation and an increase in mesangial matrix were observed (Fig. 1f), and deposits were amorphous in mesangial and paramesangial areas (Fig. 1g). No organized-structure deposits were detected. We diagnosed the patient with non-AL amyloid and non-LCDD/LHCDD/HCDD, as well as with non-organized type mIgA MIDD, which is similar to IgA nephropathy. After MP therapy (i.e., 8 mg melphalan for four days and 60 mg predonisolone for four days, monthly) was initiated, the patient's serum IgA levels declined, and after a period of several months, the patient's urinary protein excretion levels also decreased. In February 2007, after the patient had received 11 courses of MP therapy, a follow-up biopsy was performed. Light microscopy (Fig. 2a) revealed diminished mesangial expansion, and neither the necrotizing lesion nor any cellular crescent formation was detected. An immunofluorescence study showed reductions in both IgA (Fig. 2b) and κ staining (Fig. 2c). On electron microscopy, the deposit was not obvious (Fig. 2d). Based on the results of the follow-up biopsy, we terminated the MP therapy. In September 2007, the patient's serum IgA level declined to 657 mg/dL, and no monoclonal IgA-κ was detected by serum immunoelectrophoresis. In addition, both the proteinuria and microscopic hematuria had completely disappeared. We therefore concluded that the patient had achieved clinical remission.

To investigate the pathogenesis of the present case, we carried out serum IgA glycan profiling (primarily mIgA) using a mass spectrometry (MS) technique [7–9]. Purification of the IgA1 from the serum of the present case, from that of another patient with circulating mIgA lacking renal involvement, and from that of a healthy control was carried out. Each 1-mL serum sample was diluted with 9 mL of 0.01 M Tris–HCl (pH 7.4) and applied to a Cibacron Blue 3GA agarose column (Sigma). After the column had been washed with 0.01 M Tris–HCl (pH 7.4), the unbound and the washed-out fractions were collected and loaded onto an anti-IgA1 monoclonal antibody column (7303B, Institute of Immunology Co., Ltd.). After sample loading, the column was washed with phosphate-buffered saline (PBS). Then the IgA1 was eluted with 0.1 M glycine (pH 2.5) and immediately neutralized with 1 M Tris–HCl (pH 8.0). To remove all traces of IgG, fractions containing IgA1 were added to a protein G suspension, and the mixture was incubated overnight at 4°C. The supernatant was collected and dialyzed against 0.01 M NH_4HCO_3 and was then lyophilized. The purity of the preparations was determined by

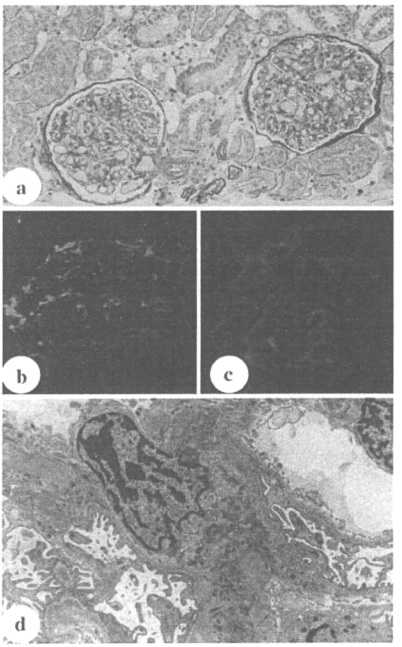


Fig. 2 Findings of the second renal biopsy. **a** Each of two glomeruli shows mild mesangial expansion of both matrix and cells (light microscopy, PAS staining, ×200). **b** The glomerulus shows weakly positive, mesangial-dominant staining for anti-IgA (immunofluorescence staining, ×200). **c** The glomerulus shows weakly positive, mesangial-dominant staining for anti-κ (immunofluorescence staining, ×200). **d** Mesangial expansion is not seen. Deposit was not obvious (electron microscopy, ×3000)

SDS-polyacrylamide gel electrophoresis and Western blotting. After adjusting concentrations, the glycans were removed from the purified IgA1 using peptide-*N*-glycosidase F (PNGaseF). The released and reduced glycans were permethylated and then subjected to MS analysis [10, 11]. The MS signals of the *N*-glycans released from each IgA1 sample were obtained (Fig. 3). The signals assigned to *N*-glycan and the glycan conformation model are both summarized in Table 1. The *N*-glycan profile of the present case was unusual (i.e., increased fucosylation and sialylation) as compared to that of the case with mIgA lacking renal involvement and that of the healthy control, whereas the *O*-glycan profiles for each of the three samples were similar (data not shown). As shown in Table 1, the present case had unique patterns of *N*-glycan glycosylation, i.e., 3 hexoses, 3 *N*-acetylhexosamines, and 1 fucose; or 4 hexoses and 3 *N*-acetylhexosamines; or 5 hexoses, 5 *N*-acetylhexosamines, and 1 sialic acid; or 5 hexoses, 5 *N*-acetylhexosamines, 1 fucose, and 1 sialic acid; or 5 hexoses, 4 *N*-acetylhexosamines, 1 fucose, and 2 sialic acids. The whole common monoclonal IgA1 analysis also revealed a specific pattern of *N*-glycan glycosylation, namely, 4 hexoses, 3 *N*-acetylhexosamines, and 1 fuctose or 4 hexoses, 4 *N*-acetylhexosamines, and 1 sialic acid in this patient.

Discussion

In the present case, the pathological findings showed mesangial proliferative glomerulonephritis with mIgA deposition predominantly in the mesangium. The pathological features of non-AL amyloid, non-LCDD/LHCDD/HCDD, and nonorganized-type MIDD vary widely from case to case. Nasr and coworkers reported ten cases of glomerulopathy with mIgG deposition (IgG1-λ, IgG3-κ, IgG2-λ) [1]. All of the ten cases in their study showed diffuse proliferative glomerulonephritis or membranoproliferative glomerulonephritis (MPGN). Alpers and colleagues [2] reported 11 cases associated with a κ-subclass light chain, i.e., seven of their 11 cases (5 IgG-κ and 2 IgA-κ) were probably non-LCDD/LHCDD/HCDD and nonorganized-type MIDD, and these seven cases showed proliferative glomerulonephritis or MPGN. Bridoux and

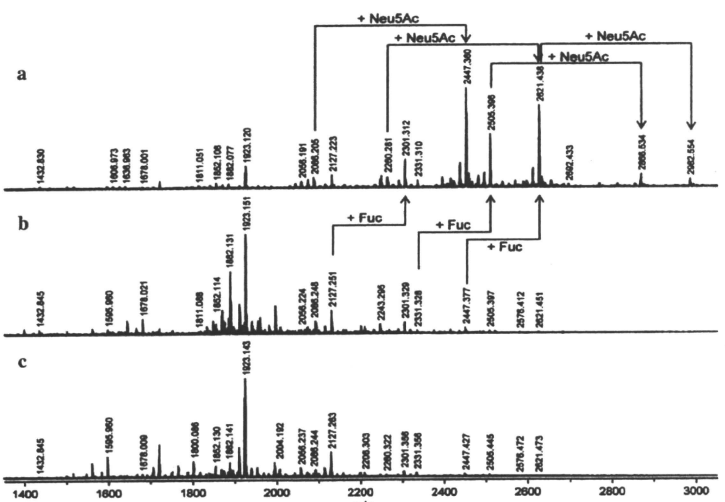
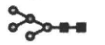
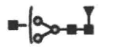
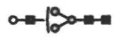
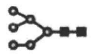
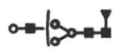
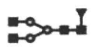
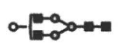
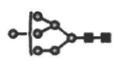
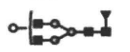
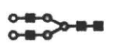
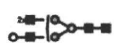
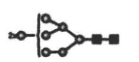
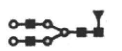
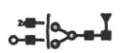
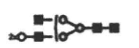


Fig. 3 The *N*-glycan profile was analyzed using mass spectrometry. **a** The *N*-glycan profile of the present case, **b** patient with circulating mIgA-related pathology lacking renal involvement, and **c** healthy control. The mass spectra were obtained in reflectron positive-ion mode with MALDI-TOF MS. All MS spectra were obtained from Na^+ adduct ions. The atypical glycan profile of the present case cannot completely account for microheterogeneity within individuals (vs. another patient with circulating mIgA-related pathology lacking renal involvement), nor for differences between individuals (vs. number of controls). *Nue5Ac*, sialic acid; *Fuc*, fucose

