伊藤貞嘉 氏

5の患者は年間約50%で透析導入となっています。

井関　健診受診者を調べたところ，クレアチニン値2 mg/dLを超えた時点から，透析導入まで平均64か月，約5年でした。

伊藤　患者数についてはいかがでしょうか。

井関　久山町研究では，1974年から10年ごとに調べられていて，eGFR 60 mL/分/1.73 m^2未満のCKDステージ3，4，5が，男女ともに28年前は5〜6%でしたが，現在10%を超えています。ステージ5Dだけではなく，そのもとになるステージ3，4も確かに増えています。

渡辺　日本腎臓学会の疫学ワーキンググループで，8つの一般住民健診のコホート約90万人のデータを解析した結果，CKDのステージ1〜5は全体の11%程度を占めました。これは国民健康保険の健診結果がほとんどで，年齢がやや高齢に偏り，多少バイアスがかかっているとは思います。ただ，米国の国民健康栄養調査（NHANES）でも全体の約10%，オーストラリアなどの先進国の調査でもほぼ10%を超えていて，日本も10%を超えていると考えてよいと思います。

■メタボリックシンドロームと関連

伊藤　CKDが増加している背景については，いかがでしょうか。

井関　高齢者人口が増えれば，eGFRの低い人が増えるはずです。米国の人口分布に補正して比較すると，ステージ3，4の患者はほぼ同率でした。日本は，これから団塊の世代が高齢者となります。それで，ステージ3が8%程度となります。日本は高齢者が多いのですが，米国でも10年前に比べ約3割増加しているので，その背景には糖尿病やメタボリックシンドローム，抗菌薬やNSAIDs（非ステロイド性消炎鎮痛薬）といった薬剤使用など，さまざまな環境要因が加わっていると考えています。久山町研究の結果も，メタボリックシンドロームを背景として，腎機能の悪い人が増加しているという解釈がほぼ成り立ちます。

渡辺　茨城県の健診をフォローアップした疫学研究によると，蛋白尿の出現率には糖尿病と高血圧の寄与が大きく，肥満，脂質異常症，喫煙と続きます。現在のCKDの主たる原因は生活習慣病であると考えられます。世界的にみても，CKDの多い地域は糖尿病の発症率が高く，アジアで糖尿病の今後の増加が見込まれているので，CKDの増加も予想されますね。

特定健康診査からみたCKD

■尿検査の必要性

伊藤　渡辺毅先生，CKDの早期発見はどこまで実現できているのでしょうか。

渡辺　CKDの早期発見・早期治療には2つの問題があります。1つは健診によって，症状もなく，かかりつけ医をもたない人のCKDをいかに見つけるかということです。もう1つは，糖尿病や高血圧など，他の疾患の受療者のなかからCKDをどう発見するかです。

前者では，健診時になんらかのかたちで腎機能を評価する必要があります。2008年に開始された特定健診では，尿蛋白測定だけが必須項目

で，血清クレアチニン測定が必須ではないため，CKD が発見しにくいという状況になりました。

井関　沖縄の調査結果をみると，透析患者で健診を受けている人もいます。その人たちを除き血清クレアチニン値 10 mg/dL で透析を受けていない人も，数はそれほど多くないですが，実際にはおられます。たしかに貧血はあるし，症状もありました。

渡辺　日本の場合には，学校検尿もあるし，健診もなんらかのかたちでほぼ全員に受ける機会はあります。2008 年は特定健診が開始されたばかりで，手続き上の問題もあって，受診率はかなり低下しました。2005 年の健診受診率は全体で約 44%でしたが，2009 年は 20%台と予想されています。今後の上昇は見込まれていますが，健診制度の整備上の問題，どの項目に重点を置くかという問題と同時に，健診の意義を市民に啓発することが重要だと考えています。

問題の 2 つめに関しては，かかりつけ医が，生活習慣病などの高リスクの方々に対して，定期的に CKD をスクリーニングする必要があります。実際には血清クレアチニン測定は行っていても，尿検査をされないことも多いようです。血清クレアチニン測定は eGFR も重要ですが，定期的な尿検査の実施が，CKD の早期発見では最も大事だと思っています。

