12）メタボリックシンドロームとCKD

Metabolic syndrome and CKD

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Key words | 肥満，蛋白尿，糸球体濾過量，糖尿病，高血圧

はじめに

肥満，メタボリックシンドロームはCKDと密接な関連があり，新たな世界的に対策が必要な非感染性の慢性病である。米国の成人ではBMI 30 kg/m^{2}以上の肥満者の頻度が11.5%（1990年）から34.1%（2004年）と3倍増加し，透析導入患者ではさらに高頻度である（図1）。わが国では透析患者のBMIの平均値は22 kg/m^{2}前後であるが，肥満者も少しずつ増加している[1)]。

日本透析医学会の調査によると，年度末透析患者数は依然として増加し続けており，効果的な対策が急務である。メタボリックシンドロームは生活習慣の改善によって修正可能であり，医療費の節減につながると期待されている。

わが国の現状

1．透析患者の増加

2008年度のわが国の年度末透析患者数は人口100万人対で2,200人を超え，国民450人に1人の割合となっている。透析導入の原因疾患は首位が慢性腎炎から糖尿病（DM）に移行し，前者が減少しつつあるのに対し，後者は直線的に増加し続けている。肥満，メタボリックシンドロームの一般人口での有病率が特に男性で増加している。また，発症の低年齢化が進行している。

2型DMによる透析導入の増加には，DM腎症の進展以外に高血圧，腎間質障害および肥満腎症の関与も否定できない。最近，増加している原因不明とされる透析患者にも一役かっている可能性が考えられる。DM腎症に限らず，かなり進行して腎臓内科を受診し1年以内に透析導入となる，いわゆる手遅れ（late referral）症例も少なくない。CKDは自覚症状に乏しく，検尿異常を健診などで指摘されても専門医を受診せず適切な治療を受けていないことが考えられる。

CKDステージ1～3では適切な生活習慣の是正，薬物療法によりさらなる悪化の予防が可能である。日本腎臓学会では蛋白尿2+以上，血尿・蛋白尿ともに1+以上，またはGFR<50 mL/min/1.73 m^{2}の症例は腎臓専門医に紹介するよう勧めている。

2．透析予備軍の増加

日本腎臓学会が健診受診者をもとに計算したCKD人口（eGFR<60 mL/min/1.73 m^2）は，20歳以上で全人口の約10.6%（約1,130万人），eGFR 50未満は2.9%（約310万人）で，ステージ1～2（蛋白尿陽性者）を含めるとCKD患者は約1,330万人と推測される。2008年度には約36,000人の透析導入があり，少なくともその数倍の予備軍の存在が推測される。5年後に透析へ移行する血清クレアチニン値2 mg/dL以上の頻度は，健診受診者の約0.2%前後（千人に2人程度）であり，メタボリックシンドロームの頻度は腎機能低下と相関する（沖縄県総合保健協会資料）（図2）。

透析導入率は末期腎不全（CKDステージ5D）

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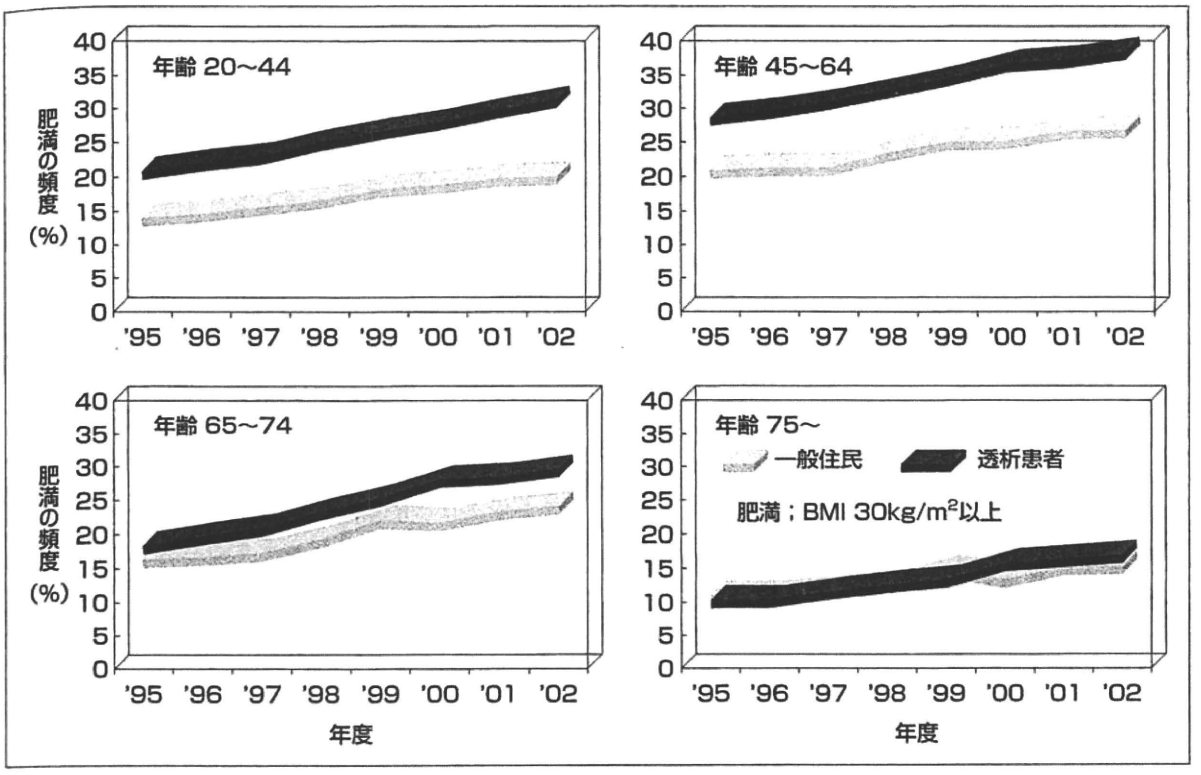

