The clinical manifestations of renal artery pseudoaneurysms may vary from incidental to causing hypertension, flank pain, hematuria, and rupture. The risk of rupture is estimated low, but it is associated with a mortality rate as high as 80%.[3] Aneurysms larger than 2 cm in diameter are considered to have a high risk of rupture, although ruptures have also been reported in smaller aneurysm.

Angiographic embolization is now considered a safe and effective treatment in patients with renal artery pseudoaneurysm. This treatment should be the procedure of choice due to its advantage of being minimally invasive and its selective treatment with maximal preservation of renal parenchyma.

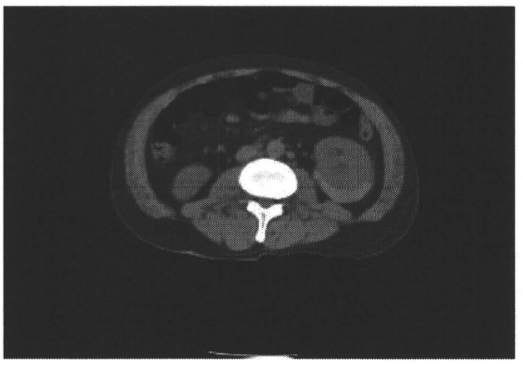
CASE REPORT

A 37-year-old was admitted to our rheumatology department of our hospital because of dyspnea and arthralgia. Systemic sclerosis was diagnosed on proximal scleroderma, Raynaud's phenomenon, and the lung abnormality of computed tomography as well as positive antinuclear antibody. Because of proteinuria and microscopic hematuria, he was moved to our department and had renal biopsy performed. After seven hours of biopsy, flank pain, severe gross hematuria, urinary clot retention, and bladder tamponade were recognized, and abdominal CT showed a large perinephric, intracapsular hematoma of the left kidney (see Figures 1a and 1b). Gross hematuria persisted the next day, so we decided to perform angiography. His angiogram revealed a left renal segmental artery pseudoaneurysm that measured 1 cm × 1 cm and its rupture, and then the subsequent coiling of this spontaneously ruptured left renal segmental artery pseudoaneurysm (see Figure 2).

DISCUSSION

Renal artery pseudoaneurysm is a rare complication of renal biopsy percutaneous renal procedures,[6] but when encountered, it is of great clinical significance because of propensity for rupture.[4] A pseudoaneurysm is the presence of arterial blood entering into adjoining tissue with continuous blood flow within this space. Symptoms may include abdominal tenderness, abdominal mass, hematuria, hypertension, and shock[8]; however, incidence for ruptured renal pseudoaneurysm and the mortality rate of pseudoaneurysm are difficult to establish due to the lack of reported cases in the literature.[1] When there is rupture, there are four spaces the blood can be redistributed (viz., retroperitoneal, intraperitoneal, intrarenal, and intrapelvic). Most intraparenchymal renal artery pseudoaneurysm ruptures are self-contained,

a



b

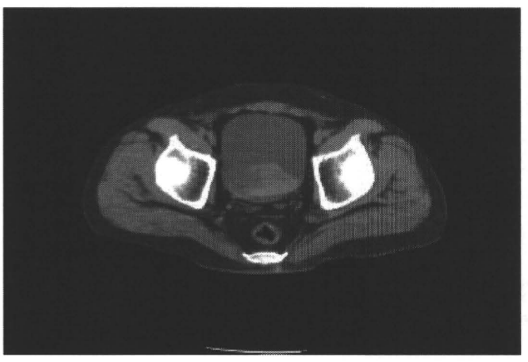


Figure 1. CT scan shows a large perinephric, intracapsular hematoma of left kidney.

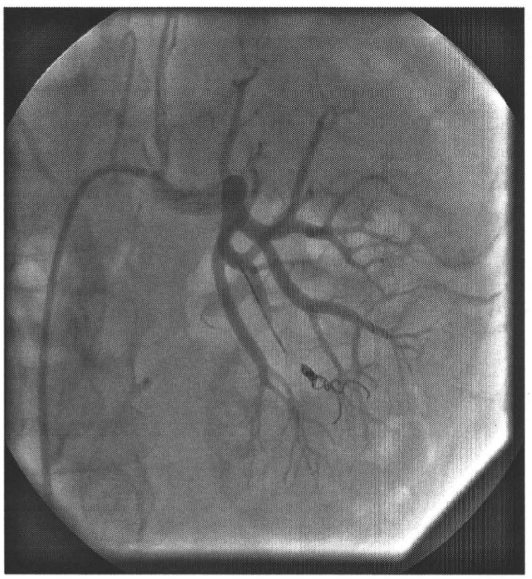


Figure 2. Selective angiogram shows a complete exclusion of the pseudoaneurysm in left renal artery.

leading to increased probability of tamponade and improved mortality.[7] The same principle may apply to extraparenchymal aneurysms that are contained in the retroperitoneum with concomitant tamponade.[5]

Early detection and embolization are important in treating this life-threatening injury with reported high success rates.[2] Treatment of renal pseudoaneurysm consists of nephrectomy, open vascular surgery, or angiographic embolization, depending on the patient's clinical condition. Angiographic embolization should be the procedure of choice due to its advantage of being minimally invasive and its selective treatment with maximal preservation of renal parenchyma. Surgical indications for repair include overt ruptures, aneurysm greater than 2 cm, renovascular hypertension, expansion of the aneurysm, and evidence of renal damage.[3]

We herein showed a case in which massive microhematuria, urinary clot retention, and bladder tamponade seven hours after renal biopsy were the presenting signs of renal pseudoaneurysm rupture, and demonstrated that it can be managed successfully with angiographic embolization.

ACKNOWLEDGMENTS

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Case Report

Improvement of Renal Function after Opening Occluded Atherosclerotic Renal Arteries

*Hiroshi Kanamori, MD, PhD, §Masanao Toma, MD, *Atsushi Fukatsu, MD, PhD

ABSTRACT: Percutaneous transluminal renal angioplasty (PTRA) with stenting has been effective in the control of hypertension, renal function and pulmonary edema caused by atherosclerotic renal artery stenosis (ARAS). However, concerning the viability of renal function, this procedure has not been fully established, especially in the presence of renal atrophy or severe renal parenchymal disease. We report a dramatically improved case of acute renal failure caused by acute worsening ARAS treated by stenting. A 72-year-old female was admitted for accelerated renal dysfunction (serum ceatinine; 1.2–2.3 mg/dl) and hypertension (190/100 mmHg). At 10 days after admission, the patient's serum ceatinine increased to 6.7 mg/dl, her pulmonary edema was exaggerated and hemodialysis was required. Ultrasonography showed bilateral high-echoic kidneys, but no apparent finding of renal artery stenosis (RAS). At day 15, computed tomographic angiography indicated bilateral ostial RAS. Renal angiography demonstrated total occlusion of the right and severe (90%) disease in the left. ARAS was diagnosed by intravascular ultrasonography. The guidewire was inserted in both renal arteries, PTRA with stenting was performed in the right and a stent was directly implanted in the left. Immediately, each kidney enlarged to almost normal size, leading to satisfactory urination. She was released from hemodialysis the next day since her serum creatinine was normal and the pulmonary edema was improved. Although there is still no reliable prognostic factor including resistive index or kidney size, it is important that PTRA with stenting in ARAS should be considered in a case of accelerated renal dysfunction because of the possible improvement.

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It is well known that renal artery stenosis causes refractory hypertension. Among the diseases that cause renal artery stenosis, including atherosclerotic renal artery stenosis (ARAS), fibromuscular dysplasia (FMD), aortic dissection, aortitis, and so on, ARAS is the most common underlying cause (approximately 90%).[1] Recently, noninvasive diagnostic techniques have been established for the examination of renal arteries including magnetic resonance angiography (MRA), computed tomographic angiography (CTA), and duplex ultrasonography, and ARAS has begun to draw attention as the cause of end-stage renal disease (ESRD).[2] It is reported that early identification and management of ARAS, especially percutaneous renal angioplasty (PTRA) followed by primary stenting, have a beneficial effect on the control of hypertension and renal function.[3] However, concerning the viability of renal function, this procedure has not been established, especially in the presence of renal atrophy or severe renal parenchymal disease.[4,5] Here we report a dramatically improved case of acute renal failure caused by possible acute worsening ARAS (total occlusion in the right renal artery and 90% stenosis in left) and treated by intravascular stent placement with or without PTRA. This case offers some clues to the appropriate indication for PTRA and stenting to treat ARAS.

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The authors report no conflicts of interest regarding the content herein.

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Case Description. *We present a case of acute renal failure with bilateral severe ARAS treated by PTRA followed by intravascular stent placement, leading to the discontinuation of hemodialysis (HD). A 72-year-old female presented with dizziness associated with hypertension (190/100 mmHg), and candesartan (8 mg) was administered. Laboratory findings showed renal dysfunction (sCr, 1.2 mg/dl). Twenty days later, the patient's serum creatinine had increased to 2.3 mg/dl and her hypertension had not improved. She was therefore admitted to our hospital for further examination. Since her renal functional decline appeared to be due to angiotensin receptor-blockers (ARB), which implied the existence of bilateral ARAS, nifedipine (40 mg) was administered as a substitute for candesartan on admission (day-0). Urine analysis showed no apparent abnormal finding. A bruit was heard beside the umbilicus. At day-10, the patient's urinary volume declined and her serum creatinine had increased to 6.7 mg/dl. Although furosemide was administered, her pulmonary edema was exaggerated (Figure 1A) and HD was required. The patient's plasma rennin activity (PRA) and serum aldosterone[6] level were revealed to be high (PRA 17.3 ng/ml/hour; Ald 402 pg/ml) (Table 1). Renal artery stenosis was suspected, however, no clear finding was confirmed with duplex ultrasonography (Table 1). Renal echography showed atrophic kidneys. These facts implied that both kidneys might not viable. However, we decided to perform an interventional study because the patient's clinical course was acute and there was a possibility of recovering renal function. At day-15, CT angiography showed bilateral ostial renal artery stenosis and atrophic kidneys (long-axis: right 74 mm; left 85 mm) (Figure 2). Renal angiography demonstrated total occlusion of the right renal artery and severe (90%) disease in the left renal artery (Figures 3A and 3E, respectively). ARAS was diagnosed for its plaque formation by intravascular ultrasonography (IVUS). The totally occluded lesion of right renal*

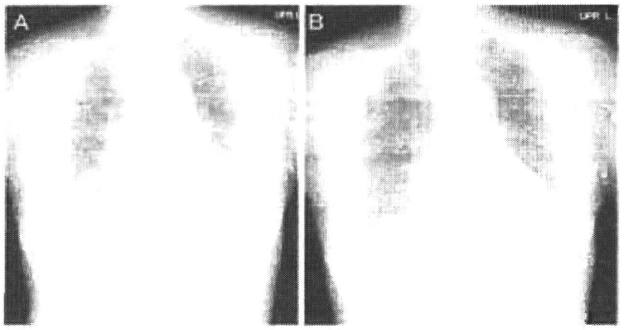

Figure 1. *Chest X-ray findings.* (A) *At day-10 (before the start of hemodialysis), pulmonary edema was apparent.* (B) *After percutaneous transluminal renal angioplasty with stenting, the patient's pulmonary edema had improved.*

Table 1. Laboratory findings at admission.