Table 1 Summary of the MS signals assigned to *N*-glycan

Panel a	Panel b	Panel c	Composition				Conformation of glycan
			Hex	HexNAc	Fuc	Neu5Ac	
1432.830	1432.845	1432.845	3	3	0	0	
1595.945	1595.960	1595.960	5	2	0	0	
1606.973	–	–	3	3	1	0	
1636.963	–	–	4	3	0	0	
1678.001	1678.021	1678.009	3	4	0	0	
–	–	1800.086	6	2	0	0	
1811.051	1811.088	–	4	3	1	0	
1852.108	1852.114	1852.130	3	4	1	0	
1882.077	1882.131	1882.141	4	4	0	0	
1923.120	1923.151	1923.143	3	5	0	0	
–	–	2004.192	7	2	0	0	
2056.191	2056.224	2056.237	4	4	1	0	
2086.205	2086.248	2086.244	5	4	0	0	
2127.223	2127.251	2127.263	4	5	0	0	
–	–	2208.303	8	2	0	0	
2243.276	2243.295	–	4	4	0	1	
2260.281	–	2260.322	5	4	1	0	
2301.312	2301.329	2301.356	4	5	1	0	
2331.310	2331.328	2331.356	5	5	0	0	
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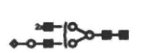
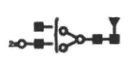
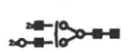
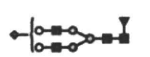
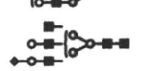
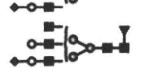
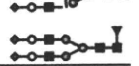
–	2488.377	2488.431	4	5	0	1	
2505.396	2505.397	2505.445	5	5	1	0	
–	2576.412	2576.472	5	6	0	0	
2621.438	2621.451	2621.473	5	4	1	1	
2692.433	–	–	5	5	0	1	
2866.534	–	–	5	5	1	1	
2982.554	–	–	5	4	1	2	

Hex, hexose; *HexNAc*, *N*-acetylhexosamine; *Fuc*, fucose; *Neu5Ac*, sialic acid

●: mannose, ○: galactose, ■: *N*-acetylglucosamine, ▲: fucose, ◆: sialic acid

coworkers [3] reported five cases of IgG-κ-type disease: atypical membranous nephropathy was seen in one case, while the other four were cases of MPGN. Soares et al. [4] reported a case of endocapillary proliferative glomerulonephritis with IgA-λ deposition. Komatsuda et al. [5] reported three cases (two IgG3-κ and one IgG1-κ) of membranous nephropathy. Recently, Miura et al. [6] reported a rare case of membranous nephropathy with IgA1-λ deposition along the glomerular peripheral wall in a patient with chronic hepatitis C infection and rectal cancer. Differences between types of mIg deposition and in affinity for the glomerulus remain uncharacterized in the literature. Only seven of a total of 27 cases were found to have circulating mIg. In contrast, the rate of occurrence of renal involvement in cases with circulating mIg is expected to be very low, based on the total number of cases (1% of the general population over 50 years old, and 3–5% of that of over 70 years old) [12–14], even if latent cases are included. These epidemiological data suggest that the pathogenesis of MIDD might be related to the quality of the circulating mIg.

On the other hand, many reports regarding the pathogenesis of IgA nephropathy have suggested that underglycosylation of the *O*-linked carbohydrate moieties of IgA1 lead to deposition in the mesangium and ultimately to disease progression. *O*-linked underglycosylation (i.e., under-galactosylation and/or under-sialylation) of IgA1 in IgA nephropathy have been demonstrated by lectin-binding enzyme-linked immunosorbent assay (ELISA) and MS analyses. Furthermore, self-aggregation, adhesion to the extracellular mesangial matrix, the formation of immune complexes, and the activation of complements have been reported with *O*-linked underglycosylated IgA1 [15–17]. *O*-linked underglycosylation of IgA has also been reported in cases of IgA myeloma presenting with Henoch–Schönlein purpura and glomerulonephritis [18, 19]. In these latter two case reports, *O*-linked underglycosylation of serum IgA from patients was demonstrated using *Helix aspersa* (HAA) lectin-binding ELISA, which is known to recognize the terminal bare *N*-acetylgalactosamine (GalNAc) of *O*-glycan. As regards the *N*-glycan of IgA1 in IgA nephropathy, abnormalities of galactosylation or sialylation may also be related to the pathogenesis of the disease [20, 21], which remains poorly understood. The aberrant
N-linked glycosylation observed in the present patient was a case of neither under-galactosylation nor under-sialylation. There are likely to be specific patterns of *N*-linked glycosylation, as well as under-galactosylation/sialylation, in which the structure of IgA1 itself cannot be stabilized, which may in turn be associated with conformational changes and progression of self-aggregation and/or adherence to the mesangial matrix.

The microheterogeneity of Ig glycosylation is widely recognized, and is probably derived from differences in each glycosylation event produced by each B cell clone. The Ig glycan profile from serum Ig might represent the average glycan profile produced by each B cell. Recently, a case of IgG3-heavy chain deposition disease was reported [22] in which the patient's total IgG glycan profile, determined during the active phase of the disease, was similar to that of an IgG3 analysis. The unusual *N*-glycan profile of the present case was not due to conventional microheterogeneity, but may have been an mIgA-related pathogenesis. Thus, the specific *N*-glycan pattern observed in the present case (see Table 1; Fig. 3) may be related to IgA deposition and cell proliferation in the mesangium, which induces proteinuria and glomerular injury. However, further investigation will be needed to elucidate the pathogenesis of the specific pattern of *N*-glycan in terms of both IgA deposition and cell proliferation in the mesangium.

Conclusions

In summary, we treated a case of mIgA deposition disease with mesangial proliferation. The patient also had an abnormal monoclonal IgA *N*-glycan profile, which was associated with hematuria, proteinuria, and mesangial proliferation. Such abnormalities appear to be related to IgA1 deposition in some cases of IgA nephropathy as well as in cases of IgA-type MIDD. Further studies of the effects of specific *N*-glycan profiles on the pathogensis of IgA-deposition diseases are still needed.

References

1. Nasr SH, Markowitz GS, Stokes MB, Seshan SV, Valderrama E, Appel GB, et al. Proliferative glomerulonephritis with monoclonal IgG deposits: a distinct entity mimicking immune-complex glomerulonephritis. Kidney Int. 2004;65:85–96.
2. Alpers CE, Tu WH, Hopper J Jr, Biava CG. Single light chain subclass (kappa chain) immunoglobulin deposition in glomerulonephritis. Hum Pathol. 1985;16:294–304.
3. Bridoux FBR, Zanetta G, Mougenot B. Glomerulopathy with non-organized and non-Randall type monoclonal immunoglobulin deposits. J Am Soc Nephrol. 2001;12:94A (abstr).
4. Soares SM, Lager DJ, Leung N, Haugen EN, Fervenza FC. A proliferative glomerulonephritis secondary to a monoclonal IgA. Am J Kidney Dis. 2006;47:342–9.
5. Komatsuda A, Masai R, Ohtani H, Togashi M, Maki N, Sawada K, et al. Monoclonal immunoglobulin deposition disease associated with membranous features. Nephrol Dial Transplant. 2008;23:3888–94.
6. Miura N, Uemura Y, Suzuki N, Suga N, Maeda K, Yamaguchi S, et al. An IgA1-lambda-type monoclonal immunoglobulin deposition disease associated with membranous features in a patient

