研究参加の可否を打診する。研究参加に同意した場合は，本実施計画書とは別に用意する日本腎臓財団戦略研究倫理委員会（平成 22 年度より腎疾患対策研究事業戦略研究運営班倫理委員会に移行）が承認した参加意思確認書を用いて，かかりつけ医本人から文書で参加意思を確認する。参加意思確認書は 2 部コピーし，1 部はかかりつけ医，1 部はデータセンターが保管する。

13.3.2 参加者の同意

かかりつけ医は，参加者が本研究に参加する前に以下の内容を説明する。

1) 本研究に参加者として参加を依頼された理由，病名及び予想される予後等の説明
2) 本研究の内容（本研究を実施する意義，研究の目的，各群の診療の内容，調査・検査の内容，研究期間，研究終了後は日本腎臓学会が中心となって調査を継続する可能性のあること）
3) 本研究の解析結果は研究終了後に伝えられること
4) 本研究に参加することによって期待される利益
5) 予想されるイベントの内容とそれらが生じた場合の対処法
6) 費用負担と補償

   治療にかかる費用は保険制度でまかなわれ，健康被害が生じた場合の補償は一般診療の場合と同様であること
7) 本研究への参加は任意であること
8) 本研究に参加しない場合の診療方法
9) 研究参加に同意しない場合でも，いかなる不利益も受けないこと
10) 参加者はいつでも同意を撤回でき，同意の撤回によっていかなる不利益も受けないこと
11) 個人情報の取扱い

   本研究は，「臨床研究に関する倫理指針」（厚生労働省　平成 20 年 7 月 31 日改），「疫学研究に関する倫理指針」（文部科学省・厚生労働省　平成 20 年 12 月 1 日改）を遵守して実施されること

   本研究の参加者の診療録をデータ収集のため CRC が閲覧することがあること

   本研究で収集されるデータはデータセンターに蓄積されるが，参加者の個人情報は漏洩しないように保護されること。

   本研究で収集されるデータは，受診促進支援センター及び栄養ケアステーションが受診促進支援，生活・食事指導の目的で使用し，データを使用する場合は個人情報を漏洩しないように取り扱うこと。

   本研究で収集されたデータは，データモニタリングのために，匿名化された状態で研究グループが閲覧すること。
12) 本研究の結果が学会または雑誌に公表される際には，個人を特定できないように人権擁護に配慮すること
13) 本研究は厚生労働省が支援していること

14) 本研究の資金源

15) 研究者等の氏名及び職名

16) 本研究は日本腎臓財団戦略研究倫理委員会（平成 22 年度より腎疾患対策研究事業戦略研究運営班倫理委員会に移行）によって審査・承認されていること

17) 問い合わせ，苦情等の連絡の窓口

以上の内容を説明し，参加者に予定するものが研究の内容等を理解したことを確認したうえで，本研究参加の可否を打診する。研究参加に同意した場合は，本実施計画書とは別に用意する日本腎臓財団戦略研究倫理委員会(平成 22 年度より腎疾患対策研究事業戦略研究運営班倫理委員会に移行）が承認した同意説明文書を用いて，参加者本人から文書で同意を取得する。同意説明文書には，説明をした医師名，同意年月日，同意した参加者の氏名，住所，電話番号（希望する連絡方法），連絡可能な時間帯を記載し，参加者及び医師の両者が署名する。同意説明文書は 3 部コピーし，1 部は参加者本人，1 部はかかりつけ医，1 部はデータセンターが保管する。

参加者が同意を撤回する場合は，日本腎臓財団戦略研究倫理委員会（平成 22 年度より腎疾患対策研究事業戦略研究運営班倫理委員会に移行）が承認した同意撤回書を用いて，参加者本人による同意撤回を文書で確認する。同意撤回書は 3 部コピーし，1 部は参加者本人，1 部はかかりつけ医，1 部はデータセンターが保管する。

なお，地区医師会は，医師会，かかりつけ医の施設内のポスター，地区の公報，ホームページ，説明会などで研究の内容を広報し，患者が研究への参加及び不参加を表明できる権利を行使できる環境を整備する。