Hemogram and Coagulation		Immunological Examinations	
WBC	6,900/ L (2,800–9,300)	IgG	1,598 mg/dL (826–1840)
RBC	373 x 104/ L (319–482)	IgA	163.4 mg/dL (93–426)
Hb	11.7 g/dL (10.2–14.6)	IgM	147.5 mg/dL (54–333)
Ht	35.0% (29.8–43.4)	C3	114.6 mg/dL (70.5–125.6)
Plt	21.2 x 104/ L (12.3–34.3)	C4	28.4 mg/dL (10.6–33.0)
PT(INR)	0.86 (0.98–1.24)	CH50	54.8U/mL (28–51)
APTT	24.9 sec (26.2–39.3)	ASO	< 30 IU/mL
Blood Chemistry			
		ANA	< x 40
TP	7.4 g/dL (6.3–8.1)	RF	30.7 IU/mL (0–11.7)
Alb	3.8 g/dL (3.9–5.1)	MPO-ANCA	< 10 EU
T-Bil	0.5 g/dL (0.3–1.3)	PR3-ANCA	< 10 EU
ChE	198 IU/mL (201–436)	Metabolism	
GOT	49 IU/L (13–33)	Rennin	17.3 ng/mL/hr (0.2–2.7)
GPT	46 IU/L (6–27)	Aldosteron	402 pg/mL (30–159)
ALP	357 IU/L (115–359)	Urinalysis	
LDH	225 IU/L (129–241)	Gravity	1.003
CPK	72 IU/L (35–141)	pH	6.0
BUN	44 mg/dL (8–22)	Protein	-- (0.1 g/day)
Cre	2.3 mg/dL (0.4–0.8)	Glucose	--
UA	9.5 mg/dL (2.6–6.2)	Occult blood	±
T-Cho	232 mg/dL (140–220)	Sediments	
TG	145 mg/dL (34–173)	RBC	1 >/HPF
AMY	240 IU/L(36–129)	Casts	--
Na	139 mmol/L (136–144)	Urine chemistry	
K	4.1 mmol/L (3.6–4.8)	u-NAG	4.9 U/L (0.5–9.1)
Cl	100 mmol/L (99–109)	Creatinine clearance (Ccr)	7 ml/min
Ca	8.0 mg/dL (8.5–9.9)		
P	3.9 mg/dL(2.6–4.5)	Ultrasonographic examination	
BS	87 mg/dL(78–110)	Peak systolic velocity (PSV)	
CRP	0.2 mg/dL (0–0.2)	Right 140 cm/sec, left 150 cm/sec	
HbA1c	5.4% (4.3–5.8)	Resistive index (RI)	
Infection		Right 0.48, left 0.42	
HBs-Ag	--		
HCV-Ab	+		

artery was successfully crossed and was dilated using a 2.0 balloon catheter and a Genesis 4.0 x 18 mm stent was implanted with IVUS guidance, followed by dilatation using 3.5 and 4.0 mm balloon catheters (Figures 3B and 3C). Final angiography showed 0% residual stenosis with normal flow (Figure 3D). A Genesis 5.0 x 18 mm stent was directly implanted in the left renal artery without predilatation (Figures 3 E and F). Immediately after the revascularization of the renal arteries, both kidneys were enlarged to almost normal size. Sufficient urination was noticed during the intervention. The patient was released from HD. Her serum creatinine and PRA normalized to 0.8 mg/dl and 0.7 ng/ml/hr, respectively. Her pulmonary edema was completely ameliorated (Figure 1B). The patient's hypertension also improved to 140/90 mmHg.

Discussion. ARAS is the most common underlying cause of renal artery stenosis.[1] Advanced age, hyperlipidemia, diabetes mellitus, smoking, heart disease and vascular disease are cited as risk factors.[6] Our case did not have any apparent risk factors except a slightly high level of serum total cholesterol and advanced age. However, severe atherosclerotic lesions in bilateral renal arteries were diagnosed by IVUS. The most crucial clinical findings associated with ARAS are hypertension and renal dysfunction. Hypertension is due to the activation of the rennin-angiotensin pathway,[7] which usually worsens rapidly refractory to antihypertensive agents. Renal dysfunction is caused by ischemic nephropathy, with renal parenchymal ischemia caused by a decrement of renal perfusion, often developing into end-stage renal disease (ESRD) and requiring dialysis therapy.[8]

Although angiography is historically the gold standard for diagnosing renal artery stenosis, it may cause atheroembolism and contrast nephropathy. Recently, various noninvasive methods such as MRA, CTA and duplex ultrasonography have been devised and developed. Although MRA and CTA are equal to angiography in terms of sensitivity and specificity (MRA: approximately 90–95%, CTA: approximately 95%), CTA poses a risk of contrast nephropathy, and MRA poses a risk of gadolinium-induced nephrogenic systemic fibrosis.[9] Taking those facts into consideration, duplex ultrasonography is the safest and most convenient on a cost/performance basis. Although the usefulness of duplex ultrasonography depends on the technical skill of the operator, it was recently reported that its sensitivity and specificity are 90–95%.[10,11] Duplex ultrasonography can provide information about the viability of kidneys with ARAS. According to Strandness et al, both a peak systolic velocity (PSV) of a renal artery > 180 cm/sec and a renal-to-aorta ratio (RAR) > 3.5 indicate renal artery stenosis > 60%.[12] It is also reported that a PSV > 200 cm/sec by ultrasonography is almost equal to a translesional pressure gradient > 20 mmHg by angiography.[13] In cases of a resistive index (RI) > 0.8, renal parenchymal dysfunction is estimated to be severe. Our patient's plasma renin activity (PRA) and serum aldosterone level were high, but duplex ultrasonography of the renal arteries did not reveal renal artery stenosis (Table 1).

Given this information and the atrophic finding in both kidneys, we hesitated to perform further studies. However, accelerated renal dysfunction, congestion (flush pulmonary edema) and hypertension that required HD led us to perform CTA (Figure 2).

In terms of treatment for renal artery stenosis, it is reported that angiotensin-converting enzyme inhibitors (ACE I) or angiotensin II receptor-blockers (ARBs) are effective in treating hypertension for 86–92% of patients.[14] Caution should be practiced because ACEIs or ARBs can cause the progression of renal dysfunction,[15] which was the case in our patient. Those agents are also contraindicated in cases of bilateral stenosis or functional unilateral stenosis. The indication for PTRA for ARAS is stated in the ACC/AHA 2005 guidelines.[4] These guidelines cite the following: "...percutaneous revascularization is reasonable for patients with hemodynamically significant RAS and accelerated hypertension, resistant hypertension, malignant hypertension, hypertension with an unexplained unilateral small kidney, and hypertension with intolerance to medication (Class IIa, LOB B), percutaneous revascularization is indicated for patients with hemodynamically significant RAS and recurrent, unexplained congestive heart failure or sudden, unexplained pulmonary edema (Class I, LOB B)."[4]

Van et al reported that in the treatment of ostial ARAS, the primary success rate employing PTRA with or without stenting was 88% and 57%, respectively, and that the restenosis rate after a successful primary procedure in patients who underwent PTRA with or without stenting was in 14% and 48%, respectively. The author concluded that PTRA with stenting is a better approach in the treatment of ostial ARAS.[16] However, concerning the recovery of renal function, it is still controversial.[5]

The resistive index (RI) has been said to predict the outcome in patients with renal artery stenosis who ate undergo intervention. It is reported that among patients with renal artery stenosis > 50% of rhe luminal diameter and who underwent PTRA or surgery, a RI of at least 0.8 reliably identifies those who will not experience improved renal function.[17] On the contrary, it is also reported that among patients with ARAS > 70% of the luminal diameter, even if the RI is > 0.8, PTRA with stenting offers favorable acute and long-term clinical results for the preservation of renal function.[18] RI is currently controversial, with no reliable data on outcomes in patients with renal artery stenosis treated with PTRA.

There is no evidence (such as randomized, controlled studies) that dilating a totally occluded renal artery is beneficial. However, recanalization of chronic total occlusions (CTOs) has been shown to be feasible in the coronary circulation.[19] It is also reported that renal function was improved after opening a totally occluded tenal artery with PTRA followed by stenting.[20,21] In our case, severe and even occluded ostial ARAS was treated by srent placement, leading to recovery of the kidneys' size, immediate satisfactory urination, and a normalized creatinine level and discontinuation of HD. At day-23 (8 days post intervention), a renogram showed that the right kidney functioned at nearly half the capacity as the left kidney (Figures 4A and B), which would

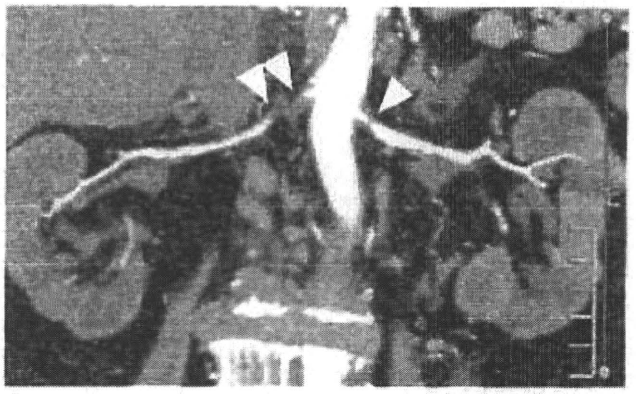

Figure 2. *Computed tomographic angiography finding. Bilateral severe ostial renal artery stenosis (arrowheads) and bilateral atrophic kidneys were seen. The kidney size (major axis) was 74 mm in the right and 85 mm in the left.*