with chronic hepatitis C viral infection and rectal cancer. Clin Exp Nephrol. 2010;14:90–3.
7. Dell A, Morris HR. Glycoprotein structure determination by mass spectrometry. Science. 2001;291:2351–6.
8. Harvey DJ. Proteomic analysis of glycosylation: structural determination of *N*- and *O*-linked glycans by mass spectrometry. Expert Rev Proteomics. 2005;2:87–101.
9. Zaia J. Mass spectrometry of oligosaccharides. Mass Spectrom Rev. 2004;23:161–227.
10. Ciucanu I, Costello CE. Elimination of oxidative degradation during the per-*O*-methylation of carbohydrates. J Am Chem Soc. 2003;125:16213–9.
11. Ito H, Kuno A, Sawaki H, Sogabe M, Ozaki H, Tanaka Y, et al. Strategy for glycoproteomics: identification of glyco-alteration using multiple glycan profiling tools. J Proteome Res. 2009;8:1358–67.
12. Iwanaga M, Tagawa M, Tsukasaki K, Kamihira S, Tomonaga M. Prevalence of monoclonal gammopathy of undetermined significance: study of 52,802 persons in Nagasaki City, Japan. Mayo Clin Proc. 2007;82:1474–9.
13. Kyle RA, Therneau TM, Rajkumar SV. Prevalence of monoclonal gammopathy of undetermined significance (MGUS) among Olmsted County, MN residents 50 years of age. Blood. 2003;102: 934a(A3476).
14. Landgren O, Katzmann JA, Hsing AW, Pfeiffer RM, Kyle RA, Yeboah ED, et al. Prevalence of monoclonal gammopathy of undetermined significance among men in Ghana. Mayo Clin Proc. 2007;82:1468–73.
15. Hiki Y, Iwase H, Kokubo T, Horii A, Tanaka A, Nishikido J, et al. Association of asialogalactosyl β1–3-*N*-acetylgalactosamine on Jacalin-reactive immunoglobulin A1 in immunoglobulin A nephropathy. J Am Soc Nephrol. 1996;7:955–60.
16. Iwase H, Ohkawa S, Ishii-Karakasa I, Hiki Y, Kokubo T, Sano T, et al. Study of the relationship between sticky human serum IgA1 and its *O*-glycan glycoform. Biochem Biophys Res Commun. 1999;261:472–7.
17. Kokubo T, Hiki Y, Iwase H, Tanaka A, Toma K, Hotta K, et al. Protective role of IgA1 glycans against IgA1 self-aggregation and adhesion to extracellular matrix proteins. J Am Soc Nephrol. 1998;9:2048–54.
18. Van Der Helm-Van Mil AH, Smith AC, Pouria S, Tarelli E, Brunskill NJ, Eikenboom HC. Immunoglobulin A multiple myeloma presenting with Henoch-Schönlein purpura associated with reduced sialylation of IgA1. Br J Haematol. 2003;122:915–7.
19. Zickerman AM, Allen AC, Talwar V, Olczak SA, Brownlee A, Holland M, et al. IgA myeloma presenting as Henoch–Schönlein purpura with nephritis. Am J Kidney Dis. 2000;36:E19.
20. Linossier MT, Palles S, Berthoux F. Different glycosylation profile of serum IgA1 in IgA nephropathy according to the glomerular basement membrane thickness: normal versus thin. Am J Kidney Dis. 2003;41:558–64.
21. Nishie T, Miyaishi O, Azuma H, Kameyama A, Naruse C, Hashimoto N, et al. Development of immunoglobulin A nephropathy-like disease in beta-1,4-galactosyltransferase-1-deficient mice. Am J Pathol. 2007;170:447–56.
22. Omtvedt LA, Royle L, Husby G, Sletten K, Radcliffe CM, Harvey DJ, et al. Glycan analysis of monoclonal antibodies secreted in deposition disorders indicates that subsets of plasma cells differentially process IgG glycans. Arthritis Rheum. 2006;54:3433–40.

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ORIGINAL ARTICLE

Measurement of health-related quality of life in patients with chronic kidney disease in Japan with EuroQol (EQ-5D)

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Abstract
Background Chronic kidney disease (CKD) is a health-related quality-of-life (HRQOL) deteriorating disease which is not only a public health but also a socioeconomic problem. Interest in developing cost-effective interventions to control CKD has increased. The aim of this study was to measure HRQOL in terms of quality-adjustment weights for cost-effectiveness analysis using EQ-5D in patients with CKD. The relationships between the measured HRQOL and clinical indices/complications were also analyzed.
Methods EQ-5D, a generic preference-based instrument, was administered to 569 CKD outpatients at Tsukuba University Hospital between November and December 2008. The response rate was 94.4% (537/569). Data on sex, age, creatinine, hemoglobin, serum albumin and eGFR were obtained from the patients' records. Data on the presence of complications such as hypertension, diabetes, and history of cardiovascular disease (CVD) were also retrieved.
Results Measured quality-adjustment weights by the CKD stage were 0.940 (95% CI 0.915–0.965), 0.918 (0.896–0.940), 0.883 (0.857–0.909), 0.839 (0.794–0.884), and 0.798 (0.757–0.839) for stages 1–5, respectively. The decrease in weight was significant by ANOVA ($P < 0.0001$), and the weight for all stages was 0.885 (0.871–0.898). There was a positive relationship between hemoglobin/serum albumin and the weight. The presence of hypertension lowered the weight from 0.910 (0.885–0.936) to 0.874 (0.858–0.891), diabetes from 0.901 (0.886–0.917) to 0.840 (0.811–0.869), and CVD from 0.892 (0.878–0.906) to 0.783 (0.718–0.848).
Conclusions HRQOL decreases with progression of CKD stage and/or presence of anemia, undernutrition, hypertension, diabetes, or history of CVD.

Keywords Health-related quality of life (HRQOL) · Quality-adjustment weight · Chronic kidney disease (CKD) · EuroQol (EQ-5D)

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Introduction

Chronic kidney disease (CKD) is not only a worldwide public health problem, but also a global socioeconomic concern, with adverse outcomes including kidney failure, cardiovascular disease (CVD), and premature death. In 2002, the Kidney Disease Outcomes Quality Initiative (K/DOQI) of the National Kidney Foundation in the United States published a definition and classification system for CKD [1]. The definition and classification of CKD were accepted by the international board of directors of Kidney Disease: Improving Global Outcomes [2]. CKD was classified into five stages based on the appearance of proteinuria and glomerular filtration rate (GFR).

It is estimated that there are more than ten million CKD patients [3], who may progress to ESRD requiring dialysis, and more than 280,000 ESRD patients in Japan [4]. The annual cost of dialysis treatment was more than 130 billion yen in Japan in 2008 [4]. The high morbidity of CKD and high cost of dialysis have promoted interest in developing not only effective but also cost-effective interventions for CKD. Previous studies have suggested that CKD is one of the most important risk factors for CVD among those known: hypertension, diabetes, hyperlipidemia, obesity, smoking, and lifestyle-related diseases [5–8]. Therefore, the early detection of and early initiation of treatment for CKD are important in order to prevent kidney failure as well as cardiovascular complications and death.

To conduct a cost-effective analysis, outcome measurement in terms of quality-adjusted life-years (QALYs) is recommended [9, 10], and is crucial to dealing with QOL-deteriorating diseases including CKD. QALYs are calculated as the sum of the adjusted life-years experienced by a patient, where the adjustment is made by multiplying time by weights linked to the changing health state of the patient. The quality-adjustment weight is a value of between 1 (for perfect health) and 0 (for death), which is a type of health-related quality of life (HRQOL) measurement. The weight, in principle, represents social preference for a certain health state, and so it should be measured in every society. However, there are few reports on such weights in regard to CKD in the literature. Therefore, the first objective of this study was to measure quality-adjustment weights for the health states of CKD patients by stage. Furthermore, Perlman et al. [11] and Leaf et al. [12] identified associations between the HRQOL of CKD patients and clinical indices such as hemoglobin or eGFR. Therefore, we examined the relationship between the measured quality-adjustment weight and clinical indices of CKD patients. The accumulation of comorbidities tends to worsen the patients' HRQOL. We further analyzed the significance of major complications of CKD such as hypertension, diabetes, and history of CVD on the HRQOL of CKD patients.

The results of this study should facilitate the economic evaluation of interventions for CKD, which will contribute to the development of efficient ways to manage the disease. They also inform physicians of how patient HRQOL alters with disease progression, which is helpful for realizing more patient-centered clinical decision-making.