図1　米国における肥満の頻度の推移（一般住民対透析導入患者）[1)]

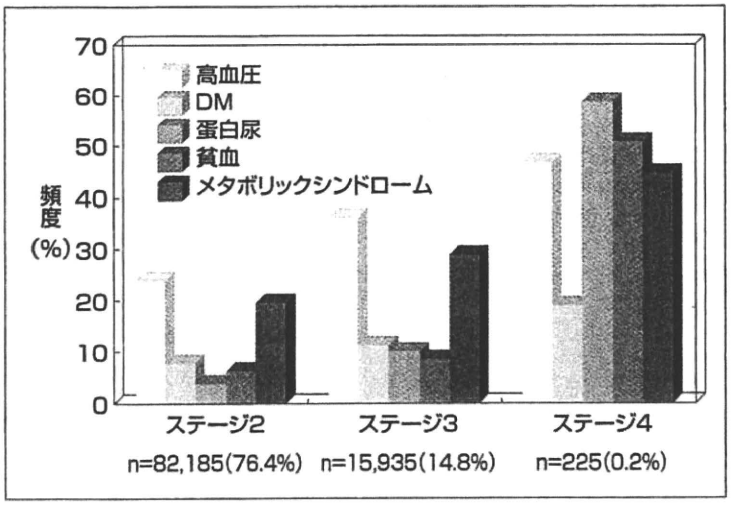

図2　住民健診受診者における CKD ステージ別の疾患頻度（沖縄県総合保健協会資料）

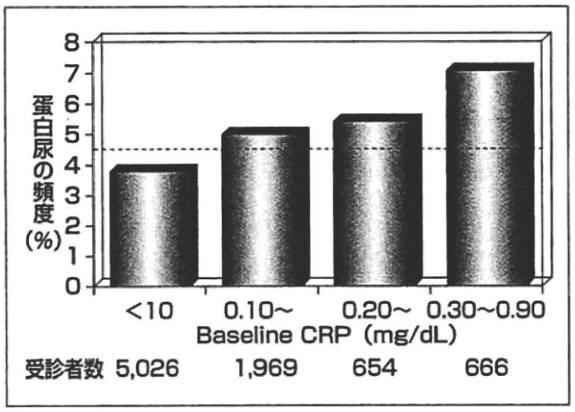

図3 健診時のCRPと蛋白尿発症率[3)]

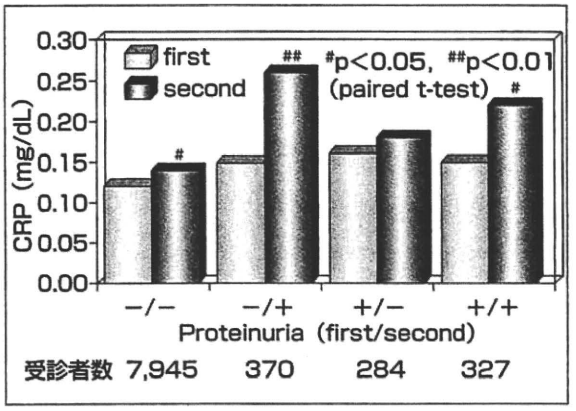

図4 健診受診時およびフォローアップ時のCRPと蛋白尿[3)]

の発症率よりも透析療法への受け入れ率（acceptance rate）である。したがって，今後しばらくは高齢者人口の増加につれて，導入患者数は増加すると予想される。

CKDは当初，検尿，画像，組織学的異常またはModification of Diet in Renal Disease（MDRD）研究のGFR推算値（eGFR）の低下（60 mL/min/1.73 m^2未満）が3カ月以上持続すればCKDと診断される。しかし，日本人ではステージ3（eGFR 30～59）にあたる人口が多く，臨床的意義はまだ定まっていない。高齢者では病気（disease）か障害（damage）かというCKDの定義そのものに関する議論が続いている。いずれにしても，高齢者では加齢によるGFRの低下があり手術，検査，薬物投与を受ける機会も増加するので，AKIからCKDへ移行する例が増加すると考えられる。

肥満，メタボリックシンドロームによるCKD発症機序

最近，肥満腎症という概念が提唱され腎生検に占める割合が増えている。減量により改善する可能性があり，比較的予後は良好とされている。しかし高血圧，DMの合併例では腎機能の低下が懸念される。