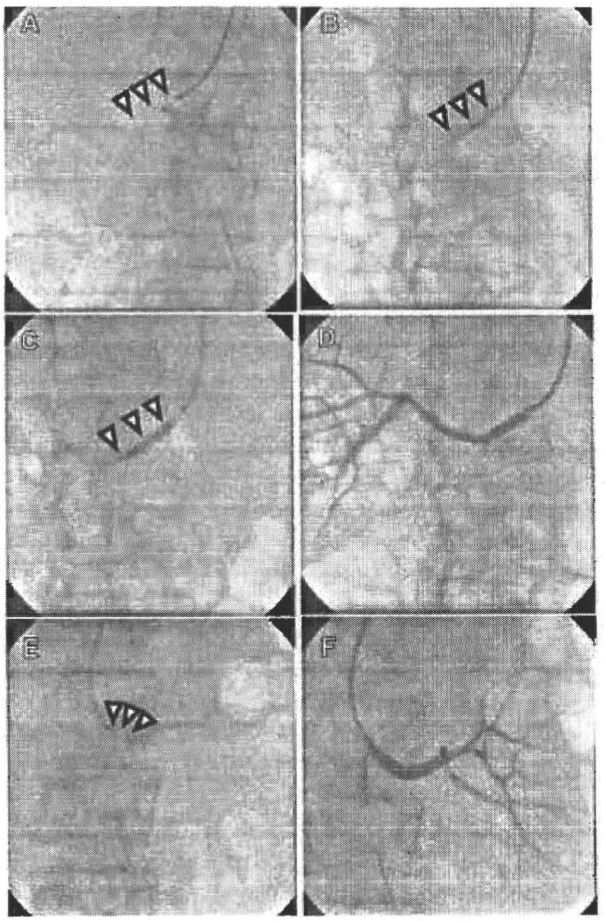

Figure 3. *Renal revascularization. Right renal artery (A–D) and left renal artery (E–F). (A) Angiography of the right renal artery showed total occlusion (arrowheads). (B) The lesion was successfully crossed with a guidewire, dilated using a Trytop 2.0 mm balloon catheter, and a Genesis 4.0 x 18 mm stent was positioned (arrowheads). (C) The lesion was dilated with a Trytop 3.5 mm balloon catheter followed by a 4.0 mm stent balloon (arrowheads). (D) Final angiography showed no stenosis. (E) Angiography of the left renal artery showed 90% stenosis (arrowheads). At the lesion, a Genesis 5.0 x 18 mm stent was directly implanted without predilatation. (F) Final angiography showed 0% residual stenosis, with normal flow.*

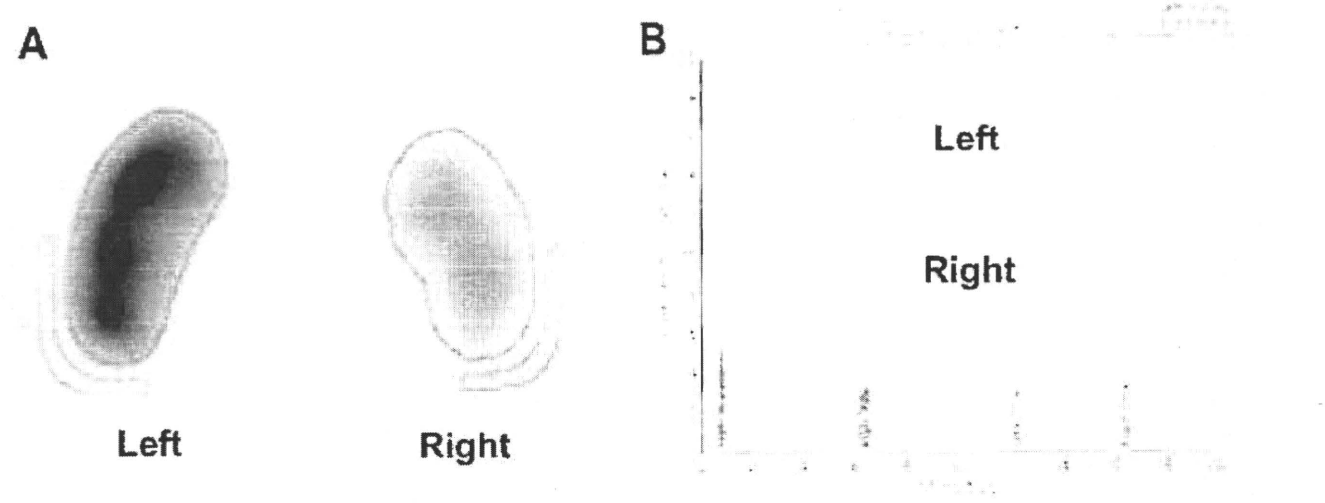

Figure 4. *Renogram (99 mTc-MAG3). (A) The uptake of 99 mTc-MAG3 was less in the right kidney than in the left kidney. (B) The effective renal plasma flow of the right and left kidneys was 63.8 mL/min and 142.1 mL/min, respectively.*

imply that opening the right occluded renal artery contributed to the improvement of renal function to some extent.

Our case provides new information regarding PTRA for ARAS and renal function prognosis due to this interventional approach. In our patient, the conditions implying negative indications and poor prognosis included: 1) small kidneys that looked atrophied and highly-echoic by ultrasound; 2) duplex ultrasonography did not show positive stenotic findings; 3) risk of contrast nephropathy; 4) total occlusion of the right renal artery. Conditions implying a favorable prognosis for our patient included: 1) acute process of renal functional decline; 2) HD was initiated, which meant no further progression of azotemia and congestion; 3) the guidewire was able to reach the totally occluded renal artery which was probably suspected of recent occlusion; 4) immediate recovery of our patient's kidney size and urine output.

Our case thus provided several insights: 1) an atrophic high-echoic appearance of the kidney does not always mean irreversible function; 2) duplex ultrasonography and the RI do not always provide the right information; 3) an acute process of renal dysfunction with ARAS should be treated as quickly as possible; 4) even a totally occluded artery can be treated with PTRA when the guidewire can cross the occlusion.

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Clinical Transplantation

Case Report

A case of living-related renal transplant from the donor with membranous nephropathy

Akioka K, Okamoto M, Ushigome H, Nobori S, Suzuki T, Sakai K, Sakamoto S, Urasaki K, Yanagisawa A, Fukatsu A, Yoshimura N. A case of living-related renal transplant from the donor with membranous nephropathy.
Clin Transplant 2009: 23 (Suppl. 20): 62–66.

Abstract: Introduction: When a patient who had renal replacement therapy becomes older, an elder donor candidate may be considered as a potential donor for living-related transplantation. Elder donor candidate might have pre-existing disease including mild renal dysfunction, such as proteinuria. Marginally appropriate donors might be considered for renal graft because of the shortage of donors. A successful outcome after kidney transplantation from a living-related donor diagnosed as membranous nephropathy is reported.
Case report: A 38-yr-old male had been on continuous ambulatory peritoneal dialysis (CAPD) since the age of 37. His 63-yr-old father had mild proteinuria, and had been diagnosed with membranous nephropathy by needle biopsy at the age of 60. However, renal function of the father was found to be stable for three yr in a preoperative examination for donor; the father had normal renal function except for mild proteinuria. After adequate informed consent, we transplanted a kidney from the father, diagnosed with membranous nephropathy, to his son with a cyclosporine A-based immunosuppression regimen. In both the recipient and the donor, postoperative course was stable without complication such as rejection or infection. At 57 months after transplantation, the serum creatine level was 1.7 mg/dL in the recipient and 1.2 mg/dL in the donor. At 39 months after transplantation, allograft needle biopsy showed mild spike formation with partial thickening of the glomerular basement membrane (GBM). Decreases in electron-dense deposits and electron-lucent washout lesions with thickening of the GBM were observed using electron microscopy. This was diagnosed as Stage IV membranous nephropathy, showing clearance of the immune complexes and histological repair of the GBM.
Conclusion: Donation of the kidney did not affect the residual renal function of the father with membranous nephropathy. Pre-existing membranous nephropathy itself might show remission after transplantation in the recipient. However, long-term careful observation for both the donor and recipient is required.

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Key words: donor – kidney transplantation – membranous nephropathy

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Introduction

When the patient who had renal replacement therapy becomes older, elder donor candidate might be considered as a potential donor for living-related kidney transplantation. Elder donor candidate might have pre-existing disease including mild renal dysfunction, such as proteinuria. Because of the shortage of donors for renal transplantation, marginally appropriate kidney donors are also considered in an attempt to widen the donor criteria.

Some papers have reported successful outcomes after kidney transplantation from donors with pre-existing nephropathy. Here, we report a successful outcome after kidney transplantation from a living-related donor diagnosed with membranous nephropathy, citing appropriate references from the literature.

Case report

A 38-yr-old male who had proteinuria since the age of 22 yr has been on CAPD since the age of 37 because of end-stage renal failure caused by glomerulonephritis. His 63-yr-old father had mild proteinuria and had been diagnosed with membranous nephropathy by needle biopsy at the age of 60. Renal function of the father was stable for last three yr. The father wished to be a donor for living-related kidney transplantation to his son. In a preoperative examination for donor, the father was observed to have normal renal function excepting mild proteinuria. Serum creatinine and 24 h creatinine clearance were 0.96 mg/dL and 106 mL/min (167 cm/77 kg). Blood pressure was normalized by angiotensin receptor blocker. Urinary protein was − or 1+ and ranged about 400 mg/d, and did not increase during the clinical course.

Second needle biopsy of the kidney also had been performed as a final examination; there was no progressive change in histologic findings of membranous nephropathy. As the patient and the donor expressed willingness to have living-related kidney transplantation, after they were given adequate verbal instructions and written informed consent for the transplantation was obtained, we performed transplantation of kidney from the father with membranous nephropathy to his son.

Immunosuppressive treatment was started and maintained using cyclosporine A (CsA), FTY720, Fingolimod (FTY) and prednisolone (PSL). Shortly, the initial dose of CsA (7 mg/kg/d) was administered orally for two d before transplantation, and then CsA (3 mg/kg/d) was administered intravenously on the day of transplantation, followed thereafter by oral administration at 6–8 mg/kg/d. The dosage of CsA was adjusted by reference to the area under the blood concentration–time curve $(AUC)_{0\text{–}9\ h}$ level. A bolus dose of 500 mg of methyl prednisolone (MP) was administered on the day of transplantation, followed by 50 mg/d PSL on days 0–3. PSL was then reduced every week, from 40 to 30, 25, 20, 15 and finally 10 mg/d. On day 1, FTY (5 mg/d) was added. The postoperative course was good and stable; protocol allograft biopsy on postoperative day (POD) 23 showed no evidence of acute rejection and nephrotoxicity except pre-existing membranous nephropathy (Fig. 1).