Materials and methods

Instrument for measuring quality-adjustment weights

There are preference-elicitation techniques that can be used when measuring quality-adjustment weights, such as the visual analogue scale (VAS), standard gamble (SG), and time trade-off (TTO) [13]. It is recommended that a representative sample of the community should be recruited when using them [9]. They also require a description of life in a particular state of health that is easy for patients to understand. Describing life at a particular stage of CKD, however, is practically impossible. Therefore, another approach, generic preference-based measures, was employed in this study. Specifically, we used the most widely used instrument, EQ-5D [13], which is standardized and validated for use in Japan [14, 15]. It is administered to representative patients in a particular state of health in Japan, who are asked to grade five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) of their health state as one of three levels ("no problem," "some problems," and "extreme problem"). "No problem" is also referred to as level 1, while "inability or extreme problem" is also referred to as level 3 such that (for example) a health state of 21232 means that the patient has some problems walking, no problem washing and dressing, some problems performing their usual activities, suffers extreme pain or discomfort, and is moderately anxious or depressed. The $3^5 = 243$ possible combinations of responses are converted to weight values according to the Japanese value set [15], and the average is calculated as a quality-adjustment weight for the health state under consideration in Japan. The weight values are based on TTO evaluations. The weight ranges from 1 for perfect health (no problem in any dimension) to 0 for death and -0.111 for severe problems in all dimensions. A positive weight means that the health status is better than dead and a negative weight is worse in EQ-5D.

Study design and subjects

We conducted a cross-sectional outpatient questionnaire survey. All 588 outpatients previously diagnosed with CKD at the Department of Nephrology Tsukuba University Hospital were recruited for this study between November and December 2008. We assumed that they comprised a near-representative sample of CKD patients in Japan to which EQ-5D could be applied, since a lack of knowledge of the descriptive epidemiology of CKD in Japan prevented us from obtaining a representative sample and making appropriate bias corrections during our analyses. The EQ-5D questionnaire was given to them to complete if they signed a written informed consent form when visiting the hospital after receiving an explanation of the purpose of this study. Nineteen patients (3.2%) were not included in this study because they were receiving renal replacement therapy. Thirty-two patients (5.4%) were excluded from the analysis because they did not respond to the questionnaire.

Study variables

From the patient records, sex and age were included in our analysis as demographic baseline characteristics. Creatinine, hemoglobin, and serum albumin on the day of the questionnaire survey were also included as routinely checked clinical indices. GFR was estimated from serum creatinine, age, and sex using the new Japanese equation as follows: eGFR (ml/min/1.73 m^2) = 194 × serum creatinine$^{-1.094}$ × age$^{-0.287}$ × 0.739 (if female) [16]. The presence of complications was also assessed using the records. Hypertension and diabetes were classified based on clinical records. A history of CVD was regarded as present if stroke, congestive heart disease, or ischemic heart disease was recorded.

Statistical analysis

All statistical analyses were performed using SAS. Quality-adjustment weights were calculated as the mean of a group of patients' weight values according to the Japanese value set for EQ-5D, and 95% confidence intervals were computed. The weight differences among CKD stages were tested by ANOVA. Correlation analyses were performed between weights and clinical indices. Multiple regression analysis was also applied to identify indices that determine weights. Nonparametric regression analysis was further applied in order to detect inflection points in the curves of quality adjustment weight versus identified indices. The level of significance was set at $P < 0.05$.

Results

The baseline characteristics of respondents are shown in Table 1. The respondents comprised 282 males (52.5%) and 255 females (47.5%). The overall mean age was 55.2 years old. Mean creatinine was 1.7 mg/dl; mean hemoglobin 12.7 g/dl; mean serum albumin 4.1 g/dl; and mean eGFR 56.1 ml/min/1.73 m^2. Regarding complications, 388 (72.2%) patients had hypertension; 146 (27.0%) patients had diabetes, with a mean HbA1c of 6.0%; and 38 (7.0%) patients had a history of CVD. Proportions of patients at various CKD stages were 15.5, 28.5, 29.4, 13.4 and 13.2% for stages 1–5, respectively. Patients at stages 1 and 2 were relatively young compared to those at stages 3–5.

The EQ-5D questionnaire responses are shown in Table 2. The proportions of the patients who responded "no problem" were 82.8% for mobility, 94.0% for self care, 79.3% for usual activities, 72.8% for pain/discomfort, and 82.1% for anxiety/depression. The frequency of "some problems" was significantly higher for mobility (4.8% in CKD 1 and 36.6% in CKD 5) and usual activities (9.6% in CKD 1 and 39.4% in CKD 5) with progression of the CKD stage. Fewer than 3% of the patients answered "extreme problem" for all dimensions.

Table 1 Baseline characteristics (total $n = 537$)

	Values	SD or %
Male, n (%)	282	52.5
Mean age (year), SD	55.2	16.0
Mean creatinine (mg/dl), SD	1.7	1.2
Mean hemoglobin (g/dl), SD	12.7	2.1
Mean albumin (g/dl), SD	4.1	0.6
Mean estimated GFR (ml/min/1.73 m^2), SD	56.1	34.1
Hypertension, n (%)	388	72.2
Diabetes, n (%)	146	27.0
History of cardiovascular disease, n (%)	38	7.0

CKD stage	n	%	Mean age	Age range
1 (GFR ≥ 90)	83	15.5	35.6	15–70
2 (60 ≤ GFR < 90)	153	28.5	54.1	27–85
3 (30 ≤ GFR < 60)	158	29.4	60.9	26–87
4 (15 ≤ GFR < 30)	72	13.4	62.1	30–94
5 (GFR < 15)	71	13.2	61.0	28–83

Table 3 shows measured quality-adjustment weights by stage: 0.940 (95% CI 0.915–0.965), 0.918 (0.896–0.940), 0.883 (0.857–0.909), 0.839 (0.794–0.884), and 0.798 (0.757–0.839) for stages 1–5, respectively. Figure 1 illustrates these in a box plot with a mark showing the mean. The decrease in weight was significant by ANOVA ($P = 0.000$), and the weight for all stages was 0.885 (0.871–0.898).

Squares of Pearson's correlation coefficient (R^2) were computed between weights and clinical indices and the patients' age. The age was included in the analysis as a controlling variable because years pass during the progression of the disease. R^2 values were relatively high for hemoglobin 0.1393 ($P = 0.000$), age 0.0737 ($P = 0.000$) and serum albumin 0.0892 ($P = 0.000$), and low for eGFR 0.0527 ($P = 0.000$) and creatinine 0.0406 ($P = 0.000$). Hemoglobin and serum albumin were positively correlated to weights, whereas age was negatively correlated. All correlations were significant upon tests of independence. Table 4 shows the results of multiple linear regression analysis aimed at identifying determinants of the weights. According to forced entry regression, hemoglobin, age, and serum albumin were found to be significant, and were selected as explanatory variables by stepwise regression. Figures 2 and 3 show the relationships between weights and hemoglobin/serum albumin based on nonparametric regression analysis, locally weighted regression, and smoothing scatterplots (LOWESS) [17]. Whereas correlations are