伊藤　滋賀県では，糖尿病患者における毎年 1 回の尿検査の実施率が約 20%でした。それで，啓発活動が重要だと思われます。患者が医師に，「私の尿蛋白は何 mg 出ていますか」など，血圧値を聞くのと同様に，自分から聞いてもらうようになるのが最善ですね。

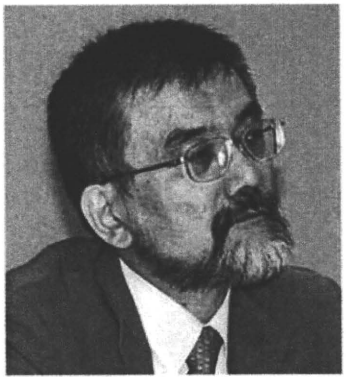
CKD と心血管病との関連

■CKD と心血管病の予後

伊藤　CKD で危惧される問題のひとつに心血管病の合併があります。斎藤能彦先生，海外で言われているように，日本でも CKD をもつ人は心血管病の予後が悪いのでしょうか。

渡辺　毅 氏

斎藤　日本循環器学会総会でも，CKD はたいへん注目されていて，関連するプログラムも多く組まれています。日本でも最近，疫学的なスタディがいくつか報告されました。1 つは，北海道大学の筒井裕之先生が行われた JCARE-CARD (Japanese Cardiac Registry in CHF-Cardiology) という慢性心不全の登録研究です。もう 1 つは，東北大学の下川宏明先生が行われた東北慢性心不全登録（CHART：Chronic Heart Failure Analysis and Registry in the Tohoku District）です。両者とも，いわゆる CKD の診断基準を満たす人が驚くほど多かった。JCARE-CARD では約 7 割の人が CKD のクライテリアに入っていますし，CHART でも半分弱の人が満たしていました。実際に ADHERE (Acute Decompensated Heart Failure National Registry) という米国の登録研究，それは心不全の急性増悪症例の登録研究ですが，男性の 60%，女性の 90%が CKD だという成績になりました。日本も米国も同様に CKD は心不全に高率に合併していることが示されています。すなわち，循環器疾患の入院患者，あるいは受診中の患者の約半数は CKD を合併していると考えて，ほぼ間違いない状況です。



井関邦敏 氏

しかも，心不全の予後は，eGFR の値が低いほど悪いことが明らかであります。循環器疾患のケアをするうえで，腎機能を無視して治療することはありえない，という時代になっています。

ところが，心不全の大規模臨床試験はこれまでにもかなり行われていて，エビデンスは集積されつつあります。しかし，多くのエビデンスでは腎機能の悪い人が除かれていることが問題となります。ただ，それは血清クレアチニン値が 3 mg/dL 程度以上を除外していることが多いので，いわゆる eGFR で分けると，腎機能の悪い人もかなり入ってきており，CKD 3 程度までは，これまでのエビデンスを利用できるかもしれません。しかし，CKD の人をきちんとスクリーニングして，それらの人だけを対象にしたエビデンスが報告されるようになってもらいたいと思います。

事実，CKD で透析をしている人では，透析をしていない患者でエビデンスのある薬剤が有効でないことが示されております。たとえばアンジオテンシン変換酵素（ACE）阻害薬でも，スタチンでも同様です。そういった意味では，循環器医と腎臓医が一緒になってエビデンスづくりをする必要があります。

伊藤　心不全などの登録研究の場合，eGFR そのものが，他のリスク因子を一致させても出てくるということですか。

斎藤　はい。独立したリスク因子なのです。最も強く影響したのが，私たちのデータでは，eGFR，その次が脳性ナトリウム利尿ペプチド（BNP）でした。

伊藤　疾患別では，心不全以外の心筋梗塞や脳卒中も同様でしょうか。

斎藤　われわれのデータでは，200 例ほどの急性心筋梗塞を対象に検討すると，eGFR できれいに予後が決まっていました。

井関　2009 年 10 月の KDIGO Controversy Conference では，115 万人のデータでメタアナリシスを行い，全死亡，心血管死，透析導入，CKD の進行の 4 つのアウトカムとの関連を検討しました。現在，論文報告の準備中ですが，4 つのアウトカムとも GFR が低下するほど増加し，また蛋白尿（アルブミン尿）が多いほど多くなります。