The serum creatinine level had reached 1.6 mg/dL at the time of hospital discharge on POD33. At 57 months after transplantation, the serum creatinine level was 1.7 mg/dL in the recipient and 1.2 mg/dL in the donor. Their renal functions were stable and no proteinuria was evident in the recipient. Postoperation course is summarized in Fig. 2. Clinical trial use of FTY was over for initial two yr, FTY was converted to 1250 mg of mycophenolate mofetil (MMF). For three yr after the

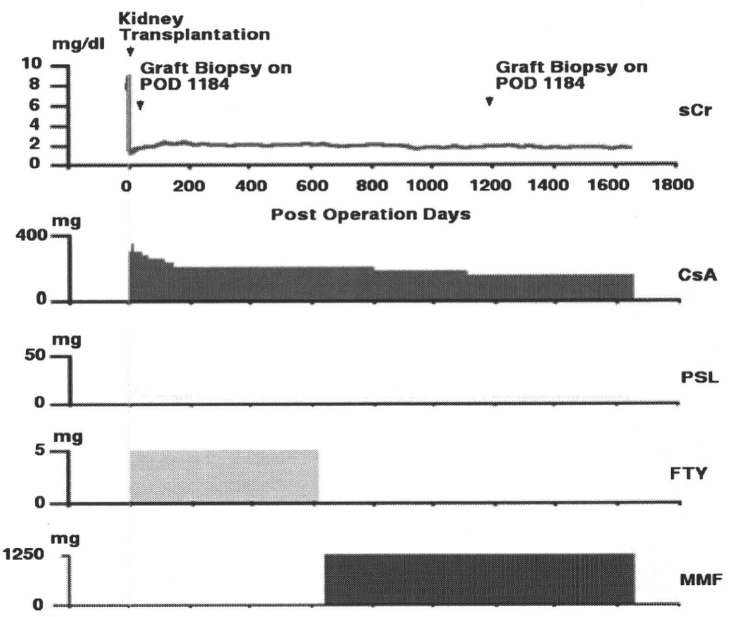

Fig. 1. Postoperative course, showing induction and maintenance of immunosuppression with time after kidney transplantation, and the levels of serum creatinine. Postoperative course, showing induction and maintenance of immunosuppression with time after kidney transplantation, and the levels of serum creatinine. Allograft biopsy was performed on POD 23 and 1184.

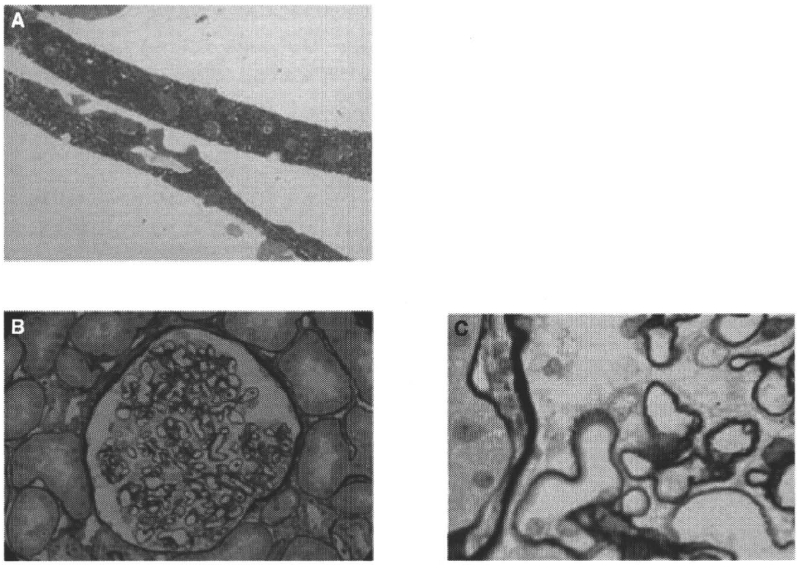

Fig. 2. Microscopic section of needle biopsy specimen obtained on postoperative day 23. (A) hematoxylin and eosin (HE) × 20, (B) Periodic acid-silver methenamine (PAM) × 400, (C) PAM × 1000. Spike formation, bubbling formation and partial thickening of the glomerular basement membrane (GBM) ware seen in PAM staining. Membranous glomerulonephritis was diagnosed. There was no evidence of acute rejection and tubulointerstitial injury.

transplantation, the graft function was stable and there was no evidence of adverse event such as rejection and infection. At 38 months after transplantation, protocol allograft needle biopsy for the recipient was performed and the specimen showed mild spike formation with partial thickening of the glomerular basement membrane (GBM) after staining with periodic acid-silver methenamine (PAM). Mild membranous glomerulonephritis was therefore diagnosed. There was no evidence of acute rejection, and focal segmental sclerotic change and tubulointerstitial injury, characteristic of chronic allograft change, were observed (Fig. 3).

Immunofluorescence staining study showed moderate deposition of IgG, C3d and weak deposition of IgA, IgM and C3c, which were observed on POD 23 in glomerulus, disappeared and only weak deposition of C3d was observed on POD 1184. Deposition of immune complexes disappeared from GBM during post-transplantation course (Fig. 4). Electron microscopy showed decreases in electron-dense deposits and electron-lucent washout lesions with thickening of the GBM. The finding was diagnosed as Stage IV membranous nephropathy, resulting from clearance of the immune complexes and histologic repair of the GBM (Fig. 5).

Discussion

Marginally appropriate kidney donors also are considered for renal transplantation in an attempt to extend the donor criteria. Two papers have described successful outcomes after cadaveric

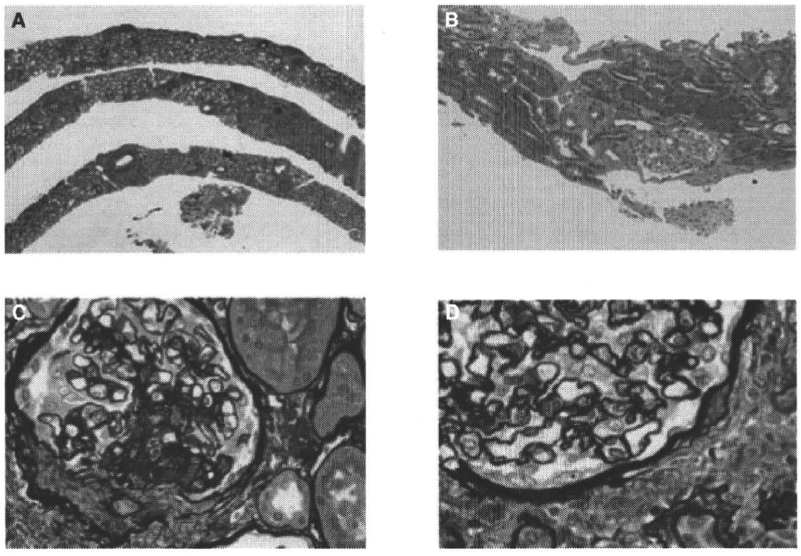

Fig. 3. Microscopic section of needle biopsy specimen obtained on postoperative day 1184. (A) Periodic acid-silver methenamine (PAM) × 20, (B) HE × 100, (C) PAM × 400, (D) PAM × 1000. Mild spike formation with partial thickening of the glomerular basement membrane (GBM) was seen in PAM staining. Mild membranous glomerulonephritis was therefore diagnosed. There was no evidence of acute rejection, and focal segmental sclerotic change and tubulointestinal injury, characteristic of chronic allograft change, were observed.

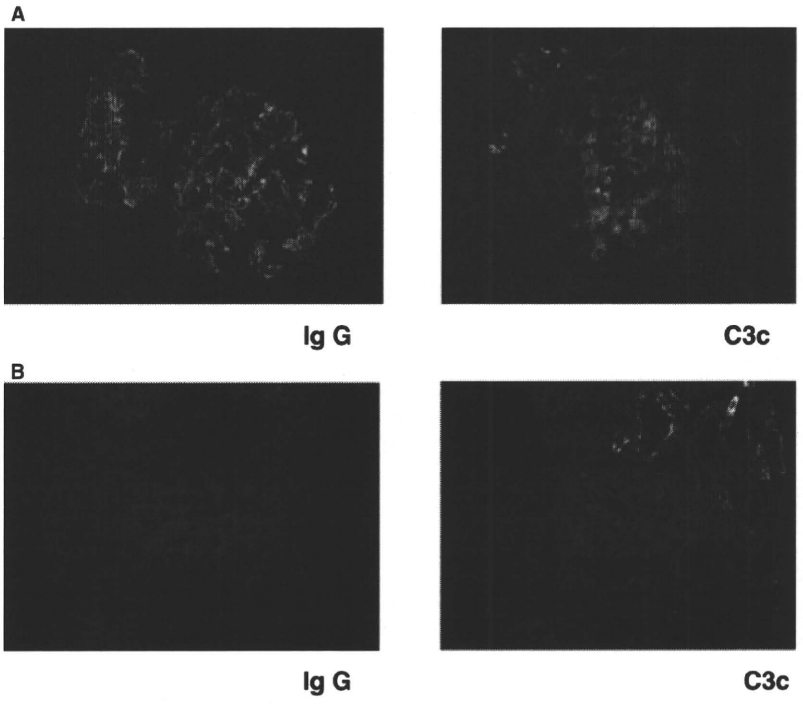

Fig. 4. Immunofluorescence staining section of needle biopsy specimen obtained on postoperative day 23 and 1184. (A) POD 23, (B) POD1184. Moderate deposition of IgG and weak deposition of C3c were observed on POD 23. Deposition of immune complexes disappeared from glomerular basement membrane (GBM) during post-transplantation course on POD 1184.