Table 2 Responses to the five dimensions of EQ-5D by CKD stage and complications

	n	Mobility			Self-care			Usual activities			Pain/discomfort			Anxiety/depression		
		No problem (%)	Some problems (%)	Extreme problem (%)	No problem (%)	Some problems (%)	Extreme problem (%)	No problem (%)	Some problems (%)	Extreme problem (%)	No problem (%)	Some problems (%)	Extreme problem (%)	No problem (%)	Some problems (%)	Extreme problem (%)
CKD stage																
1	83	95.2	4.8	–	97.6	2.4	–	89.2	9.6	1.2	89.2	10.8	–	89.2	10.8	–
2	153	91.5	8.5	–	98.0	2.0	–	87.6	11.8	0.7	82.4	15.7	2.0	86.3	13.7	–
3	158	81.7	17.7	0.6	94.3	5.1	0.6	82.3	17.1	0.6	77.9	21.5	0.6	76.6	22.8	0.6
4	72	72.2	25.0	2.8	88.9	8.3	2.8	66.7	27.8	5.6	75.0	25.0	–	84.7	15.3	–
5	71	63.4	36.6	–	85.9	14.1	–	56.3	39.4	4.2	60.6	38.0	1.4	74.7	25.4	–
All stages	537	82.8	16.6	0.6	94.0	5.4	0.6	79.3	18.8	1.9	78.2	20.9	0.9	82.1	17.7	0.2
Presence of HT																
CKD stage																
1	37	97.3	2.7	–	100.0	–	–	89.2	10.8	–	83.8	16.2	–	86.5	13.5	–
2	99	89.9	10.1	–	98.0	2.0	–	87.9	11.1	1.0	78.8	19.2	2.0	84.8	15.2	–
3	122	83.6	16.4	–	94.3	4.9	0.8	82.8	16.4	0.8	79.5	19.7	0.8	78.7	20.5	0.8
4	66	72.7	25.8	1.5	89.4	9.1	1.5	69.7	25.8	4.5	75.8	24.2	–	86.4	13.6	–
5	64	60.9	39.1	–	84.4	15.6	–	53.1	42.2	4.7	57.8	40.6	1.6	73.4	26.6	–
All stages	388	80.9	18.8	0.3	93.3	6.2	0.5	77.6	20.4	0.5	75.5	23.5	1.0	81.4	18.3	0.3
Absence of HT																
CKD stage																
1	45	93.3	6.7	–	95.6	4.4	–	88.9	8.9	2.2	93.3	6.7	–	91.1	8.9	–
2	54	94.4	5.6	–	98.1	1.9	–	87.0	13.0	–	88.9	9.3	1.9	88.9	11.1	–
3	36	75.0	22.2	2.8	94.4	5.6	–	80.6	19.4	–	72.2	27.8	–	69.4	30.6	–
4	6	66.7	16.7	16.7	83.3	–	16.7	33.3	50.0	16.7	66.7	33.3	–	66.7	33.3	–
5	7	85.7	14.3	–	100.0	–	–	85.7	14.3	–	85.7	14.3	–	85.7	14.3	–
All stages	148	87.8	10.8	1.4	95.9	3.4	0.7	83.8	14.9	1.4	85.1	14.2	0.7	83.8	16.2	–
Presence of DM																
CKD stage																
1	14	85.7	14.3	–	92.9	7.1	–	71.4	28.6	–	78.6	21.4	–	92.9	7.1	–
2	35	91.4	8.6	–	97.1	2.9	–	88.6	11.4	–	77.1	20.0	2.9	88.6	11.4	–
3	38	68.4	31.6	–	89.5	7.9	2.6	71.1	26.3	2.6	65.8	34.2	–	65.8	34.2	–
4	25	72.0	24.0	4.0	92.0	8.0	–	68.0	28.0	4.0	80.0	20.0	–	92.0	8.0	–
5	34	55.9	44.1	–	85.3	14.7	–	52.9	38.2	8.8	50.0	50.0	–	64.7	35.3	–

Table 2 continued

	n	Mobility			Self-care			Usual activities			Pain/discomfort			Anxiety/depression		
		No problem (%)	Some problems (%)	Extreme problem (%)	No problem (%)	Some problems (%)	Extreme problem (%)	No problem (%)	Some problems (%)	Extreme problem (%)	No problem (%)	Some problems (%)	Extreme problem (%)	No problem (%)	Some problems (%)	Extreme problem (%)
All stages	146	87.8	10.8	1.4	95.9	3.4	0.7	83.8	14.9	1.4	85.1	14.2	0.7	83.8	16.2	–
Absence of DM																
CKD stage																
1	69	97.1	3.0	–	98.6	1.4	–	92.8	5.8	1.4	91.3	8.7	–	88.4	11.6	–
2	118	91.5	8.4	–	98.3	1.7	–	87.3	11.9	0.8	83.9	14.4	1.7	85.6	14.4	–
3	120	85.8	13.3	0.8	95.8	4.2	–	85.8	14.2	–	81.7	17.5	0.8	80.0	19.2	0.8
4	47	72.3	25.5	2.0	87.2	8.5	4.3	66.0	27.7	6.4	72.3	27.7	–	80.9	19.1	–
5	37	70.2	29.7	–	86.5	13.5	–	59.5	40.5	–	70.3	27.0	2.7	83.8	16.2	–
All stages	391	86.4	13.0	0.5	95.1	4.3	0.5	82.6	16.1	1.3	81.8	17.1	1.0	83.6	16.1	0.3
Presence of CVD																
CKD stage																
1	0	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
2	7	85.7	14.3	–	85.7	14.3	–	85.7	14.3	–	85.7	14.3	–	85.7	14.3	–
3	11	54.5	45.5	–	81.8	9.1	9.1	54.5	36.4	9.1	63.6	18.2	9.1	54.5	45.5	–
4	6	66.7	33.3	–	100	–	–	33.3	50	16.7	83.3	16.7	–	100	–	–
5	14	50	50	–	78.6	21.4	–	42.9	50	7.1	35.7	64.3	–	42.9	57.1	–
All stages	38	60.5	39.5	–	84.2	13.2	2.6	52.6	39.5	7.9	60.5	36.8	2.6	63.2	36.8	–
Absence of CVD																
CKD stage																
1	83	95.2	4.8	–	97.6	2.4	–	89.2	9.6	1.2	89.2	10.8	–	89.2	10.8	–
2	146	91.8	8.2	–	98.6	1.4	–	87.7	11.6	0.7	82.2	15.8	2.1	86.3	13.7	–
3	147	83.7	15.6	0.7	95.2	4.8	–	84.4	15.6	–	78.9	21.1	–	78.2	21.1	0.7
4	66	72.7	24.2	3	87.9	9.1	3	69.7	25.8	4.5	74.2	25.8	–	83.3	16.7	–
5	57	66.7	33.3	–	87.7	12.3	–	59.6	36.8	3.5	66.7	31.6	1.8	82.5	17.5	–
All stages	499	84.6	14.8	0.6	94.8	4.8	0.4	81.4	17.2	1.4	79.6	19.6	0.8	83.6	16.2	0.2

Table 3 Quality-adjustment weights by CKD stage

	n	Mean	95% CI	*P* value
CKD stage				
1	83	0.940	0.915–0.965	<0.0001
2	153	0.918	0.896–0.940	
3	158	0.883	0.857–0.909	
4	72	0.839	0.794–0.884	
5	71	0.798	0.757–0.839	
All stages	537	0.885	0.871–0.898	

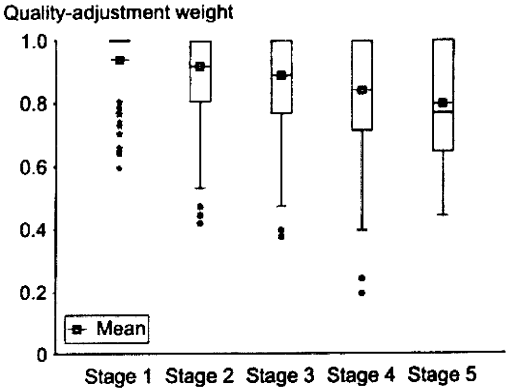

Fig. 1 Box and whisker plots of quality-adjustment weights by CKD stage. Quality-adjustment weights decrease with progression of CKD stage. Quality-adjustment weights at CKD stages 4 and 5 are significantly lower than those at CKD stages 1–3

not very clear when plots of cases are studied, smoothing curves reveal nonlinear relationships. The curves are stable regardless of the chosen bandwidth. Notable inflections in the weight against hemoglobin are seen at around 10.0 and 13.0 g/dl in Fig. 2. Similarly, inflections against serum albumin are seen at around 3.2 and 4.2 g/dl in Fig. 3.

The results from an analysis of the effect of comorbidity on HRQOL are shown in Table 5. The presence of hypertension lowers the weight from 0.910 (0.885–0.936) to 0.874 (0.858–0.891), diabetes from 0.901 (0.886–0.917) to 0.840 (0.811–0.869), and CVD from 0.892 (0.878–0.906) to 0.783 (0.718–0.848). There was a significant relationship between quality-adjustment weights and the presence of complications.

Discussion

We measured the HRQOL in terms of quality-adjustment weight using EQ-5D in patients with CKD. Measured weights by stage were: 0.94 for stage 1, 0.918 for stage 2, 0.883 for stage 3, 0.839 for stage 4, 0.798 for stage 5, and 0.885 for all stages. This is the first report on such weights using EQ-5D, and it can be used in cost-effectiveness analysis with a preferred outcome measure, QALYs, of interventions for CKD. The weights illustrate that CKD patient HRQOL lowers according to the progression of the disease, as expected. We consider that these results show the health-related quality of CKD patients' lives to a certain extent.