伊藤　実は，それに異を唱える成績が宮城県陵の調査から出ました。慢性腎炎の患者は，収縮期血圧が 130 mmHg 程度にきちんと管理されていれば，心血管疾患の年間発症率は，高血圧，糖尿病患者などと比べ，非常に低いという結果になりました。ですから，CKD の人は心血管病を起こさないということになります。

渡辺　それは大事なポイントを含んでいます。今までの多くの研究は，原疾患を無視して，CKD などの心血管イベントの発生率を解析します。一方で，脳卒中や心筋梗塞を発症したほうから振り返ってみると，糖尿病が半数以上，CKD が 1/3 という結果です。CKD の原因別に予後を解析すると，どのような結果になるのでしょうか。

斎藤　そこまではまだ明らかではないと思います。CKD の定義では，たとえば eGFR が 60 mL/分/1.73 m^2 以上の症例は蛋白尿や形体異常を伴っていることになりますが，CKD でみるとステージ 3 のところで人数が増えているのです。だから，ステージ 3 のなかには 60 mL/分/1.73

m^2未満というだけでステージ 3 に分類されている人が多く含まれ，蛋白尿を呈さない人がかなり含まれていますね。

糖尿病性腎症を対象にわれわれが実施した調査でも，eGFR60mL/分/1.73 m^2未満で顕性蛋白尿の人は 10 数%でした。だから，明らかに違う病態が混じっているので，そこを分けて考えていかないと，その後のケアに影響します。

■尿蛋白・アルブミン尿測定の意義

伊藤　尿蛋白が出ていると，本当に心血管系のリスクが高くなるのでしょうか。

渡辺　心血管イベントに関しては，有名なオランダの PREVEND（Prevention of Renal and Vascular End Stage Disease）研究という住民健診結果解析をみると，かなり低い程度のアルブミン尿から，つまり，微量アルブミン尿とされる範囲よりさらに低いところから，心血管系イベントのリスクが上昇しています。アルブミン尿に関しては腎不全の予知マーカーというより，心血管系イベントの予知マーカーで，なんらかの血管障害をみていると推測されます。これは腎臓病という概念でとらえるのがよいのかどうかは不明ですが，CKD の観点からアルブミン尿の問題を言えば，日本の統計ではステージ 1，2 がきわめて過小評価されていると考えられます。なぜなら，日本の健診では尿定性検査のみ実施しているので，アルブミン尿がほとんど見逃されているからです。米国の NHANES にはアルブミン測定が含まれています。だから，ステージ 1，2 が日本に比べ何倍も多くなっているのです。日本にもアルブミン測定が加われば，CKD 患者が多くなると思います。

井関　CKD の定義である「慢性」の意味は「3 か月以上」ということです。健診は年 1 回だけですから，通常 1 回のみのデータで CKD としています。3 か月以内で 2 回以上を慢性とするという可能性もあります。現在，急性腎障害（acute kidney injury：AKI）の慢性化と関連して

斎藤能彦 氏

議論されています。

伊藤　一般住民健診などでも，蛋白尿にさらに注目すべきです。一般住民のなかで腎炎患者はそれほど数が多くないので，マスとしてみると，尿蛋白がプラスマイナスと出ている人は明らかに血管や糸球体に障害があると考えて，間違いないと思います。

渡辺　アルブミン尿測定または尿蛋白擬陽性をどう位置づけるかが大事だと思います。高血圧患者でも微量アルブミン尿は 3〜4 割にみられ，糖尿病患者とそれほど変わりません。基本的に，血管障害を反映する検査で糖尿病性腎症の早期診断に特化する検査ではありません。

CKD と医療経済

伊藤　特定健診などを含め，社会的に問題になるもののひとつが医療経済です。CKD は，医療経済的にみて，いかがでしょうか。

渡辺　これは，井関先生が委員長をされている検尿の効果検証委員会でも大きなテーマのひとつです。たとえば，特定健診で血清クレアチニン値を測ることのコストベネフィットの解析です。でも，これは非常にむずかしいです。早期に発見して早期に介入するために，健診の費用