肥満による腎障害の発症には種々の機序が考えられる。なかでも腎血行動態の異常，糸球体の過剰濾過が注目される。肥満を伴う症例での正確なGFRの推定は困難であるが，初期には過剰濾過（GFRの機能的上昇）があり，持続すると糸球体硬化を生じ急速にGFRが低下する。

肥満に伴い炎症のマーカー（CRP）や酸化ストレス（F2-isoprotein）が増加し，CKD発症との関連が考えられる[2)]。われわれは，住民健診受診者においてベースラインのCRP値と蛋白尿発症の関連を検討し，CRPの正常範囲から値が上昇するにつれて蛋白尿発症率が増加することを報告した[3)]（図3，4）。

BMIとCKDの関連をみた18編の論文のメタ解析によると，BMIが1.0 kg/m^2上昇するごとにCKDが6%増加する。わが国の報告でもCKDの頻度および発症率は，メタボリックシンドロームの構成因子数が増加するにつれ高くなる。メタボリックシンドロームを有する群は5年間で約2倍のCKD発症危険度が認められる。

沖縄県の健診受診者の成績では，男性においてBMIと透析導入率に有意な相関が認められる。女性においてはBMIと透析導入率に有意な相関を認めない理由については不明である。1983年当時は，女性に肥満者が少なかったことなどが関連している可能性もある。

Ryuらは9,000名の韓国人男性の平均4.1年の観察により，ベースラインのBMIとCKD発症に有意な関連を認めなかった[4)]。しかし，体重が0.75 kg/年以上増加した群ではCKD発症のリスクが

表　CKDのリスクファクター[5)]

1．ESRDの家族歴：白人6.4%，黒人14%
2．糖尿病患者，糖尿病の家族歴
3．人種：Native American
4．CKDの家族歴
5．高血圧：SBP＞PP＞DBP
6．低出生体重児
7．肥満，メタボリックシンドローム
8．高尿酸血症
9．感染症：C型肝炎，歯槽膿漏

4.21～4.32であり，体重変化とCKD発症のリスクにはU字現象が認められた。一番リスクが低い群は，体重変化が0.25 kg/年未満の群であった。体重変化とCKD発症のリスクは高血圧，糖尿病の発症とは独立して認められ，ベースラインの体重が低い群においても体重増加とCKD発症には相関が認められた。

対　策

透析患者は南に多く北が少ない。その要因については明らかでないが，気候および生活習慣の違いも一因と考えられる。肥満，メタボリックシンドロームはCKDの存在を疑う根拠となる[5)]（表）。低出生体重児ではネフロン数が少なく，成人後に肥満になると残存ネフロンへの過剰負荷となることが考えられる。メタボリックシンドローム，肥満者はしばしば高尿酸血症を合併している。介入研究よる高尿酸血症治療のCKD進行抑制の効果は現時点では不明である。しかし，男女ともに7 mg/dL未満を目標にコントロールすべきとされている。

肥満，メタボリックシンドロームによる腎障害の治療は一義的には体重減少である。肥満の増加は世界的傾向であり，大量生産される安価な高カロリー食品や嗜好性の高い食品の普及，運動不足など，社会経済的要因も関与している。CKDと肥満，メタボリックシンドロームの関連についての啓発活動が必要である。しかし，過度のカロリー制限，栄養不良などは避けなければならない。

まとめ

わが国の透析導入患者の約43%はDMであり，依然として増加傾向にある。原因となるメタボリックシンドローム，肥満は男性および高齢者で頻度が増加している。現在，わが国で実施されている特定健診（いわゆるメタボ健診）はメタボリックシンドロームの早期発見，指導を通じ合併症の発症予防，医療費の減少を目指している。生活習慣の是正によりCKDの発症，進展の阻止が期待される[5)]。

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ORIGINAL ARTICLE

Design and methods of a strategic outcome study for chronic kidney disease: Frontier of Renal Outcome Modifications in Japan

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Abstract

Background The continuous increase in the number of people requiring dialysis is a major clinical and socioeconomical issue in Japan and other countries. This study was designed to encourage chronic kidney disease (CKD) patients to consult a physician, enhance cooperation between nephrologists and general practices, and prevent the progression of kidney disease.

Methods Subjects comprise CKD patients aged between 40 and 74 years consulting a general physician, and patients in CKD stage 3 with proteinuria and diabetes or hypertension. This trial is a stratified open cluster-randomized study with two intervention groups: group A (weak intervention) and group B (strong intervention). We have recruited 49 local medical associations (clusters) in 15 different prefectures, which were classified into four

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regions (strata) based on the level of increase rate of dialysis patients. The patients in group A clusters were instructed initially to undergo treatment in accordance with the current CKD treatment guide, whereas patients in group B clusters were not only instructed in the same fashion but also received support from an information technology (IT)-based system designed to help achieve the goals of CKD treatment, consultation support centers, and consultations by dietitians visiting the local general practice offices. We assessed the rates of continued consultation, collaboration between general practitioners and nephrologists, and progression of CKD (as expressed by CKD stage).

Conclusion Through this study, filling the evidence-practice gap by facilitating effective communication and supporting general physicians and nephrologists, we will establish a CKD care system and decrease the number of advanced-stage CKD patients.