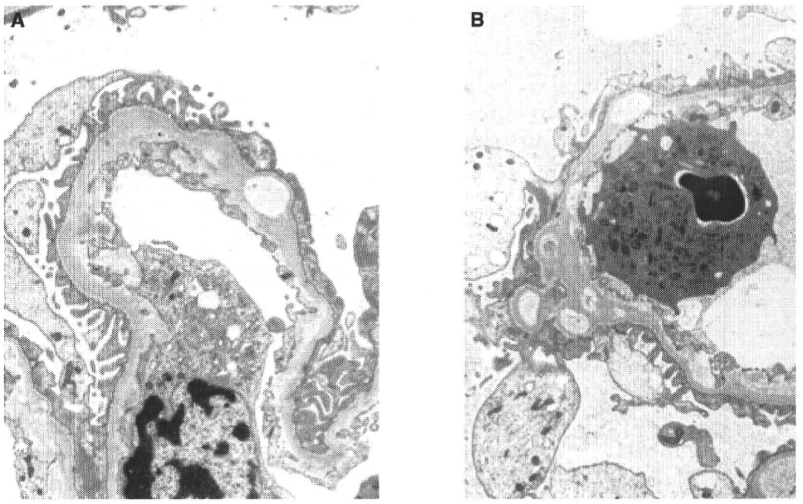

Fig. 5. Electron microscopic section of needle biopsy specimen obtained on postoperative day 1184. Electron microscopy showed decreases in electron-dense deposits and electron-lucent washout lesions with thickening of the glomerular basement membrane (GBM). This was diagnosed as Stage IV membranous nephropathy, resulting from clearance of the immune complexes and histologic repair of the GBM.

kidney transplantation from donors with pre-existing membranous nephropathy (1, 2). In these cases, from the finding of graft biopsies of the donor kidney performed at the time of transplantation, the donors were diagnosed to have pre-existing membranous nephropathy. These reports showed stable graft function after kidney transplantation for a couple of years, and histologic repair of the GBM was also observed. The report mentioned that membranous nephropathy itself, as well as IgA nephritis and diabetic nephropathy, resolves after kidney transplantation and deposition of IgG markedly decreases within a few months after transplantation, but that complete histologic restoration of the basement membrane needs at least a few years (2). Our histologic findings at 39 months after transplantation showed resolution and remission of membranous nephropathy. The natural history of the membranous nephropathy is variable; however, spontaneous remissions of proteinuria with stable renal function eventually occur in 40–50% of patients and the remainder slowly progress to end-stage renal disease or die of complications or of unrelated disease after 5–15 yr, whereas approximately one third of them progress towards renal insufficiency (3, 4). It

is difficult for us to find discriminately which case can enter remission of membranous nephropathy. It is said that outcome in non-nephrotic patients with membranous nephropathy invariably is good and 10-yr renal survival rate is reported approximating 100% (5). Other paper mentioned that the presence of focal segmental glomerulosclerosis (FSGS)-type glomerular lesions on membranous nephropathy is the prognostic factor, which portends a significantly worse outcome in terms of nephrotic syndrome and renal insufficiency (6). In our case, renal function of the father was stable for three yr, proteinuria was < 400 mg/d and there was no progressive change in histologic findings such as focal glomerulosclerosis (FGS)-type glomerular lesion from second needle biopsy. Then, we expected the favorable prognosis and stable residual kidney function after donation of the kidney. After obtaining adequate verbal and written informed consent, we decided kidney transplantation from the father with membranous nephropathy to his son. At that time of the transplantation, we did not have Amsterdam forum guidelines (7), which mention that proteinuria more than 300 mg/d is contraindication to donation. Karpinski et al. proposed slight relaxation of current rigid criteria. They defined that potentially acceptable proteinuria as 150–300 mg/dL (8). So we dared to qualify the father as marginally appropriate donor. Therefore, kidney transplantation from living donor with membranous nephropathy has never been reported in the literature; this might be the first case.

Here, we reported a favorable outcome of kidney transplantation from a donor with membranous nephropathy. For the present donor, donation of the graft did not affect his residual renal function. Pre-existing membranous nephropathy itself might show remission after transplantation and immunosuppression in the recipient. An attempt to extend the donor criteria for the family in this case would be an alternative choice for living-related transplantation. It was effective enough to achieve successful result; however, a report said prognosis for life and renal survival was worse in the older onset patients (> 60 yr) (9). It is also known that kidney donation results in small increases in urinary protein, but initial decrement in glomerular filtration rate (GFR) is not followed by accelerated losses over a subsequent span of 15 yr (10). Long-term careful observation for both the donor and recipient is required. Marginally appropriate donors could be considered to extend the donor criteria.

Conflict of interest

The authors have no conflict of interest to declare.

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Revised Equations for Estimated GFR From Serum Creatinine in Japan

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Background: Estimation of glomerular filtration rate (GFR) is limited by differences in creatinine generation among ethnicities. Our previously reported GFR-estimating equations for Japanese had limitations because all participants had a GFR less than 90 mL/min/1.73 m^2 and serum creatinine was assayed in different laboratories.

Study Design: Diagnostic test study using a prospective cross-sectional design. New equations were developed in 413 participants and validated in 350 participants. All samples were assayed in a central laboratory.

Setting & Participants: Hospitalized Japanese patients in 80 medical centers. Patients had not participated in the previous study.

Reference Test: Measured GFR (mGFR) computed from inulin clearance.

Index Test: Estimated GFR (eGFR) by using the modified isotope dilution mass spectrometry (IDMS)-traceable 4-variable Modification of Diet in Renal Disease (MDRD) Study equation using the previous Japanese Society of Nephrology Chronic Kidney Disease Initiative (JSN-CKDI) coefficient of 0.741 (equation 1), the previous JSN-CKDI equation (equation 2), and new equations derived in the development data set: modified MDRD Study using a new Japanese coefficient (equation 3), and a 3-variable Japanese equation (equation 4).

Measurements: Performance of equations was assessed by means of bias (eGFR − mGFR), accuracy (percentage of estimates within 15% or 30% of mGFR), root mean squared error, and correlation coefficient.

Results: In the development data set, the new Japanese coefficient was 0.808 (95% confidence interval, 0.728 to 0.829) for the IDMS–MDRD Study equation (equation 3), and the 3-variable Japanese equation (equation 4) was eGFR (mL/min/1.73 m^2) = 194 × Serum creatinine$^{-1.094}$ × Age$^{-0.287}$ × 0.739 (if female). In the validation data set, bias was −1.3 ± 19.4 versus −5.9 ± 19.0 mL/min/1.73 m^2 ($P = 0.002$), and accuracy within 30% of mGFR was 73% versus 72% ($P = 0.6$) for equation 3 versus equation 1 and −2.1 ± 19.0 versus −7.9 ± 18.7 mL/min/1.73 m^2 ($P < 0.001$) and 75% versus 73% ($P = 0.06$) for equation 4 versus equation 2 ($P = 0.06$), respectively.

Limitation: Most study participants had chronic kidney disease, and some may have had changing GFRs.

Conclusion: The new Japanese coefficient for the modified IDMS–MDRD Study equation and the new Japanese equation are more accurate for the Japanese population than the previously reported equations.
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INDEX WORDS: Glomerular filtration rate; Japanese; inulin clearance; serum creatinine.

Editorial, p. 932

Glomerular filtration rate (GFR) is the most accurate index for assessing overall kidney function and an important tool for making diagnostic decisions in clinical practice.[1] GFR may be measured by using the clearance of an exogenous marker; inulin is the gold standard, but the method is not applicable to daily practice because it is time consuming, labor intensive, and expensive. Kidney function usually is assessed from serum creatinine (SCr) concentration alone, but SCr is affected by creatinine generation, including muscle mass and dietary intake, in addition to GFR.[2] GFR can be estimated from SCr level by using equations that include age, sex, race, and serum urea nitrogen (SUN) and albumin levels, as surrogates for creatinine generation, and are more accurate than estimates based on SCr level alone.[1,3,4]

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A list of the investigators who helped develop the Japanese equation for estimated GFR appears at the end of the article.

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The Modification of Diet in Renal Disease (MDRD) Study equation[5] and Cockcroft-Gault (CG) equation[6] are most commonly used for GFR estimation worldwide. Recently, the 4-variable MDRD Study equation was reexpressed by Levey et al[7] for use with isotope dilution mass spectrometry (IDMS)-standardized SCr values (the IDMS–MDRD Study equation). Several studies have validated the MDRD Study equation in whites and blacks.[8-14] In studies of more than 5,500 participants, Stevens et al[15,16] reported that GFR estimates using the IDMS–MDRD Study equation were unbiased and accurate for interpretations of GFR less than 60 mL/min/1.73 m^2, but warned that estimates just less than 60 mL/min/1.73 m^2 must be interpreted with caution to prevent misclassification of chronic kidney disease. The equation is less accurate for Asians, with greater bias at estimated GFR (eGFR) less than 60 mL/min/1.73 m^2.[17-19] Accordingly, both Ma et al[17] and our investigators[18,19] modified the MDRD Study equation by using separate "correction coefficients" for Chinese and Japanese. In both studies, the new equations were more accurate than the MDRD Study equation, but the correction coefficients were considerably different, with a Chinese coefficient of 1.233[17] and Japanese coefficient of 0.741.[19]

The difference in correction coefficients between Japanese and Chinese has not been explained. In our previous study, there may have been nonuniformity of creatinine assays because study samples for SCr were assayed in multiple laboratories and during different periods. Furthermore, data from participants with GFR greater than 90 mL/min/1.73 m^2 were not used for deriving the equation in the study. To verify results of our previous study, a new project was launched by the Japanese Society of Nephrology (JSN) with cooperation of nephrologists nationwide. The new study was conducted in 763 individuals to measure GFR and SCr by using inulin clearance (Cin) and standardized assays. A new Japanese correction coefficient was derived, as were new 3- and 5-variable Japanese equations.

METHODS

Inclusion and Exclusion Criteria

Inclusion criteria were: (1) age 18 years and older; (2) relatively stable kidney function, assessed by using SCr level; and (3) patient's agreement to have urinary Cin measured using a continuous infusion.

Exclusion criteria were: (1) acute kidney injury, (2) apparent malignancy, (3) problems in micturition, (4) pregnancy, (5) inulin allergy, (6) amputation, and (7) individuals for whom the investigator judged that measuring Cin was inappropriate. Although some study participants were hospitalized for diagnosis of rapidly progressive or acute glomerulonephritis, renal biopsies and Cin measurements were performed after their conditions became relatively stable. We did not record data for day-to-day SCr level changes.