Although it is known that a direct international comparison of quality-adjustment weights is not possible, and that the measurement is sensitive to the technique/instrument used, Gorodetskaya et al. [18] report such weights by stage of CKD with TTO and Health Utility Index Mark 3 (HUI3); that is, a generic preference-based measures instrument [19]. TTO yields 0.90 for stages 1 and 2, 0.87 for stage 3, 0.85 for stage 4, 0.85 for stage 4, 0.85 for stage 5, and 0.72 for stage 5D; HUI3 yields 0.67 for stages 1 and 2, 0.67 for stage 3, 0.55 for stage 4, 0.54 for stage 4, 0.54 for stage 5, and 0.72 for stage 5D. The weight decreases along with progression of the stage, which is similar to our results. Gorodetskaya's weights, however, are lower than ours, which may be due to differences in social preferences between Japan and the United States, in the characteristics of the technique/instrument used, or in other factors including measurement errors. A well-designed international comparative study is needed in order to explore the causes of these differences.

There are more reports of weights for ESRD from several countries obtained with various techniques/instruments, although we have not assessed them. The weights for the ESRD range from 0.39 up to 0.93 using TTO, SG, or EQ-5D [20]. Limiting the instrument to EQ-5D, the reported weights were 0.66–0.81 for hemodialysis and 0.71–0.81 for peritoneal dialysis from the Netherlands [21], 0.76 for dialysis from Germany [22], 0.62 for hemodialysis and 0.55 for peritoneal dialysis from Canada [23], and 0.44 for hemodialysis and 0.65 for peritoneal dialysis from Sweden [24]. These values do not raise any concerns over our measurement of 0.798 for stage 5, although no straightforward comparison can be made.

The measured quality-adjustment weights were correlated with routinely checked clinical indices such as hemoglobin, serum albumin, eGFR, and creatinine. Additionally, they significantly depend on hemoglobin and serum albumin after controlling for age. The significance of hemoglobin as a determinant of the HRQOL of CKD patients is consistent with the findings of previous studies, which measured HRQOL along with other measurements, such as SF-36 [11, 12]. The significance of serum albumin has also been pointed out [11]. These results suggest that a patient's HRQOL more closely depends on a general secondary state such as anemia or undernutrition than the primary pathology of CKD, i.e., a low GFR. A notable inflection in the weight at around a hemoglobin level of 10.0 g/dl is also noted in the relationship between the

Table 4 Multiple linear regression analysis of clinical determinants of HRQOL

Variable	Coefficient	SE	*t* Value	*P* value
Forced entry regression[a]				
Alb	0.0465	0.013	3.497	0.001
Hb	0.0148	0.004	3.434	0.001
sCre	−0.0065	0.006	−1.124	0.261
eGFR	−0.0002	0.000	−0.732	0.465
Age	−0.0021	0.001	−4.069	0.000
Sex dummy ("0" for male; "1" for female)	−0.0323	0.015	−2.219	0.027
Constant	0.6607	0.085	7.427	0.000

Step	Variable added	Coefficient	SE	*F* value	Adjusted R^2
Stepwise regression[b]					
1	Hb	0.0165	0.004	79.896	0.133
2	Age	−0.0019	0.000	49.961	0.160
3	Alb	0.0458	0.013	37.584	0.176
4	Sex dummy ("0" for male; "1" for female)	−0.0280	0.014	29.402	0.181

[a] $n = 537$, $R^2 = 0.189$, adjusted $R^2 = 0.180$, $F = 19.785$, $P = 0.000$

[b] Forward selection method, critical $F_{in} = 0.05/F_{out} = 0.1$, other variables considered: sCre, eGFR

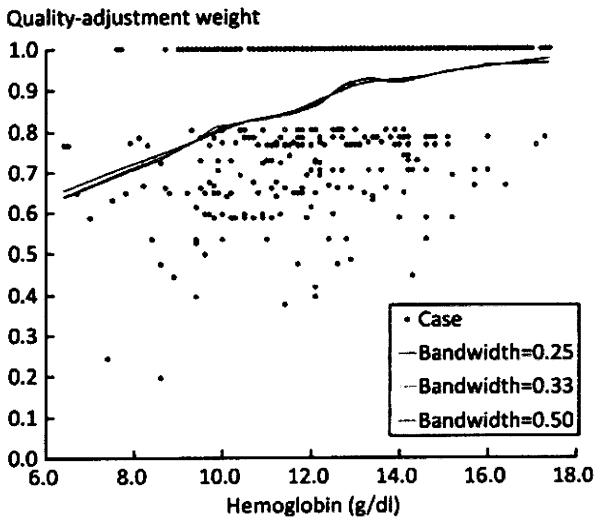

Fig. 2 Smoothing scatterplots of quality-adjustment weight and hemoglobin. Bandwidth is a smoothing parameter that specifies the weighting between the central point and points further away in local linear regressions. The greater the bandwidth, the greater the smoothing. Smoothing curves are stable irrespective of the bandwidth. Inflections in the weight against hemoglobin can be seen at around 10.0 and 13.0 g/dl

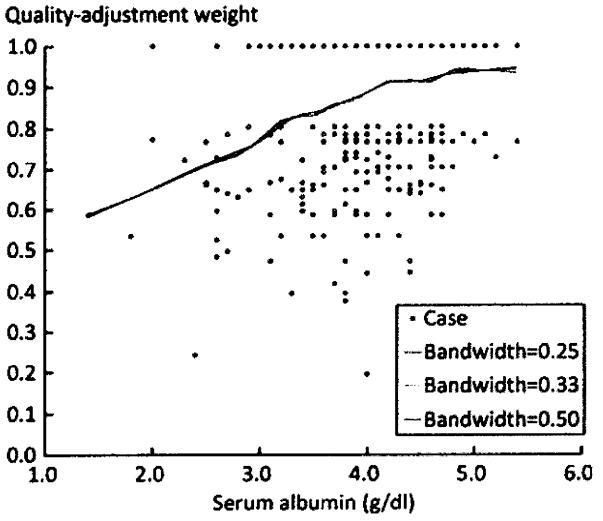

Fig. 3 Smoothing scatterplots of the quality-adjustment weight and serum albumin. Bandwidth is a smoothing parameter that specifies the weighting between the central point and points further away in local linear regressions. The greater the bandwidth, the greater the smoothing. Smoothing curves are stable irrespective of the bandwidth. Inflections in the weight against serum albumin can be seen at around 3.2 and 4.2 g/dl

weight and hemoglobin. This finding corresponds to what Lefebvre et al. [25] reported in an intervention study to improve HRQOL measured by Kidney Disease Questionnaire (KDQ) on the administration of erythropoietin, whereby the maximal gain in HRQL occurred between hemoglobin values of 10 and 12 g/dl. This could be an additional rationale from the viewpoint of HRQOL supporting a target hemoglobin level of 10–12 g/dl for CKD patients as recommended in the CKD Clinical Practice Guideline in Japan of 2007 [26].

The presence of comorbidities such as hypertension, diabetes, or a history of CVD is found to lower quality-adjustment weights, i.e., the HRQOL, of CKD patients, as anticipated. HRQOL deterioration is most severe in the

Table 5 Quality-adjustment weights by CKD stage and complications

	Presence of hypertension				Absence of hypertension			
	n	Mean	95% CI	*P* value	*n*	Mean	95% CI	*P* value
CKD stage								
1	37	0.935	0.896–0.974	0.0000	45	0.942	0.909–0.975	0.0017
2	99	0.909	0.880–0.938		54	0.935	0.901–0.969	
3	122	0.889	0.861–0.917		36	0.862	0.800–0.924	
4	66	0.851	0.807–0.895		6	0.708	0.470–0.946	
5	64	0.782	0.740–0.824		7	0.941	0.825–1.057	
All stages	388	0.874	0.858–0.891	0.0229*	148	0.910	0.885–0.936	
	Presence of diabetes				Absence of diabetes			
	n	Mean	95% CI	*P* value	*n*	Mean	95% CI	*P* value
CKD stage								
1	14	0.867	0.818–0.976	0.0041	69	0.948	0.923–0.973	0.0001
2	35	0.911	0.862–0.960		118	0.920	0.895–0.945	
3	38	0.826	0.767–0.885		120	0.901	0.873–0.929	
4	25	0.843	0.770–0.916		47	0.837	0.780–0.894	
5	34	0.757	0.700–0.814		37	0.836	0.779–0.893	
All stages	146	0.840	0.811–0.869	0.0001*	391	0.901	0.886–0.917	
	Presence of CVD				Absence of CVD			
	n	Mean	95% CI	*P* value	*n*	Mean	95% CI	*P* value
CKD stage								
1	0	–	–		83	0.940	0.915–0.965	0.0000
2	7	0.912	0.793–1.031	0.1731	146	0.918	0.895–0.941	
3	11	0.773	0.633–0.913		147	0.891	0.866–0.916	
4	6	0.816	0.695–0.937		66	0.841	0.793–0.889	
5	14	0.713	0.620–0.806		57	0.819	0.774–0.899	
All stages	38	0.783	0.718–0.848	0.0018*	499	0.892	0.878–0.906	

* *P* value, presence vs. absence of complication at all stages

presence of a history of CVD, and least in the presence of hypertension.