14. 品質マネジメント

研究代表者は，研究の実施並びにデータの作成，記録及び報告が本実施計画書を遵守して行われることを保証するために，モニタリング，データマネージメント，記録の保存等に関する業務手順書を必要に応じて定めることができる。

15. イベント発生時の対応

参加者の研究参加継続に影響を及ぼすイベントが発生した場合，発見者はただちに研究代表者に報告する。研究代表者は，ただちに対応及び再発防止策を協議し，その内容をすべての関係者に周知する。協議の結果，報告された事象が研究全体の中止または中断に及ぶ可能性があると判断された場合，研究代表者は腎疾患対策研究事業戦略研究運営班倫理委員会に審議を求める。

16. 研究実施計画書からの逸脱

本研究に参加する医療関係者は本実施計画書を遵守する責務を負う。腎疾患対策研究事業戦略研究運営班倫理委員会の事前の承認を得ることなく，本実施計画書から逸脱することはできない。

ただし，参加者の緊急の危険を回避する等，医療上やむを得ない場合，かかりつけ医または腎臓専門医は，事前の文書による合意及び腎疾患対策研究事業戦略研究運営班倫理委員会の事前の承認を得ることなく，本実施計画書から逸脱することができる。その場合，かかりつけ医または腎臓専門医はすみやかに逸脱の内容及び理由を腎疾患対策研究事業戦略研究運営班倫理委員会に提出する。

17. 研究実施計画書の改訂

研究実施中に実施計画書を改訂する必要が生じた場合，研究代表者は実施計画書の改訂案を作成し，腎疾患対策研究事業戦略研究運営班倫理委員会に審査を依頼する。審査終了後，研究代表者は腎疾患対策研究事業戦略研究運営班倫理委員会の答申に従って実施計画書を改訂し，改訂した内容をすべての関係者に通知する。

18. 研究全体の中止または中断

研究実施中に腎疾患対策研究事業戦略研究運営班倫理委員会が研究全体を中止または中断するように勧告した場合，別に設置される腎疾患対策研究事業戦略研究運営班運営委員会は勧告への対応を決定し，すべての関係者に周知する。研究を中止または中断する場合，かかりつけ医は研究実施中の参加者にその旨を説明し，参加者の安全を確認したうえで他の適切な治療に変更する。

19. 研究の終了手続き

研究代表者は，最終解析報告書の内容を総括し，研究全体の結論，問題点，結果の解釈と考察，今後の指針等を主として臨床的観点からまとめた「最終研究報告書」を作成し，腎疾患対策研究事業戦略研究運営班運営委員会に提出し，最終研究報告書が承認された時点で本研究は終了する。

研究代表者は，研究終了後，地区医師会及びかかりつけ医に研究が終了した旨と，研究結果の概要を文書で報告する。

研究終了後のデータは社団法人日本腎臓学会が保管する。ただし，社団法人日本腎臓学会が追加調査を行う可能性がある。

20. 公表に関する取り決め

研究代表者は本研究で得た結果を適切な医学雑誌に公表することができる。

かかりつけ医が本研究で得た情報を専門の学会等外部に公表する場合は，事前に文書によって研究代表者の承諾を得るものとする。

21. インセンティブ

21.1 拠点施設へのインセンティブ

拠点施設が担当する地域の広報活動を支援する。

21.2 地区医師会へのインセンティブ

地区医師会を介して行われるCKDに関する広報活動のための支援を行う。

「増加し続けるCKDとそれを基盤とする心血管疾患の増加に対して，その対策法を開発するための重要な研究に積極的に取り組んでいる地域」として，ポスターやパンフレットなどで公開する。

拠点施設が作成した地域の腎臓専門医リストを配布する。

21.3 腎臓専門医へのインセンティブ

公表を承諾した者のみ,「増加し続けるCKDとそれを基盤とする心血管疾患の増加に対して，その対策法を開発するための重要な研究に積極的に取り組んでいる腎臓専門医」として，ポスターやパンフレットなどで公開する。