Keywords Chronic kidney disease · Evidence-practice gap · Cluster-randomized study · Educational intervention · Cooperation between nephrologists and general physicians

Introduction

The number of dialysis patients is continually increasing, with consequent rises in medical costs for the treatment of end-stage kidney disease (ESKD) patients becoming a socioeconomical concern worldwide. In fact, there are 2,153.2 dialysis patients per million of population in Japan [1]. Chronic dialysis treatment not only reduces the quality of life (QOL) of patients [2, 3] but also places considerable financial strain on society, with annual medical costs of five to six million yen per dialysis patient, or total expenses of one trillion yen. Moreover, it is estimated that there are more than ten million chronic kidney disease (CKD) patients in Japan [4]. Previous studies suggested that CKD is one of the most important risk factors for cardiovascular disease, among known risk factors of diabetes, hypertension, hyperlipidemia, obesity, smoking, and lifestyle-related disease [5–8]. Therefore, early detection and control of CKD are also important in terms of preventing cardiovascular complications and deaths.

The definition of CKD first appeared in the Kidney Disease Outcome Quality Initiative (KDOQI) Guidelines issued by the National Kidney Foundation (NKF) in 2002 [9], and was revised by Kidney Disease: Improving Global Outcomes (KDIGO) in 2005 [10]. Since then, the definition of CKD and renal function assessment methods are being accepted worldwide. CKD is defined as kidney damage or glomerular filtration rate (GFR) <60 ml/min/1.73 m^2 for 3 months or more, irrespective of cause. The concept of CKD comprehensively addresses a wide range of kidney patients, including ESKD and transplant patients. It is important to establish appropriate, consistent, and specific treatment and prevention-based care systems according to the progression of kidney disease. The Ministry of Health, Labor, and Welfare organized a study group to design strategic outcome studies and discuss the following research subjects: prevention of diabetes, prevention of suicide and depression (2005), cancer prevention, and AIDS/HIV prevention (2006), which have been started. Following these studies, a strategic study to improve the progression of CKD was planned based on these social and scientific demands to reduce new patients with initiation of renal replacement therapy due to ESKD, termed the Frontier of Renal Outcome Modifications in Japan (FROM-J).

Diabetic nephropathy, nephrosclerosis due to hypertension, and chronic glomerulonephritis are three major primary renal diseases in ESKD, not only in Japan but also in Western countries [1]. In Japan, the proportion of new ESKD patients due to chronic glomerulonephritis has recently been decreasing, while that of diabetic nephropathy is rapidly increasing. If this trend continues, in 5 years, patients undergoing dialysis due to diabetic nephropathy will account for 50.82% of the total whereas those with chronic glomerulonephritis will account for 19.54%. In other words, the primary renal disease in half of dialysis patients will be diabetic nephropathy, and the number of dialysis patients with chronic glomerulonephritis will decrease by 17%. The decreasing trend in chronic glomerulonephritis is due to annual urinalysis screening programs established by the Japanese government [11]. Also, more attention should be paid to preventing deterioration of renal function in patients with diabetic nephropathy and nephrosclerosis.

Although diabetic nephropathy is the primary underlying disease in dialysis patients in many developed countries, it has been showing a decreasing trend in some regions and countries, including Denmark. In Denmark, after a steady increase from 52 in 1990 to 183 in 2002, the number of dialysis patients with diabetic nephropathy decreased by 15%, to 155–156 patients per million people [12]. This indicates that aggressive management of both blood pressure and glucose, administration of renin angiotensin system (RAS) inhibitors, and advice on lifestyle can reduce ESKD with diabetic nephropathy by more than 15%. According to the 2002 diabetes survey conducted by the Ministry of Health, Labor, and Welfare of Japan, only 33.3% of patients in Japan had controlled their HbA1c to less than 6.5%, and these interventions are expected to achieve marked effects. Furthermore, although 50.2% of males and 38.3% of females aged 40 years or

older in Ibaraki Prefecture showed hypertension, only 41.9% and 49.2% of them, respectively, were receiving antihypertensive treatment [13], and blood pressure was not adequately controlled in about 50% of those who were receiving treatment [14]. Appropriate interventions are assumed to bring about noticeable effects in Japan, in which RAS inhibitors have not been used effectively as antihypertensive therapy, although a slight increase has occurred in recent years [15].

Recently, the CKD Clinical Practice Guide for future treatment methods was developed by the Japanese Society of Nephrology [16], describing the treatment target for every CKD stage. Although all items of the treatment method were supported by clinical evidence, there were no prospective studies showing the effect of practices such as the CKD Clinical Practice Guide targets on renal and cardiovascular outcomes in sufficient number of CKD patients.

In this strategic CKD study, a prospective stratified cluster-randomized trial to examine the effectiveness of a care system designed to prevent progression of CKD through collaboration between nephrologists and general physicians was selected. One of the goals of the study is a 15% reduction in the estimated number of new dialysis patients in 5 years by increasing the rates of compliance with the CKD Clinical Practice Guide. The study also aims to encourage CKD patients to see their family physician, consult a nephrologist, and receive nutritional and lifestyle advice, while discussing health care measures to reduce the number of new dialysis patients.