Study Population of the Data Set

The study recruited participants from 80 medical centers throughout Japan between December 2006 and July 2007. Participants included mostly nephrology inpatients. Hospitalization of 5 to 14 days for kidney biopsy or education about lifestyle change was commonly practiced in Japan. Data for Cin and SCr were collected from 878 participants, mostly those with chronic kidney disease and a small number of healthy kidney donors. A total of 115 participants were excluded for the following reasons: 36 lacked data for urine volume, 11 were 17 years and younger, 2 had high serum inulin concentrations, 4 had lack of data for inulin blank, 51 had high values for inulin blank, 9 had a low volume of voided urine (<10 mL), and 2 had extraordinarily high GFRs. The final study population included 763 participants. Data collected from December 1, 2006, to April 20, 2007 (n = 413), were used as the development data set, and those obtained from April 21, 2007, to July 31, 2007 (n = 350), were used as the validation data set. The institutional review board at all the study institutions approved anonymous use of data for the present study. All patients signed written informed consent.

Cin and Creatinine Renal Clearance

Cin and creatinine clearance (Ccr) were measured simultaneously in 757 participants. In 6 participants, only Cin was measured. The method for measuring renal Cin was described elsewhere.[18] Briefly, Cin and Ccr were calculated from serum and urine concentrations and urine flow rate. Inulin (1%) was administered by means of a continuous intravenous infusion for 2 hours under overnight fasting, but hydrated, conditions. During the inulin infusion, serum samples were collected 4 times at 0 (blank), 45, 75, and 105 minutes for creatinine and inulin, and urine samples were collected between 30 and 60, 60 and 90, and 90 and 120 minutes for inulin and creatinine after completely emptying the bladder at 30 minutes from the start of the inulin infusion. Inulin samples were assayed by means of an enzymatic method using a kit (Diacolor Inulin; Toyobo Co, Osaka, Japan). The mean value of 3 measurements was used for the Cin and Ccr study.

SCr Measurement

Serum samples were assayed for creatinine in a central laboratory (Central Laboratory; SRL Co, Hachioji, Japan) by means of the enzymatic creatinine assay method using an

Table 1. Participant Characteristics

	Development Data Set	Validation Data Set
No. of participants (men/women)	413 (262/151)	350 (203/147)
Age (y)	51.4 ± 16.5 (18-88)	53.9 ± 17.5 (19-91)
Serum creatinine (mg/dL)	1.62 ± 1.59 (0.41-10.75)	1.57 ± 1.38 (0.34-10.28)
Albumin (g/dL)	3.80 ± 0.64 (1.70-5.20)	3.91 ± 0.56 (1.70-5.10)
Serum urea nitrogen (mg/dL)	22.0 ± 15.5 (5.0-107.3)	22.4 ± 14.2 (6.1-81.2)
GFR (mL/min/1.73 m^2)	59.1 ± 35.4 (3.0-199.3)	57.2 ± 34.7 (2.6-228.7)
0-29	108 (26%)	93 (27%)
30-59	115 (28%)	113 (32%)
60-89	102 (25%)	73 (21%)
>90	88 (21%)	71 (20%)
Creatinine clearance (mL/min/1.73 m^2)	81.2 ± 47.2 (3.1-274.1)	79.7 ± 44.9 (5.3-268.5)
Height (cm)	163.3 ± 8.8	161.6 ± 9.5
Weight (kg)	61.0 ± 12.9	60.4 ± 12.7
Body surface area (m^2)	1.65 ± 0.19	1.63 ± 0.19
Diagnosis		
Chronic glomerulonephritis	219	173
Acute glomerulonephritis	4	3
RPGN	10	4
Interstitial nephritis	6	3
Diabetes mellitus	46	44
Polycystic kidney disease	2	0
Nephrosclerosis	25	30
Lupus	10	3
Kidney donor	1	10
Kidney recipient	9	2
Hereditary nephritis	3	1
Hypoplasia	3	0
Unilateral nephrectomy	6	3
Miscellaneous	69	74

Note: Conversion factors for units: serum creatinine in mg/dL to μmol/L, ×88.4; urinary albumin in g/dL to g/L, ×10; serum urea nitrogen in mg/dL to mmol/L, ×0.357; GFR in mL/min/1.73 m^2 to mL/s/1.73 m^2, ×0.01667.

Abbreviations: GFR, glomerular filtration rate; RPGN, .

Hitachi creatinine auto-analyzer, model 7170 (Hitachi, Tokyo, Japan) and enzyme solution (Preauto-SCrE-N; Daiichi Pure Chemicals Co, Tokyo, Japan). SCr values obtained in the central laboratory were compared with those of the Cleveland Clinic (Cleveland, OH) by using a calibration panel of 40 samples, provided by Dr Frederick Van Lente, Cleveland Clinic.

Comparison of Measured Versus Expected Creatinine Excretion

Creatinine excretion was measured in 90-minute urine samples obtained during Cin measurements and predicted based on previously published formulas.

Creatinine excretion rates were based on published equations for Japenese[20] and whites[21] and are given in the notes to Table 2.

Development of the Correction Coefficient for the IDMS–MDRD Study Equation

The new Japanese coefficient to modify the IDMS–MDRD Study equation[7] for Japanese was calculated from the development data set of 413 participants. The coefficient was derived by minimizing the root mean squared error (RMSE) of the estimate calculated as the square root of (sum of squared errors of the estimate/[N]).

Development of the New Equations for Japanese

The new 3- and 5-variable Japanese equations were derived in the development data set by using a multiple linear regression model and the variables age, sex, and SCr, SUN, and serum albumin levels in relation to measured GFR (mGFR). All variables were log transformed.

Development of the Correction Coefficient for the CG Equation

The CG equation was modified by a Japanese CG coefficient that was calculated in the development data set. The correction coefficient was determined by minimizing the RMSEs of the estimate.

Validation of Equations

GFR was estimated by using all equations and compared with mGFR in the development and validation data

Table 2. Participant Characteristics

	Men (n = 462)	Women (n = 296)
Age (y)	53.7 ± 17.1	50.8 ± 16.8
Height (cm)	167.4 ± 7.1	154.9 ± 6.3
Weight (kg)	65.7 ± 11.9	52.7 ± 9.5
Body surface area (m^2)	1.74 ± 0.16	1.49 ± 0.13
Body mass index (kg/m^2)	23.4 ± 3.7	22.0 ± 3.8
Measured creatinine excretion (mg/kg/d)	20.2 ± 0.8	16.7 ± 4.6
Estimated creatinine excretion (for Japanese)	18.4 ± 1.2	14.3 ± 1.0
Estimated creatinine excretion (for whites)	19.0 ± 2.9	16.1 ± 1.9

Note: Data expressed as mean ± SD. Measured creatinine excretion was obtained during the measurement of inulin clearance. Expected creatinine excretion for Japanese was calculated by using the following equations: Creatinine excretion rate (mg/kg/d) = 22.1 − 0.068 × Age (in men) or 17.2 − 0.057 × Age (in women). Estimated creatinine excretion for whites was calculated by the following equations: Creatinine excretion rate (mg/kg/d) = 28.2 − 0.172 × Age (in men) or 21.9 − 0.115 × Age (in women).

sets. We compared all equations, but specifically focused on the comparison in the validation data set of the IDMS–MDRD Study equations modified by the previously published JSN Chronic Kidney Disease Initiative (JSN-CKDI) coefficient and the new Japanese coefficient, as well as the JSN-CKDI equation and new Japanese equations. Metrics for comparison were RMSE, bias, accuracy, and r^2. The RMSE of GFR estimated by using the equation was calculated as the square root of (sum of squared errors of the estimate/[N]). Bias of the equations was expressed as the mean difference between eGFR and mGFR (eGFR − mGFR). Accuracy was expressed as percentage of participants with eGFR less than 15% and 30% from mGFR. RMSE and correlation coefficients were computed on the raw scale. Data sets were combined for correlation between eGFR and mGFR. Intercepts and slopes were evaluated in a linear regression model.

Statistical Analysis

Data are expressed as mean ± SD. Measured versus predicted creatinine excretion was compared by using Student *t*-test. Creatinine values were calibrated by using the calibration panel and evaluated by means of linear regression. Differences in accuracy of eGFR were evaluated between equations by means of χ^2 tests. Differences in bias of eGFR were evaluated between equations by using Student *t*-test. A difference with *P* less than 0.05 was considered statistically significant. Statview, version 4.02 (SAS Institute, Cary, NC), and JMP, version 6.02 (SAS Institute), were used for statistical analysis and calculation of correction factors and confidence intervals (CIs).

RESULTS

Patient Characteristics in the Development and Validation Populations

Characteristics of the development population (n = 413) and validation population (n = 350) are listed in Table 1. Distributions of participant numbers by cause of kidney disease and mean age, SCr level, albumin level, SUN level, height, weight, and body surface area were similar between the 2 populations. Mean Cin was also similar between them at 59.1 ± 35.4 mL/min/1.73 m^2 in the development population and 57.2 ± 34.7 mL/min/1.73 m^2 in the validation population. Proportions of participants with mGFR less than 60 mL/min/1.73 m^2 were 54% in the development population and 60% in the validation population.

Body Size and Creatinine Excretion

Body size and creatinine excretion in the combined development and validation data sets are listed separately for men and women in Table 2. The creatinine excretion rate was greater in men than women (20.2 versus 16.7 mg/kg/d). Measured values were significantly, but not substantially, greater than expected values for both Japanese ($P < 0.001$) and whites ($P < 0.001$).

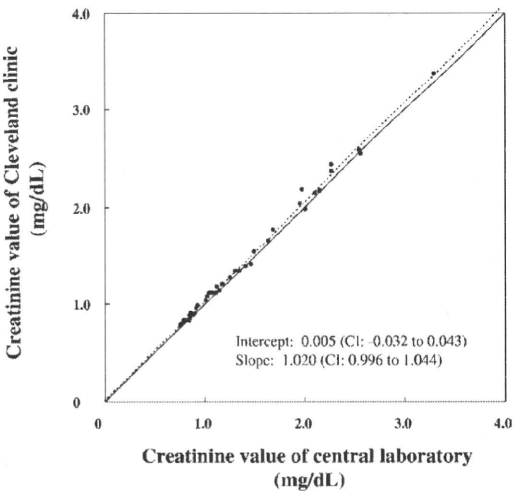

Figure 1. Correlation between creatinine values of the Cleveland Clinic and a central laboratory. Y = X (solid line), and regression line (dotted line). Abbreviation: CI, confidence interval.