地区医師会・かかりつけ医へ配布される腎臓専門医リストへの掲載

21.4 かかりつけ医へのインセンティブ

すべてのかかりつけ医に簡易版CKDガイドの小冊子を配布する。

すべてのかかりつけ医に初期登録費及びデータ登録協力費を支給する。

公表を承諾した者のみ,「増加し続けるCKDとそれを基盤とする心血管疾患の増加に対して，その対策法を開発するための重要な研究に積極的に取り組んでいるかかりつけ医」として，ポスターやパンフレットなどで公開する。

拠点施設が作成した地域の腎臓専門医リストを配布する。

21.5 参加者へのインセンティブ

すべての参加者にCKD管理ノート及び血圧計を配布する。

22. 実施体制

本研究は平成19年度より日本腎臓財団が研究代表者となり施行され、平成22年度より研究代表者が筑波大学　山縣邦弘に代わり引き続き研究が継続されている。体制変更に伴い平成22年度より一部組織の名称が変更された（各項参照）。

22.1 研究代表者

筑波大学大学院人間総合科学研究科疾患制御医学専攻腎臓病態医学分野

教授　山縣邦弘

研究代表者は，本実施計画書に従って研究を実施する。筑波大学は本実施計画書に関する問い合わせ，データ漏洩及び参加者の研究参加継続に影響を及ぼす事象への対応，本実施計画書の改訂等に対応する。また，研究代表者は栄養ケアステーションの管理栄養士に対する教育プログラムを作成し，本研究に関する研修を行う。

22.2 研究グループ統計家

筑波大学大学院人間総合科学研究科生命システム医学専攻疫学分野

准教授　高橋秀人

筑波大学大学院人間総合科学研究科生命システム医学専攻疫学分野

講師　　岡田昌史

22.3 アドバイザー委員会

アドバイザー委員会は以下の業務を行う。

・研究実施計画書に対する助言

・拠点施設設定に対する助言

・目標参加者数の登録のための助言，協力

アドバイザー委員会の構成（敬称略，五十音順）

委員長	山縣　邦弘（筑波大学大学院人間総合科学研究科疾患制御医学専攻腎臓病態医学分野 教授）
副委員長	槇野　博史（岡山大学大学院医歯薬学総合研究科腎・免疫・内分泌代謝内科学 教授）
委　員	秋澤　忠男（昭和大学医学部腎臓内科 教授）
委　員	井関　邦敏（琉球大学医学部附属病院血液浄化療法部 准教授）
委　員	伊藤　貞嘉（東北大学大学院医学系研究科医学部医科学専攻 教授）
委　員	木村健二郎（聖マリアンナ大学腎臓・高血圧内科 教授）
委　員	古家　大祐（金沢医科大学内分泌代謝科 教授）
委　員	椿原　美治（大阪府立急性期･総合医療センター腎臓･高血圧内科 主任部長）
委　員	成田　一衛（新潟大学医歯学総合研究科腎・膠原病内科　教授）
委　員	御手洗哲也（埼玉医科大学総合医療センター腎高血圧内科 教授）
委　員	宮崎　正信（宮崎内科医院 院長）
委　員	和田　隆志（金沢大学大学院医学系研究科血液情報統御学 教授）
委　員	渡辺　　毅（福島県立医科大学内科学第三講座 教授）