Hypotheses of study

The study hypothesis encompasses the following four core issues:

1. Clinical practice in accordance with the Japanese CKD Clinical Practice Guide will improve the prognosis of CKD patients and reduce the speed of renal function deterioration.
2. Education-based interventions for CKD patients by registered dietitians and other co-medicals will help achieve strict CKD treatment goals in accordance with the Japanese CKD Clinical Practice Guide.
3. Collaboration concerning clinical practices among general physicians, nephrologists, and co-medicals will reduce the gap between clinical practice and evidence-based care measures, and improve the rate of continued consultation and prognosis in CKD patients.
4. These active interventions to improve CKD treatment will achieve the desired effects in terms of medico-economics.

Subjects and methods

Study organization and duration

Since the increase in the rate of dialysis patients varies from region to region in Japan [17], we divided the country into four regions (Fig. 1) as strata, so that they would

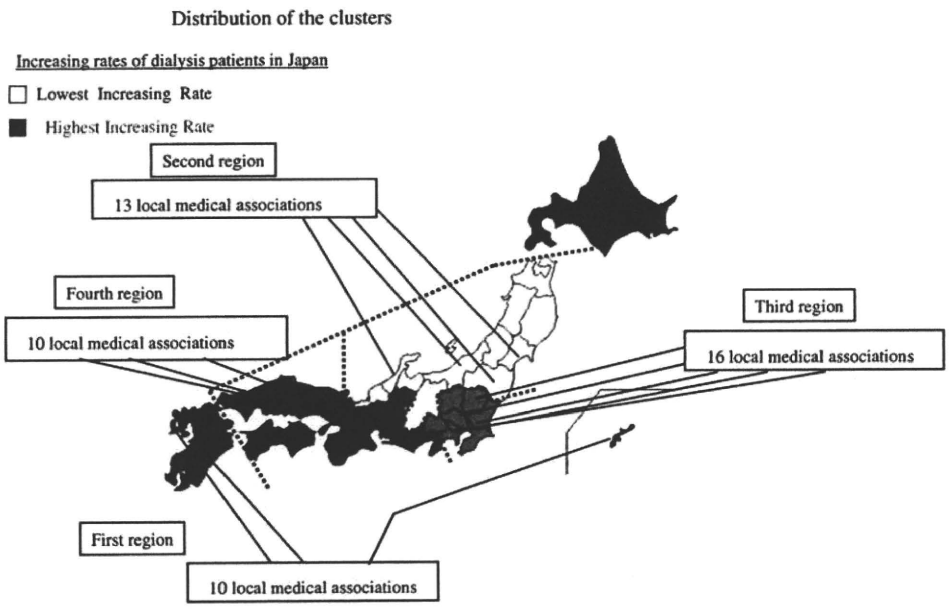

Fig. 1 Distribution of the clusters. We have recruited 49 local medical associations (clusters) in 15 different prefectures, which were classified into four regions (strata) based on the level of increase in the rate of dialysis patients [17]

include at least one managing facility and two or more clusters. The primary intervention study duration is from October 2008 to March 2012.

Rationale for setting the number of patients

This project aims to examine whether or not intervention can reduce the incidence of dialysis patients by 15% over the next 5 years. Regarding the calculation, we estimated the annual decrease in GFR as 0.59 ml/min/year (standard deviation (SD) 0.04 ml/min/year), based on changes in renal function among healthy Japanese people who underwent health checkups [17, 18] and the rate of renal deterioration in patients in CKD stage 3 with diabetes or hypertension [mean serum creatinine = 1.69 mg/dl (SD = 0.57 mg/dl), annual decrease rate = 5.93 ml/min/year (SD 4.321 ml/min/year), $n = 569$] [18, 19]. The required study size was calculated as 2,038 when the unknown intracluster correlation coefficient was assumed to be 0.5. We determined the required number as 2,264 for groups A and B, assuming that 10% would withdraw. We applied the simple number of 2,500 (1,250 for each group) as the target number of patients to perform this study.

Eligible patients

Each registered general physician obtained written informed consent for the study from eligible patients. They were formerly registered after the data center verified their eligibility. Inclusion criterion were: (1) age between 40 and 74 years; (2) in CKD stage 1, 2, 4, or 5; (3) in CKD stage 3 with proteinuria (ratio of urinary protein/urinary creatinine $\geq$0.3, or proteinuria $\geq$1+) and diabetes or hypertension.

Dialysis patients and those who did not consent were excluded from this study.

Assignment and randomization

This trial is a stratified open cluster-randomized study with two intervention groups: group A (weak intervention) and group B (strong intervention). We have recruited 49 local medical associations (clusters) in 15 different prefectures, which were classified into four regions (strata) based on the level of increase in the rate of dialysis patients (Fig. 1). Each local medical association recruited 10–58 general physicians by whom patients in this study has been treated. Local medical associations are randomized when the enrolment period is completed.

Intervention methods

Patients in group A clusters are instructed initially to undergo treatment in accordance with the current CKD treatment guide only, whereas patients in group B clusters are not only instructed in the same fashion but also receive consultations by dietitians visiting the local general practice offices. In addition, the data center closely monitors the treatment status and provides the group B general practice office with comments on the data.