Table 3. Intercepts and Coefficients for GFR-Estimating Equations in the Development Population

Equation	Exponent-Transformed Intercept (95% CI)	Coefficient of Continuous Parameters (95% CI)				Exponent-Transformed Coefficient Of Dichotomous Variables (95% CI)
		SCr	Age	SUN	Alb	
IDMS–MDRD Study	175	−1.154	−0.203	–	–	0.742 if female 1.01 if white 1.212 if black
1	175	−1.154	−0.203	–	–	0.742 if female 0.741 if Japanese
2	171	−1.004	−0.287	–	–	0.782 if female
3	175	−1.154	−0.203	–	–	0.742 if female 0.808 if Japanese (0.728 to 0.829)
4	194 (143 to 262)	−1.094 (−1.139 to −1.048)	−0.287 (−0.366 to −0.208)	–	–	0.739 if female (0.695 to 0.786)
5	142 (93 to 217)	−0.923 (−0.997 to −0.849)	−0.185 (−0.263 to −0.108)	−0.233 (−0.319 to −0.148)	0.414 (0.272 to 0.557)	0.772 if female (0.728 to 0.818)
6	–	–	–	–	–	0.85 if female (0.769 to 0.810)

Equation 1: IDMS–MDRD Study equation with previously reported JSN-CKDI coefficient: eGFR = $0.741 \times 175 \times SCr^{-1.154} \times Age^{-0.203} \times 0.742$ (if female).

Equation 2: Previously reported JSN-CKDI equation: eGFR = $171 \times SCr^{-1.004} \times Age^{-0.287} \times 0.782$ (if female).

Equation 3: IDMS–MDRD Study equation with new Japanese coefficient: eGFR = $0.808 \times 175 \times SCr^{-1.154} \times Age^{-0.203} \times 0.742$ (if female).

Equation 4: New 3-variable Japanese equation: eGFR = $194 \times SCr^{-1.094} \times Age^{-0.287} \times 0.739$ (if female).

Equation 5: New 5-variable Japanese equation: eGFR = $142 \times SCr^{-0.923} \times Age^{-0.185} \times Alb^{0.414} \times SUN^{-0.233} \times 0.772$ (if female).

Equation 6: $0.789 \times$ CG equation: eGFR = $0.789 \times (140 - Age) \times BW/SCr/72 \times 1.73/BSA \times 0.85$ (if female).

Abbreviations: Alb, albumin; BSA, body surface area; BW, body weight; CG, Cockcroft-Gault; CI, confidence interval; CKDI, Chronic Kidney Disease Initiative; eGFR, estimated glomerular filtration rate; IDMS, isotope dilution mass spectrometry; JSN, Japanese Society of Nephrology; MDRD, Modification of Diet in Renal Disease; SCr, serum creatinine; SUN, serum urea nitrogen.

Calibration of Creatinine Assays

Creatinine values for the calibration panel assigned in our laboratory were compared with values assigned by Cleveland Clinic Laboratory (Fig 1). Mean SCr level was 1.415 ± 0.100 (SEM) versus 1.449 ± 0.102 mg/dL. Creatinine values correlated highly with values assigned by the Cleveland Clinic as judged by the intercept of 0.005 (95% CI, −0.0032 to 0.043), close to zero, and the slope of 1.020 (95% CI, 0.996 to 1.044), close to 1.0. Because there was no significant systemic bias, creatinine values were not adjusted in the present study.

Cin and Ccr

Cin and Ccr were measured simultaneously in 757 patients. Mean serum inulin concentrations were 18.4 ± 4.9, 18.3 ± 5.1, and 19.3 ± 5.9 mg/dL at 45, 75, and 105 minutes, respectively. The median coefficient of variation for Cin was 10.9% (95% CI, 5.8 to 20.4) during the 90-minute renal Cin test. The median coefficient of variation for Ccr was 13.3%. Cin and Ccr significantly correlated ($r = 0.889$; $r^2 = 0.790$). The slope was 0.698 (95% CI, 0.672 to 0.724) and the intercept was 2.339 (95% CI, 0.143 to 4.622). Ccr was significantly greater than Cin, and the correction coefficient for the bias was determined to be 0.715 (95% CI, 0.703 to 0.726).

eGFR Equations

All equations are listed in the notes to Table 3.

The new Japanese correction coefficient calculated for modification of the IDMS–MDRD Study equation was 0.808 (95% CI, 0.728 to 0.829; equation 3) in the development population, whereas the previously reported coefficient was 0.741 (equation 1), as listed in Table 3.

Using the development data set, we derived a new 3-variable Japanese equation (equation 4) and a new 5-variable Japanese equation (equation 5; Table 3).

Table 4. Performance of GFR-Estimating Equations in the Development Population

Equation	RMSE (mL/min/1.73 m^2)	Accuracy	
		Within 15% of mGFR (95% CI)	Within 30% of mGFR (95% CI)
IDMS–MDRD Study equation	23.6	36 (32-41)	59 (55-64)
Equation 1	18.4	38 (34-43)	73 (69-77)
Equation 2	19.2	39 (35-44)	73 (68-77)
Equation 3	17.6	44 (39-48)	77 (72-81)
Equation 4	17.3	44 (39-48)	78 (74-82)
Equation 5	16.4	52 (47-57)	83 (79-86)
Equation 6	17.7	44 (39-49)	76 (72-80)

P

15% Accuracy Level							30% Accuracy Level						
	IDMS	Eq 1	Eq 2	Eq 3	Eq 4	Eq 5		IDMS	Eq 1	Eq 2	Eq 3	Eq 4	Eq 5
IDMS							IDMS						
Eq 1	0.6						Eq 1	<0.001					
Eq 2	0.4	0.7					Eq 2	<0.001	0.9				
Eq 3	0.03	0.1	0.2				Eq 3	<0.001	0.2	0.2			
Eq 4	0.03	0.1	0.2	0.9			Eq 4	<0.001	0.09	0.06	0.6		
Eq 5	<0.001	<0.001	<0.001	0.01	0.01		Eq 5	<0.001	<0.001	<0.001	0.03	0.1	
Eq 6	0.03	0.1	0.2	0.9	0.9	0.02	Eq 6	<0.001	0.3	0.3	0.8	0.5	0.02

Note: Accuracy given as percentage of participants whose estimated GFR was within 15% or 30% of measured GFR.

Abbreviations: CI, confidence interval; Eq, equation; GFR, glomerular filtration rate; IDMS, isotope dilution mass spectrometry; MDRD, Modification of Diet in Renal Disease; RMSE, root mean squared error.

The CG equation was modified with a correction coefficient. The Japanese coefficient of 0.789 (95% CI, 0.769 to 0.810) was obtained from the development data set and is provided as equation 6 in Table 3.

Comparison of Performance of the Equations

Performance in GFR estimation was evaluated among equations by using the development and validation data sets based on RMSE, bias, and accuracy of eGFR in reference to mGFR.

Accuracy in the Development Data Set

Performance of each derived equation was evaluated by using the development data set, as listed in Table 4. Bias is not compared because it is expected to be approximately zero for equations developed in the development data set. There were no significant differences in accuracy within 15% or 30% between equations 3 and 1 or between equations 4 and 2, reflecting no significant different in precision.

Bias and Accuracy in the Validation Data Set

Performance of each derived equation was evaluated by using the validation data set, as listed in Table 5. Bias was significantly less in equation 3 than in equation 1 ($P = 0.002$) and in equation 4 than in equation 2 ($P < 0.001$). Equation 3 provided GFR with significantly better accuracy within 15% than equation 1 ($P = 0.02$), but no significant difference in accuracy within 30% deviation ($P = 0.6$) between the 2 equations. There was a trend toward improved accuracy within 15% and 30% between equations 4 and 2 ($P = 0.06$). Equation 5 performed similarly to equation 4.

Correlation Between eGFR and mGFR

The correlation between eGFR and mGFR was evaluated in the combined population as shown for each equation in Fig 2. Intercepts and slopes for equations are listed in Table 6.

DISCUSSION

We previously reported that eGFR calculated using either the IDMS–MDRD Study equation modified by using the JSN–CKDI coefficient (0.741; equation 1) or the JSN–CKDI equation (equation 2) was more accurate than the unmodified MDRD Study equation in Japanese individu-

Table 5. Performance of GFR-Estimating Equations in the Validation Population

Equations	RMSE (mL/min/1.73 m^2)	Bias (mL/min/1.73 m^2)	Accuracy	
			Within 15% of mGFR (95% CI)	Within 30% of mGFR (95% CI)
IDMS–MDRD Study equation	25.2	12.0 ± 22.2	39 (34-45)	59 (54-64)
Equation 1	19.9	−5.9 ± 19.0	34 (29-39)	72 (67-76)
Equation 2	20.3	−7.9 ± 18.7	36 (31-41)	73 (69-78)
Equation 3	19.4	−1.3 ± 19.4*	43 (38-48)	73 (59-78)
Equation 4	19.1	−2.1 ± 19.0†	43 (38-48)	75 (70-79)
Equation 5	17.7	−1.2 ± 17.6	49 (44-54)	79 (75-83)
Equation 6	19.4	−1.7 ± 19.6	45 (40-50)	75 (70-79)

P

15% Accuracy Level							30% Accuracy Level						
	IDMS	Eq 1	Eq 2	Eq 3	Eq 4	Eq 5		IDMS	Eq 1	Eq 2	Eq 3	Eq 4	Eq 5
IDMS							IDMS						
Eq 1	0.1						Eq 1	<0.001					
Eq 2	0.4	0.5					Eq 2	<0.001	0.6				
Eq 3	0.4	0.02	0.08				Eq 3	<0.001	0.6	0.9			
Eq 4	0.3	0.01	0.06	0.9			Eq 4	<0.001	0.3	0.06	0.6		
Eq 5	0.01	<0.001	<0.001	0.1	0.1		Eq 5	<0.001	0.02	0.08	0.08	0.2	
Eq 6	0.1	0.003	0.02	0.5	0.6	0.3	Eq 6	<0.001	0.3	0.7	0.7	0.9	0.2

Note: Accuracy given as percentage of participants whose estimated GFR was within 15% or 30% of measured GFR.