22.4 拠点施設

・拠点施設は本研究に参加する腎臓専門医を選定し，そのリストを地区医師会に公表する。

・拠点施設は，地区医師会が選定したかかりつけ医をデータセンターに登録する。

・拠点施設は参加者の登録状況をデータセンターの報告により把握し，登録者数が目標に達しない場合は地区医師会を通じてかかりつけ医に登録を促す。

・拠点施設は，腎臓専門医に対して，本研究に関する講習会を開催する。

・拠点施設は，腎臓専門医からかかりつけ医へ診療情報が確実にフィードバックされるよう，腎臓専門医にかかりつけ医との連携を促す。

・拠点施設は，地域内で CKD に関する啓発広報活動を行う。啓発広報活動の内容は別途

定める。
・拠点施設は，かかりつけ医から参加者の研究参加継続に影響を及ぼす事象の報告を受けた場合，その旨をただちに研究代表者に報告する。

・拠点施設代表者を以下に示す（敬称略，五十音順）。
井関　邦敏（琉球大学医学部附属病院血液浄化療法部 准教授）
伊藤　貞嘉（東北大学大学院医学系研究科内科病態学講座　腎・高血圧・内分泌学分野 教授）
木村健二郎（聖マリアンナ大学腎臓・高血圧内科 教授）
草野　英二（自治医科大学内科学講座腎臓内科学部門　教授）
柴田　孝則（昭和大学医学部腎臓内科 准教授）
冨田　公夫（熊本大学大学院医学薬学研究部　教授）
成田　一衛（新潟大学医歯学総合研究科腎・膠原病内科 教授）
藤垣　嘉秀（浜松医科大学医学部第一内科　准教授）
西野　友哉（長崎大学医学部歯学部付属病院第二内科 腎臓内科部門　講師）
槇野　博史（岡山大学大学院医歯薬学総合研究科腎・免疫・内分泌代謝内科学 教授）
松尾　清一（名古屋大学大学院医学系研究科・腎臓内科学　教授）
御手洗哲也（埼玉医科大学総合医療センター腎・高血圧内科 教授）
山縣　邦弘（筑波大学大学院人間総合科学研究科疾患制御医学専攻腎臓病態医学分野 教授）
和田　隆志（金沢大学大学院医学系研究科血液情報統御学 教授）
渡辺　　毅（福島県立医科大学内科学第三講座 教授）

22.5 データセンター

・データセンターは，CRC が収集した本研究に関するデータを集積する。
・データセンターは集積されたデータの内容を定期的に確認し，入力内容に明らかな不備がある場合は CRC に内容を確認する。
・データセンターは集積したデータを整理し，研究代表者が要請した場合は随時かつ遅滞なく，要請された条件でデータを抽出・処理し，データを提供する。
・データセンターは，集積されたデータの完全性を保証するため，データサーバ上で必要な措置をとる。週に 1 回以上の頻度で全データをリムーバブル記録メディア上にバックアップするとともに，そのメディアをデータセンター及び筑波大学以外の者が開けることができない倉庫に，過去のものも含めて研究期間を通じて保管する。同時に，1 日に 1 回以上の頻度で，全データをリムーバブル記録メディア上にバックアップする（このバックアップメディアは別の日のバックアップのために再利用しても差し支えないが，利用しなくなった場合にはデータを完全消去したうえで廃棄する）。
・データセンターに集積されたデータは，データセンター，筑波大学以外が閲覧すること

がないようアクセスを制限する。他の者がデータを閲覧する必要が生じた場合は，筑波大学にその旨を要請し，筑波大学を通じてデータを得るものとする。
・データセンターは診療達成目標支援 IT システムを構築し，運用する。診療達成目標支援ＩＴシステムには，データセンターに報告された項目の一部がコピーされる場合があるが，コピーされた情報についても元の情報と同等のアクセス制限を適用する。

22.6 受診促進支援センター

・受診促進支援センターは診療達成目標支援 IT システムに基づいて，参加者に対するかかりつけ医への受診及び生活･食事指導受診の促進を支援する。
・受診促進支援センターは，診療達成目標支援 IT システムで作成したかかりつけ医から腎臓専門医への紹介基準を満たす参加者リストをかかりつけ医へ送付し，腎臓専門医への紹介を促進する。
・受診促進支援センターは，個人情報を適切に扱う責を負う。

22.7 栄養ケアステーション

・栄養ケアステーションは，かかりつけ医の指示に従って，参加者に対する栄養療法支援及び生活指導を実施する。
・栄養ケアステーションは，診療達成目標支援 IT システムに入力された検査データや実施率，達成度の内容・意義を参加者に説明する。
・栄養ケアステーションは，個人情報を適切に扱う責を負う。