Goals for the treatment of chronic kidney disease (groups A and B)

Participants in the study, or patients, will receive treatment according to the CKD Clinical Practice Guide [16]. Table 1 shows a summary of targets for CKD treatment applied to all patients. In patients with CKD, lifestyle modifications to avoid obesity and stop smoking are necessary. Strict blood pressure control (less than 130/80 mmHg), strict blood sugar control (HbA1c <6.5%), and low-density lipoprotein (LDL)-cholesterol control (LDL-C <120 mg/dl) are shown as targets for CKD treatment. The standards for referral from general physicians to nephrologists are as follows: (1) ratio of urinary protein/urinary creatinine $\geq$0.5, or proteinuria $\geq$1+; (2) estimated GFR (eGFR) <50 ml/min/1.73 m^2; (3) both proteinuria and hematuria positive ($\geq$1+); and (4) when family physicians judge that patients should consult a nephrologist. Estimated GFRs in this study are calculated using the following formula:

$$\mathrm{eGFR(ml/min/1.73\ m^2)} = 194 \times \mathrm{Age}^{-0.287} \times \mathrm{Cre}^{-1.094} (\times 0.739 \text{ in the case of women}).$$

Monitoring of treatment status by the data center (only group B)

The data center closely monitors the treatment status and provides the group B general practice office with comments on the data. In addition, the data center will provide information on the patients scheduled to visit the office, examinations, and treatment that patients should undergo on their next visit, patients who did not visit hospitals as scheduled, those who are going to receive lifestyle/dietary advice, and those who meet the conditions for referral to nephrologists. The center also monitors patients and their schedules: the next consultation date, required examinations, details of treatment and care provided, and advice on lifestyle and nutrition. The centers will contact patients by mail, telephone, or email a week before the consultation day and encourage those who have not consulted a physician for over 2 months to receive care, trying to prevent their withdrawal from treatment. To facilitate referrals to nephrologists, the centers send a list of patients who meet the criteria for referral to the physicians and clinical research coordinators (CRCs).

Table 1 CKD practice guide target in this study

CKD stages	Lifestyle	Diet	Blood pressure	Blood sugar	Lipid metabolism	Hemoglobin
Stage 1	Smoking cessation BMI <25 kg/m^2	Sodium chloride <6 g/day for hypertensives	<130/80 mmHg	HbA1c <6.5%	LDL-C <120 mg/dl	
Stage 2	Smoking cessation BMI <25 kg/m^2	Sodium chloride <6 g/day for hypertensives	<130/80 mmHg	HbA1c <6.5%	LDL-C <120 mg/dl	
Stage 3	Smoking cessation BMI <25 kg/m^2	Sodium chloride <6 g/day for hypertensives DPI: 0.6-0.8 g/kg/day	<130/80 mmHg	HbA1c <6.5%	LDL-C <120 mg/dl	Hb 10–12 g/dl
Stage 4	Smoking cessation BMI <25 kg/m^2	Sodium chloride <6 g/day for hypertensives DPI: 0.6–0.8 g/kg/day Potassium restriction	<130/80 mmHg	HbA1c <6.5%	LDL-C <120 mg/dl	Hb 10–12 g/dl
Stage 5	Smoking cessation BMI <25 kg/m^2	Sodium chloride <6 g/day for hypertensives DPI: 0.6–0.8 g/kg/day Potassium restriction	<130/80 mmHg	HbA1c <6.5%	LDL-C <120 mg/dl	Hb 10–12 g/dl
Others			<125/75 mmHg If proteinuria >1 g/day			

BMI body mass index, *DPI* dietary protein intake

Nutrition and lifestyle improvement (only group B)

Registered dietitians provide support according to the instructions and advice from family physicians. They help patients achieve their CKD treatment goals, explaining to patients about examination results, achievements in CKD care, and their implications. Registered dietitians receive training so that they will be able to provide integrated and consistent advice.

Data collection

At each consultation, physicians will measure patients' blood pressure, and check their blood pressure conditions at home. Examinations or surveys will be performed every 6 months regarding body weight, abdominal circumference, smoking status, fasting serum creatinine, blood urea nitrogen (BUN), potassium, hemoglobin (Hb), high-density lipoprotein cholesterol (HDL-C), total cholesterol (TC), triglyceride (TG), uric acid, total protein, albumin, fasting blood glucose, HbA1c (only in the case of diabetes), urinary creatinine levels, amount of urinary proteins, eGFR, number of patients referred by nephrologists, number of new dialysis patients, and incidence of cardiovascular events.

Parameters for assessment

Primary parameters for assessment are: (1) the rate of continuous clinic visits of CKD patients, (2) the proportion of patients under cotreatment between general physicians and nephrologists, and (3) annual changes in CKD stage.

Secondary parameters are: (1) the proportion of adherence to the complete CKD treatment guide, (2) the rate of achievement of blood pressure goals, (3) the number of subjects with 50% reduction in urinary protein, (4) the number of subjects with a doubling of serum creatinine or 50% reduction in eGFR, (5) yearly changes in the number of patients starting renal replacement therapy, and (6) the incidence of cardiovascular events.