In regard to the presence of diabetes, Sakamaki et al. [27] reported the HRQOL of type 2 diabetes mellitus Japanese patients using EQ-5D. Nephropathy was classified as present with an early-stage urinary albumin/creatinine ratio of >20 mg/g. The quality-adjustment weights of patients with nephropathy were 0.81 (95% CI 0.72–0.90) and 0.87 (0.85–0.89) in those without nephropathy ($P = 0.193$) [27]. In our study, the weights of CKD patients with diabetes were 0.840 (0.811–0.869) and 0.901 (0.886–0.917) in those without diabetes ($P = 0.0001$). We noted slightly higher weights than Sakamaki et al. This may be due to a difference in the age of respondents according to our analysis of weight determinants. The mean age of respondents in our study, 55.2 years old, was younger than that in the report by Sakamaki et al., at 63.3 years old.

This study has several limitations. Firstly, the employment of an established HRQOL measurement tool, EQ-5D [14, 15], improves the reliability of our study and its results. However, its plausibility depends on our sample's representativeness of CKD patients. We made an assumption that outpatients at our department could be considered to comprise a near-representative sample, since a better sampling method such as simple random sampling of CKD patients in the community is not feasible due to the limitations on our epidemiologic knowledge. Therefore, we can neither exclude the possibility of sample selection bias nor implement a bias correction. Further epidemiologic studies are awaited. Secondly, we assessed the effect of the presence or absence of cormobidities (hypertension, diabetes, and CVD) on HRQOL, but not the influence of the severities of these comorbidities on HRQOL.

Finally, the utilization of quality-adjustment weights of CKD patients is a valuable aid when devising an effective

strategy to solve both socioeconomic and public health problems like CKD.

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References

1. K/DOQI Clinical Practice Guidelines for Chronic Kidney Disease. Evaluation, classification, and stratification. Part 5. Evaluation of laboratory measurements for clinical assessment of kidney disease. Am J Kidney Dis. 2002;39:76–110.
2. Levey AS, Eckardt KW, Tsukamoto Y, Levin A, Coresh J. Definition and classification of chronic kidney disease: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int. 2005;67:2089–100.
3. Imai E, Horio M, Watanabe T, Iseki K, Yamagata K, Hara S, et al. Prevalence of chronic kidney disease CKD in Japanese general population. Clin Exp Nephrol. 2009;13:621–30.
4. Japanese Society for Dialysis Therapy. An overview of regular dialysis treatment in Japan as of Dec 31, 2008. Tokyo: Japanese Society for Dialysis Treatment; 2009 (in Japanese).
5. Mann JF, Gerstein HC, Pogue J, Bosch J, Yusuf S. Renal insufficiency as a predictor of cardiovascular outcomes and the impact of ramipril: the HOPE randomized trial. Ann Intern Med. 2001;134:629–36.
6. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med. 2004;351:1296–305.
7. Hillege HL, Girbes AR, de Kam PJ, Boomsma F, de Zeeuw D, Charlesworth A, et al. Renal function, neurohormonal activation, and survival in patients with chronic heart failure. Circulation. 2000;102:203–10.
8. Brugts JJ, Knetsch AM, Mattace-Raso FU, Hofman A, Witteman JC. Renal function and risk of myocardial infarction in an elderly population: the Rotterdam Study. Arch Intern Med. 2005;165:2659–65.
9. Gold RM, Siegel JE, Russell LB, Weinstein MC. Cost-effectiveness in health and medicine. New York: Oxford University Press; 1996.
10. Drummond MF, Sculpher MJ, Torrance GW, O'Brien BJ, Stoddart GL. Methods for the economic evaluation of health care programmes. 3rd ed. Oxford: Oxford University Press; 2005.
11. Perlman RL, Finkelstein FO, Liu L, Roys E, Kiser M, Eisele G, Burrows-Hudson S, et al. Quality of life in chronic kidney disease (CKD): a cross-sectional analysis in the Renal Research Institute-CKD Study. Am J Kidney Dis. 2005;45:658–66.
12. Leaf DE, Goldfarb DS. Interpretation and review of health-related quality of life in CKD patients receiving treatment for anemia. Kidney Int. 2009;75:15–24.
13. Brazier J, Ratcliffe J, Salomon JA, Tsuchiya A. Measuring and valuing health benefits for economic evaluation. Oxford: Oxford University Press; 2007.
14. Japanese EuroQol Translation Team. The development of the Japanese EuroQol instrument. J Health Care Soc. 1997;8:109–23. (in Japanese).
15. Tsuchiya A, Ikeda S, Ikegami N, Nishimura S, Sakai I, Fukuda T, et al. Estimating an EQ-5D population value set: the case of Japan. Health Econ. 2002;11:341–53.
16. Matsuo S, Imai E, Horino M, Yasuda Y, Tomita K, Nitta K, et al. Revised equations for estimated GFR from serum creatinine in Japan. Am J Kidney Dis. 2009;53:982–92.
17. Cleveland WS. Robust locally weighted regression and smoothing scatterplots. J Am Stat Assoc. 1979;74:829–36.
18. Gorodetskaya I, Zenion S, McCulloch CE, Bostrom A, Hsu CY, Bindman AB, et al. Health-related quality of life and estimates of utility in chronic kidney disease. Kidney Int. 2005;68:2801–8.
19. Furlong WJ, Feeny DH, Torrance GW, Barr RD. The health utilities index (HUI) system for assessing health-related quality of life in clinical studies. Ann Med. 2001;33:375–84.
20. Dale PL, Hutton J, Elgazzar H. Utility of health states in chronic kidney disease: a structured review of the literature. Curr Med Res Opin. 2008;24:193–206.
21. de Wit GA, Ramsteijn PG, de Charro FT. Economic evaluation of end stage renal disease treatment. Health Policy. 1998;44:215–32.
22. Greiner W, Obermann K, Schulenburg JM. Socio-economic evaluation of kidney transplantation in Germany. Arch Hell Med. 2001;18:147–55.
23. Manns B, Johnson JA, Taub K, Mortis G, Donaldson GC. Quality of life in patients treated with haemodialysis or peritoneal dialysis: what are the important determinants? Clin Nephrol. 2003;60:341–51.
24. Sennfält K, Magnusson M, Carlsson P. Comparison of haemodialysis and peritoneal dialysis—a cost-utility analysis. Perit Dial Int. 2002;22:39–47.
25. Lefebvre P, Vekeman F, Sarokhan B, Enny C, Provenzano R, Cremieux PY. Relationship between hemoglobin level and quality of life in anemic patients with chronic kidney disease receiving epoetin alfa. Curr Med Res Opin. 2006;22:1929–37.
26. Japanese Society of Nephrology. Clinical practice guidebook for diagnosis and treatment of chronic kidney disease. Tokyo: Igakusha; 2007 (in Japanese).
27. Sakamaki H, Ikeda S, Ikegami N, Uchigata Y, Iwamoto Y, Origasa H, et al. Measurement of HRQL using EQ-5D in patients with Type 2 diabetes mellitus in Japan. Value Health. 2006;9:47–53.

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ORIGINAL ARTICLE
Peripheral Vascular Disease

Characteristics of Revascularization Treatment for Arteriosclerosis Obliterans in Patients With and Without Hemodialysis

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Background: Limb ischemia is a major complication in patients who are receiving hemodialysis (HD). In this study, distinctive features and factors affecting the outcome of HD patients with limb ischemia are identified.