Abbreviations: CI, confidence interval; Eq, equation; GFR, glomerular filtration rate; IDMS, isotope dilution mass spectrometry; MDRD, Modification of Diet in Renal Disease; RMSE, root mean squared error.

als.[19] The present study verifies our previous results, and accuracy of GFR estimation is improved further by means of newly derived equations, the modified IDMS–MDRD Study equation with the new Japanese coefficient (0.808; 95% CI, 0.728 to 0.829; equation 3) and the new 3-variable equation (equation 4). Bias was significantly reduced in equation 3 and 4 from that in equations 1 and 2 in the validation population. We also developed a 5-variable equation (equation 5). The new Japanese equations and the new Japanese coefficient for the IDMS–MDRD Study equation provided more reliable eGFRs in Japanese individuals. The present study had a larger number of participants than the previous study, and all samples were assayed for inulin and creatinine in a central laboratory.

In both the previous[18,19] and present studies, the original IDMS–MDRD Study equation overestimated GFR in comparison to mGFR by using Cin in Japanese patients with CKD (Fig 2). The correction coefficient less than 1.0 indicates lower SCr levels in Japanese than in whites in the MDRD Study for equivalent levels of GFR.

SCr level is affected by 3 major factors: level of kidney function, skeletal muscle mass,[2] and amount of protein intake.[22] In the steady state, creatinine excretion is a measure of creatinine generation from muscle or protein intake. Our data suggest that creatinine excretion was slightly greater than expected per kilogram of body weight, but less than observed in the MDRD Study because of lower body weight. Mean creatinine excretion values were 20.2 and 16.7 mg/kg/d in men and women in our study compared with 19.2 and 15.8 mg/kg/d in the MDRD Study, respectively.[23] Mean body weight was 60 kg in our study compared with 79 kg in the MDRD Study. Mean body mass index (BMI) was 23 kg/m^2 in the present study and 27 kg/m^2 in the MDRD Study.[23]

Differences in creatinine excretion, body weight, and BMI between participants in our study and the MDRD Study are consistent with studies that have shown a mean skeletal muscle mass assessed by means of magnetic resonance imaging data significantly less in Japanese (men, 24.8 ± 3.5 kg; women, 14.7 ± 2.3 kg)[24] than in North Americans (men, 33.0 ± 5.3 kg; women,

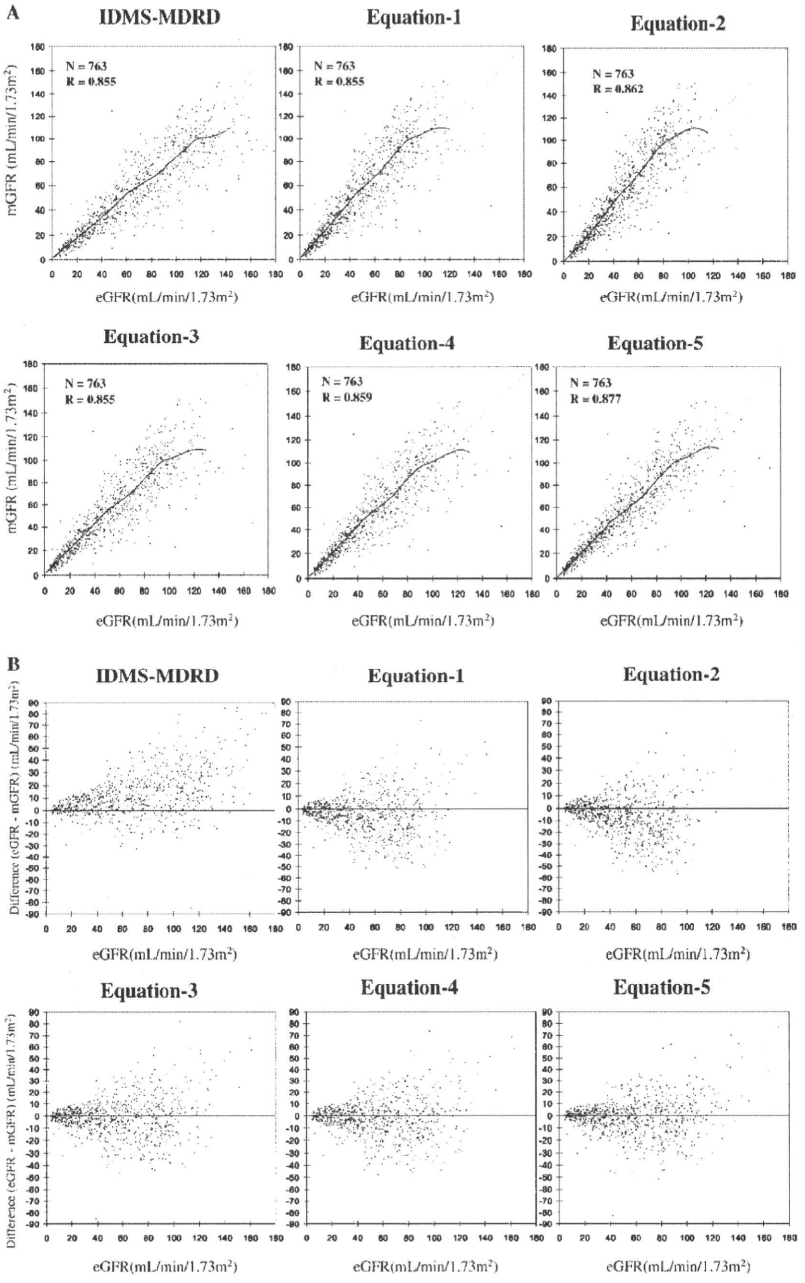

Figure 2. Correlation between estimated glomerular filtration rate (eGFR) using each equation and measured GFR (mGFR) in the combined population. (A) mGFR versus eGFR and (B) eGFR minus mGFR versus eGFR. Smoothed lines show the fit of the data. Abbreviations: IDMS-MDRD, isotope dilution mass spectrometry Modification of Diet in Renal Disease.

21.0 ± 3.8 kg; study population included whites [67%], blacks [17%], Asians [8%], and Hispanics [7%]).[25]

These differences in muscle mass are reflected as differences in SCr levels between Japanese and North American populations. Muscle mass significantly decreases with aging in Japanese men,[24] but does not significantly change in North American men.[25] SCr values were lower and remained constant until age 70 years in Japanese for both men and women,[26] whereas values were greater and increased after age 40 years in whites and blacks[27]: 0.831 mg/dL at age 20 to 39 years, 0.822 mg/dL at age 40 to 59 years, and 0.868 mg/dL at age 60 to 79 years in Japanese men versus 0.865 mg/dL at age 20 to 39 years, 0.883

Table 6. Intercepts and Slopes for GFR-Estimating Equations

Equations	Intercept (95% CI)	Slope (95% CI)	*R2*
IDMS–MDRD Study equation	6.1 (3.5 to 8.6)	0.740 (0.708 to 0.771)	0.731
Equation 1	6.1 (3.5 to 8.6)	0.998 (0.955 to 1.041)	0.731
Equation 2	1.8 (−0.9 to 4.5)	1.123 (1.076 to 1.170)	0.743
Equation 3	6.1 (3.5 to 8.6)	0.915 (0.876 to 0.955)	0.731
Equation 4	5.1 (2.5 to 7.7)	0.943 (0.903 to 0.983)	0.738
Equation 5	4.5 (2.1 to 6.9)	0.944 (0.907 to 0.980)	0.770
Equation 6	6.7 (4.1 to 9.3)	0.908 (0.869 to 0.948)	0.730

Abbreviations: CI, confidence interval; GFR, glomerular filtration rate; IDMS, isotope dilution mass spectrometry; MDRD, Modification of Diet in Renal Disease.

mg/dL at age 40 to 59 years, and 0.998 mg/dL at 60 years and older as calibrated to IDMS-traceable creatinine in white men. Mean noncalibrated SCr values in the Third National Health and Nutrition Examination Survey (NHANES III) were 1.14 mg/dL at age 20 to 39 years, 1.16 mg/dL at age 40 to 59 years, and 1.28 mg/dL at 60 years and older[28] in white men (calibrated SCr = [SCr − 0.23] × 0.95).[29,30] After age 50 years, urinary creatinine excretion decreases as body weight decreases in Japanese men. However, in whites body weight is not as good a marker to estimate urinary creatinine excretion as muscle mass. Lean body mass, not body weight, correlates with urinary creatinine excretion and muscle mass in whites.[31]

Differences in muscle mass are parallel to differences in obesity. The obese population (BMI > 25 kg/m^2) increases with age in white Americans: 61% at age 20 to 39 years, 70% at age 40 to 59 years, and 74% at 60 years and older.[32] However, obesity decreases after age 50 years in Japanese men: BMI greater than 25 kg/m^2 is 20% at age 20 to 29 years, 28.9% at age 30 to 39 years, 32.7% at age 40 to 49 years, 30.8% at age 50 to 59 years, 29.7% at age 60 to 69 years, and 26% at 70 years and older (Japanese Ministry of Health, Labor, and Welfare). It was reported that an increase of 5 kg/m^2 in BMI resulted in increase of 1.1% in SCr level.[33] With aging, skeletal muscle mass and protein intake decrease at a greater rate in Japanese than in whites, whereas the prevalence of obesity increases in whites, but not Japanese.

Altogether, these data are consistent with a correction coefficient less than 1.0 for modification of the MDRD Study equation for Japanese. In contrast, the correction coefficient for Chinese is 1.233. Possible explanations for the large difference in correction coefficients between Japanese and Chinese studies may be differences in muscle mass in the study populations, creatinine assays, or GFR measurement methods. Additional study is required to understand the difference in GFR-estimating equations between Chinese and Japanese.

In the present study, no significant systemic bias was observed in SCr values used for the development of new equations by the panel of the Cleveland Clinic Laboratory. SCr values assayed using the enzymatic method were more accurate and had greater precision than other methods.[2] Although 95% of laboratories in Japan have switched to the enzymatic method from the Jaffé method, creatinine values must be standardized for use of the new equations.

Limitations of the present study are as follows. (1) The new Japanese GFR-estimating equations may not be applicable to the healthy population because they were derived mostly from patients with chronic kidney disease. Rule et al[10] also suggested that the MDRD Study equation might systematically underestimate GFR in the normal healthy population. (2) Equations were derived from data for inpatients and outpatients. Some participants were hospitalized for renal biopsy as is customary practice in Japan, although some inpatient participants may have had clinical conditions related to creatinine metabolism.[14] (3) About 15% of patients had diabetes, and GFR was estimated accurately for patients with diabetes with our new equations. However, GFRs calculated by using the MDRD Study equation and CG equations were underestimated in patients with diabetes over the range of eGFR of 90 mL/min/1.73 m^2 or greater.[34] We must further