Statistical analysis

Statistical analyses will be performed using an intent-to-treat approach. Differences in primary endpoints between intervention groups are described by their 95% confidence intervals. The declining velocity of eGFR is tested by analysis of variance, using the efficacy of interventions as fixed effects and cluster effects as random effects. We employ a generalized linear model with age, gender, complications, and previous GFR as covariates where appropriate. The significance level on both sides in hypothesis testing is set at 0.05.

For secondary endpoints, we will use analysis of variance with a generalized linear model.

Ethical considerations

This study is being conducted in accordance with the Ethical Guidelines for Clinical Studies (revised on December 28, 2004, of the Ministry of Health, Labor, and Welfare) and the Ethical Guidelines for Epidemiological Studies (revised on August 16, 2007, of the Ministries of Education, Culture, Sports, Science, and Technology/ Health, Labor, and Welfare). All medical professionals involved in this study must comply with these ethical standards. This study is a Central Institutional Review Board (Central IRB) program, and the Committee on Ethics in Strategic Research of the Kidney Foundation, Japan, will examine and approve implementation plans and their revision.

Discussion

The purpose of this study is to enhance cooperation between nephrologists and general physicians, improve lifestyle and dietary advice provided by registered dietitians at general physicians' offices, and offer measures to control blood pressure and other critical parameters in practice, thereby filling the evidence-practice gap, which will slow the progression of kidney disease.

Recently, the concept of chronic kidney disease has been announced not only in Japan, but also throughout the world [9, 10]. There are more than ten million CKD patients in Japan [4], and so CKD is regarded as a public health problem.

CKD guidelines for general physicians or patients have been published in European countries [9, 20–22]. The USA is also preparing similar measures for CKD [23, 24]. In Japan, annual urinalysis for early detection of renal disease started in the 1970s [11, 25], and a serum creatinine test was included in health examinations as early as 1989 to detect kidney failure among adults aged 40 years or older [26]. However, the number of dialysis patients is increasing by approximately 4% each year. It is necessary to implement more appropriate measures to reduce the rate of new dialysis patients in Japan as soon as possible.

In 2007, the Japanese Society of Nephrology established the CKD Clinical Practice Guide to help family physicians provide care for CKD patients. The guide suggests that lifestyle and dietary advice on obesity prevention [27], smoking cessation [28], and a sodium-restricted diet, and treatment for metabolic disorders [29, 30], hypertension [31], and hyperlipidemia [32] are effective to prevent progression of CKD. However, most people are not making sufficient efforts to manage their own health condition [13]. It is necessary to show the effect on the progression of CKD of treatment as part of the Clinical Practice Guide. Our challenge is to obtain sufficient evidence regarding the efficacy of filling the evidence-practice gap in preventing deterioration of renal function among Japanese patients.

We set the following conditions for patient eligibility in this study: CKD patients aged between 40 and 74 years; patients in CKD stage 1, 2, 4 or 5; and patients in CKD stage 3 with a high level of urinary protein and diabetes or hypertension. Proteinuria is known as the strongest predictor of decreasing renal function [13, 33], and the aggressive management of blood pressure and glucose [29, 31] and administration of RAS inhibitors [34–36] prevent the deterioration of renal function. The reason for the condition regarding urinary proteins in stage 3 patients is that we need to register patients showing significant deterioration in renal function [37].

Regarding lifestyle and dietary advice, we have prepared a list of instructions and advice for individual patients on a priority basis, so that registered dietitians can design a guidance schedule based on the priority list and provide consistent advice. In this study, we focus on preventing progression of CKD in the early stage by giving priority to Japanese CKD practice guide goals. We are preparing a long-term guidance method covering a wide range of health management items while seeking ways to reduce the evidence-practice gap as much as possible.

We predict significant positive effects in intervention group B (increased collaboration in clinical practice) in terms of increases in the rate of continued consultation and collaboration between nephrologists and other physicians, and reduced CKD stage progression as a result of instructions and advice from registered dietitians, compared with intervention group A. This study was designed to examine the effectiveness of a support system for collaborative CKD diagnosis and treatment by conducting a cluster-randomized controlled trial. We expect that this study will help improve clinical practices for CKD patients and provide high-quality clinical findings of global standard. Although the number of CKD patients in Japan is estimated to be more than ten million, there are only 3,000 nephrologists. If effective collaboration is established among nephrologists in CKD care, it will have a significant positive impact on renal care systems. In the area of renal care, few large-scale intervention studies have been performed on kidney care systems, except those aimed to assess the efficacy of drug interventions. Little progress has been made in the development of infrastructure for clinical studies and research environments in Japan. This study is expected not only to help develop the infrastructure required for clinical renal studies but also to generate valuable findings.