Methods and Results: One hundred and eighty consecutive symptomatic limb ischemic patients who were or were not receiving HD and who successfully underwent surgical bypass grafting (bypass, n=75) or endovascular angioplasty (percutaneous transluminal angioplasty (PTA), n=105) were retrospectively compared at our hospital. The endpoint of this study was amputation of the ischemic leg or death. Median follow up was 2.25 years. The amputation-free survival of HD patients was significantly lower than that of non-HD patients (P<0.0001). In the bypass group, the amputation-free survival of HD patients was significantly lower than that of non-HD patients (P=0.0002), even if the graft was patented or not (P=0.77). In contrast, in the PTA group, the amputation-free survival of HD patients was lower than that of non-HD patients (P=0.03), and with a significantly lower patency rate (P=0.0004). Predictors of amputation-free survival differed between HD and non-HD patients; predictors were diabetes mellitus and gender in HD patients, while they were Fontaine classification and hyperlipidemia in non-HD patients. The infectious death rate was higher in HD patients than in non-HD patients (53% vs 22%, P<0.05).

Conclusions: This study clearly showed a poorer prognosis in HD patients than in non-HD patients especially after bypass surgery, even if the the graft was patented or not. (*Circ J* 2010; **74:** 2426–2433)

Key Words: Angioplasty; Bypass surgery; Hemodialysis outcomes; Peripheral arterial disease

Peripheral artery disease (PAD) is one of the major complications in patients on hemodialysis (HD). The number of patients with PAD is increasing due to increases in the number of patients on HD, the elderly population and patients with diabetic nephropathy. Surgical bypass grafting (bypass) and percutaneous transluminal angioplasty (PTA) are the 2 main interventional treatments for PAD. The advantages of surgery over than PTA were reported to be good long-term anatomical patency and clinical durability.[1–3] In contrast, balloon angioplasty was reported to have the advantages of low procedural morbidity and mortality, and a shortened hospital stay.[4,5] A recent randomized controlled trial that compared the outcomes of bypass and PTA in patients with severe limb ischemia and concluded that their outcomes were similar.[6]

In HD patients, however, several studies described the outcome of dialysis patients with PAD who were treated by bypass surgery.[7–10] The survival at 1 and 2 years was in the range of 50–60% and 40–50%, respectively. The cumulative limb salvage rate and primary patency rate at 1 year were in the range of 50–80% and 50–70%, respectively. Also PTA was considered as feasible and effective in HD patients with severe PAD.[11,12] However, these studies did not directly compare the outcomes of these 2 treatments in patients on HD, and treated years were different between these 2 groups. The primary endpoint of this retrospective study was to compare the outcomes between HD and non-HD patients, and the secondary endpoint of this study was to reveal the characteristics of PAD treatments in HD patients by directly determining the outcome associated with bypass or PTA between

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Table 1. Patients' Characteristics (n=180)

	HD (n=41)	Non HD (n=139)	P value
Gender, F/M	8/33	13/126	0.09
Age	63.3±8.7	68.9±7.9	<0.01
Fontaine, II/III/IV	27 (65.9%)/6/8	121 (87.1%)/8/10	0.01
IHD history	23 (56.1%)	57 (41.0%)	0.09
Hypertension	31 (75.6%)	106 (76.3%)	0.93
Smoking	31 (75.6%)	123 (88.5%)	0.05
Diabetes mellitus	21 (51.2%)	80 (57.6%)	0.47
Hyperlipidemia	10 (24.4%)	5 (38.9%)	0.08
Bypass/PTA	23 (56.1%)/18 (43.9%)	52 (37.4%)/87 (62.6%)	0.03

Data are presented as number (%) unless otherwise stated. Plus-minus values are mean±SD.
P values were calculated with the use of the chi-square test for categorical variables and the t-test for continuous variables.
HD, history of hemodialysis; IHD, history of ischemic heart disease (angina pectoris or myocardial infarction).

patients who were or were not receiving HD.

Methods

The study population included 231 symptomatic patients with chronic limb ischemia who underwent bypass or PTA at our hospital between 1999 and 2006. Patients who could not achieve clinical success (12 patients in PTA and 1 patient in bypass), who had been treated with in-stent restenosis (10 patients), had a past history (within 3 months) of angioplasty (16 patients), had had a scheduled amputation after the procedure (2 patients in PTA), had symptomatic advanced malignancy (1 patient in PTA), could not be followed up after discharge (4 patients in PTA and 2 patients in bypass), and who were considered inadequate to follow up (2 patients in PTA and 1 patient in bypass) were excluded from this study. As a result, 180 symptomatic patients with chronic limb ischemia who underwent bypass or PTA were included in this study. The primary endpoint of this study was amputation of the ischemic leg or death, and the secondary endpoint was occlusion after treatment. We compared these outcomes between HD and non-HD patients, and then determined outcomes associated with bypass or PTA between them. Whether to perform bypass or PTA was considered according to the Trans Atlantic Inter-Society Consensus (TASC) criteria[13,14] after discussion among cardiovascular specialists.

Clinical success was defined by the absence of residual obstructions after treatment.[12] All subjects were diagnosed with limb ischemia by clinical symptoms, angiographic examinations and the ankle-brachial pressure index (ABI) (form PWV/ABI; Omron Colin, Tokyo, Japan). Patients' previous histories were examined by using clinical records. A history of ischemic heart disease was defined as a history of angina pectoris or myocardial infarction. Renal function of the patients who did not receive hemodialysis was calculated by using an estimated glomerular filtration rate (eGFR) formula by Matsuo et al.[15] Follow up continued until the patients had reached an endpoint (amputation of the ischemic leg or death) or were lost to follow up. To find the prognostic factor differences, we examined patient characteristics, time to death from any cause, time to amputation of the ischemic leg or death (whichever came first) (amputation-free survival), and the primary patency period in both groups. The primary patency period was defined as the time after treatment to occlusion. Occlusion after treatment was defined as angiographic occlusion, loss of distal pulsation after treatment or worsened symptoms requiring another treatment. Hypertension, hyperlipidemia, and diabetes mellitus (DM) were defined as a systolic blood pressure of 140 mmHg or higher, a total cholesterol of 220 mg/dl and/or a LDL cholesterol of 140 mg/dl or higher, and a fasting blood glucose of 126 mg/dl or higher, respectively.

Statistical Analysis

Baseline characteristics of patients were compared using the 2-tailed t-test, or the Mann-Whitney test where appropriate, for continuous data, and the chi-square test for categorical data. Cumulative event rates were estimated with Kaplan-Meier survival curves, and possible statistical differences were evaluated by the log-rank test. Multiple linear regression analysis was used to determine factors affecting survival and amputation-free survival. The Cox proportional hazards model was used to obtain hazard ratios (HR) and 95% confidence intervals (CI) for overall survival and amputation-free survival. Any covariates that were significant on univariate analysis were assessed by multivariate analysis. The considered variables were as follows: age, gender, treatment methods, Fontaine classification, DM, hypertension, hyperlipidemia, smoking history, ischemic heart disease, history of dialysis, and time from dialysis start. Among the explanatory variables, qualitative variables were evaluated by a marginal method, and stepwise analysis was performed by an increasing variable method. A P value <0.05 was considered statistically significant. Data were entered and analyzed using the statistical software, JMP 8.0 (SAS Institute, Cary, NJ, USA).

Results

The baseline characteristics of the patients in each group are shown in Table 1. Over 70% of the patients had a history of hypertension and a smoking history in each group. Approximately half of the patients had a history of DM. The percentage of CLI (Fontaine III+IV) patients was 34.1% in the HD group and 12.9% in the non-HD group, respectively (P=0.01). There were greater numbers of older patients, patients with a history of smoking and who treated by PTA in the non-HD group than in the HD group. The mean duration of HD was 9.9±9.2 years; 9.4±9.9 years in the bypass group, and 10.7±8.5 years in the PTA group (P>0.05). The mean eGFR of non-HD patients was 67.5±25.0 ml/min in the bypass group and 63.0±20.1 ml/min in PTA group (P>0.05). The types of endovascular treatment lesions in patients with HD were: TASC A, 16%; TASC B, 38%; and TASC C, 46%;