22.8 CRC

・CRC はかかりつけ医から意思確認を取得する際の補助業務を担当し，かかりつけ医のリストを拠点施設及びデータセンターに送付する。
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・CRC は，研究開始時及び 6 ヶ月に 1 回，かかりつけ医のもとで CKD 管理ノート及び診療録からデータを収集し，収集したデータをデータセンターに送付する。
・CRC は，サブコホート研究での参加者への調査補助を行う。

厚生労働科学研究費補助金（腎疾患対策研究事業）

研究成果の刊行物・別刷

研究成果の刊行に関する一覧表

論文発表

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
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Clin Exp Nephrol (2010) 14:144–151
DOI 10.1007/s10157-009-0249-4

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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Received: 11 June 2009 / Accepted: 10 November 2009 / Published online: 18 December 2009

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

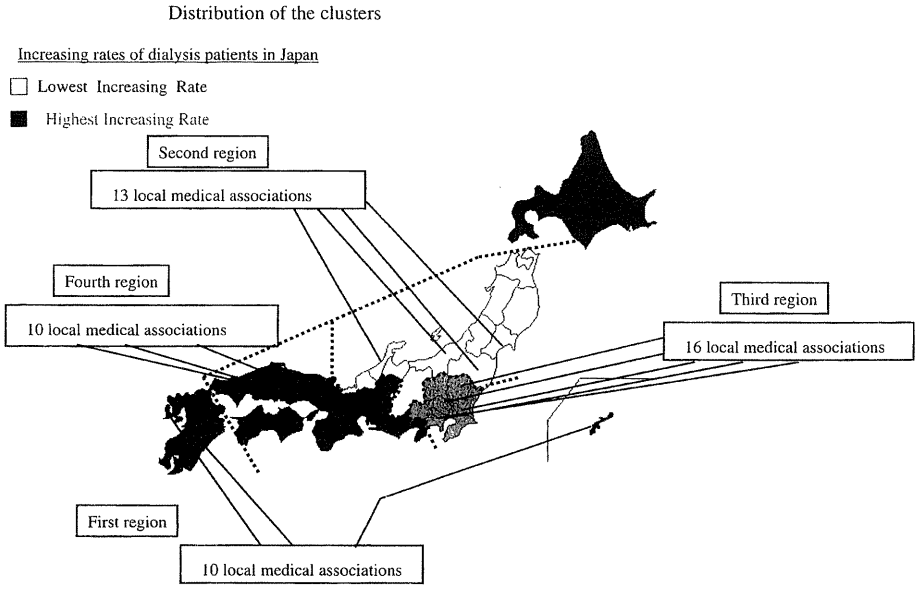

Fig. 1 Distribution of the clusters. We have recruited 49 local medical associations (clusters) in 15 different prefectures, which were classified into four regions (strata) based on the level of increase in the rate of dialysis patients [17]

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 ≥ 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 ≥ 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:

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

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.

Acknowledgments We express our thanks to the doctors and dietitians who participated in this study. We also express our thanks for the continuous support from members of the Japanese Society of Nephrology, the Japan Dietetic Association, and the Japanese Medical Association. We further thank Dr. Toshiyuki Imasawa, Dr. Chie Saitoh, Dr. Hirayasu Kai, Dr. Hideto Takahashi, Dr. Masafumi Okada, and Ms. Mariko Doi for valuable discussion and preparation of this manuscript. This study was supported by a grant for a strategic outcome study project from the Ministry of Health, Labor, and Welfare of Japan.

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Clin Exp Nephrol (2010) 14:340–348
DOI 10.1007/s10157-010-0304-1

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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Received: 10 December 2009 / Accepted: 25 May 2010 / Published online: 22 June 2010

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

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

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Introduction

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

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

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

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

Materials and methods

Instrument for measuring quality-adjustment weights

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

Study design and subjects

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

Study variables

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

Statistical analysis

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

Results

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

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

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

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

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

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

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