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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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

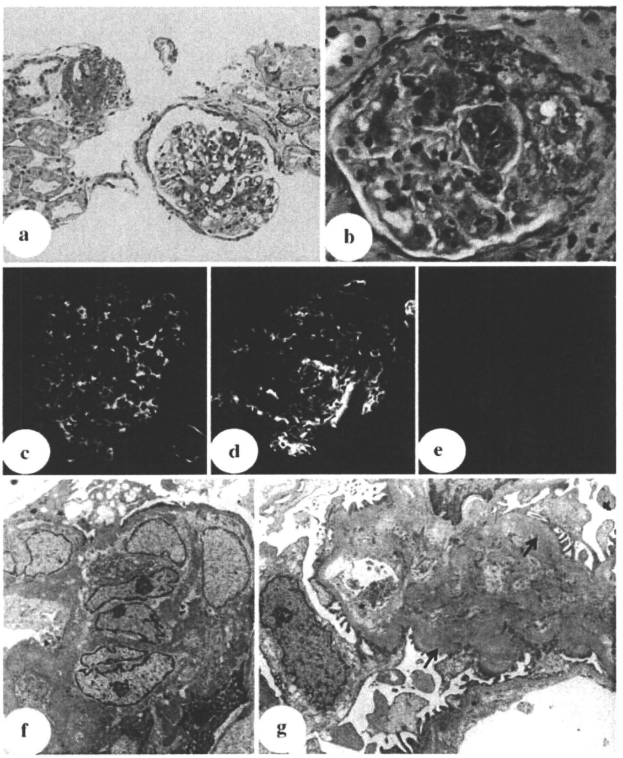


Fig. 1 Findings of the first renal biopsy. **a** The right glomerulus shows mild mesangial proliferation of both matrix and cells accompanying fibrous crescents (light microscopy, PAS staining, ×200). **b** The glomerulus shows endocapillary proliferation accompanying a necrotizing lesion and cellular 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

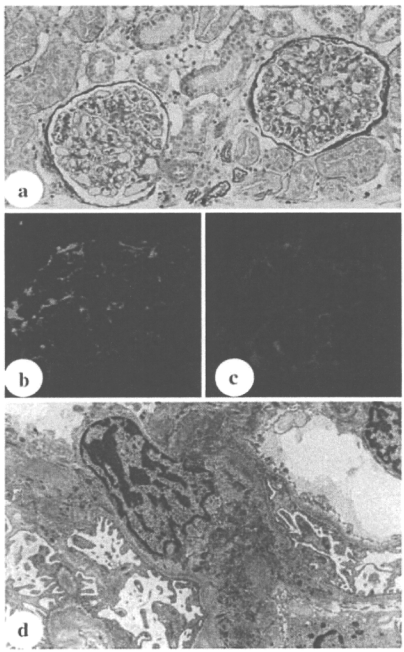


Fig. 2 Findings of the second renal biopsy. **a** Each of two glomeruli shows mild mesangial expansion of both matrix and cells (light microscopy, PAS staining, ×200). **b** The glomerulus shows weakly positive, mesangial-dominant staining for anti-IgA (immunofluorescence staining, ×200). **c** The glomerulus 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

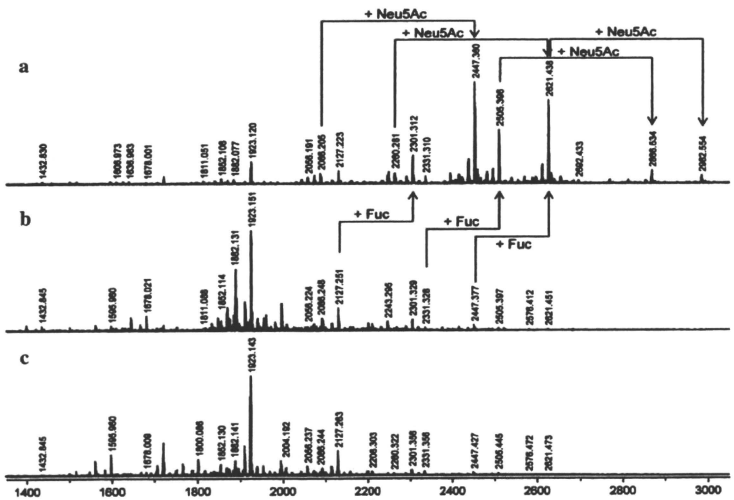
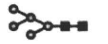
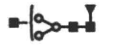
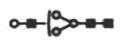
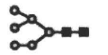
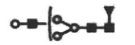
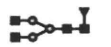
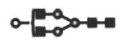
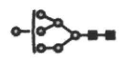
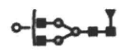
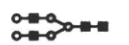
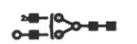
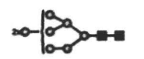
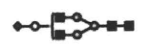
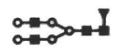
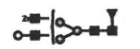
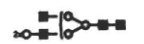
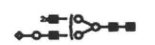
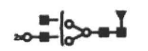
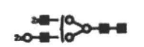
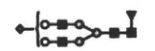
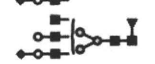
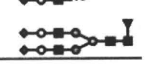


Fig. 3 The *N*-glycan profile was analyzed using mass spectrometry. **a** The *N*-glycan profile of the present case, **b** patient with circulating mIgA-related pathology lacking renal involvement, and **c** healthy control. The mass spectra were obtained in reflectron positive-ion mode with MALDI-TOF 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	
2447.360	2447.377	2447.427	5	4	0	1	
–	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.

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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).