が多くなります。また，介入すると，薬剤費やその他で多数の費用を投入することになるので，さらに増加します。しかし，その結果，透析費用の削減と，またCKDは末期になればなるほど，さまざまな治療費が加算されていくので，それらの費用をいかに減らせるかです。マルコフモデルという医療経済モデルから算出するプロジェクトが進んでいますが，結果はまだ出ていません。現在，健診データなどを含めて，既存のデータから健診システムごとに収支の算出を試みています。ただし問題なことに，多数の人々を健診するわけですから，医療経済的に持ち出しが多くなる可能性もあるような気がしています。しかし，こういう問題は医療経済の立場のみで議論してもらっては困ります。われわれ医学者がなすべきことは，必要となる経費の収支を具体的に提示したうえで，同様にメリットも示すことだと思います。研究者ができるのはここまでで，そのあとは，一般の人々や政治家，行政者がどの程度ベネフィットを収支との比較で評価するかにかかっています。つまり，政治的になるのです。

井関　医療費に関しては，米国のデータはありますが，それを日本に当てはめるわけにはいきません。

渡辺　腎炎患者の割合がまったく違います。医療経済解析は，疾患構造，医療制度の異なる国ごとに行う必要があります。

伊藤　おそらくコストは，原疾患によっても違ってくるし，その後に寝たきりや介護の問題が入ってくるので，算出は相当に困難です。ただ，これは経済だけの問題ではなく，福祉や健康をどう考えるかという基本的な姿勢を，社会全体で議論していかないといけません。

今後の課題

■スクリーニング後の指導

伊藤　CKD診療の課題はいかがでしょうか。

渡辺　最大の問題は，一般市民がどの程度CKDを理解しているかということだと思います。非常に厳しい状況にあります。J-CKDIには，日本腎臓学会，日本透析医学会，日本小児腎臓学会，日本医師会の代表が参加し，オブザーバーとして日本腎臓財団も加わっています。J-CKDIは数年前からCKD啓発のため，さまざまなイベントを全国で展開しています。2009年から，厚生労働省が，CKD対策費として予算をつけてくれ，都道府県単位で組織を整備し，糖尿病対策推進会議に相互協力してもらうよう推奨しています。まだ，J-CKDIの活動は始まったばかりです。

伊藤　こういう大きな問題には，マスコミが関与しないといけないと思っています。たとえば，米国では，“ファイトザストローク”といったキャンペーンが成功しています。簡潔で明確なメッセージをテレビやラジオで繰り返し実施するといった，多くの人に知ってもらう努力をするべきだと思いますね。

渡辺　公共放送に関しては，いろいろ取り上げていただいてはいますが，まだ不十分ですね。米国では，たとえばコレステロールに関しては公共的なキャンペーンの成果が現れ，国民の血清コレステロール値は減少してきています。一方で，日本は逆ですね。女性の平均血清コレステロール値は米国を抜き去りました。

伊藤　かかりつけ医の方々に対する啓発は，すでに十分なわけですか。

斎藤　CKDはほぼ認知されているようですが，大事なのは，かかりつけ医の先生方には最初の一ことを患者さんに告げる際に留意していただきたいと思います。「このくらいは大丈夫ですよ」と言ってしまうと，一般の人は「症状が何

もないから，このままでよいのだ」と，誤解してしまいます。その時に「これは，腎機能が低下しているので，十分に気をつけ，血圧やその他原因になる因子の治療を行う必要があります」と言ってほしいのです。実地医家の先生に対するコンセンサスづくりが重要になっていると思います。特定健診の次に受診する医師が必ずしも内科専門ではなかったりするので，最初のひとことへの注意を喚起する必要があると考えています。

伊藤　確かに，実地医家や専門外の医師が，CKD のステージ 3 の患者に対し，次の対応はどうすればよいのか，さらにどこにいったらよいのかを，きちんと示す必要がありますね。

渡辺　特定健診に関して腎臓だけでみると，健診項目に血清クレアチニン値がないことは問題を感じていますが，それが本当に問題なのかどうかを証明しないといけません。特定健診は，本来は一次予防を重視している保健指導を含む制度で，一次予防をシステム化した点は評価しないといけないと思います。しかし，メタボリックシンドロームに偏りすぎている感は否めません。日本の健診データで調べてみると，CKD 患者の 6 割以上はメタボリックシンドロームではありませんでした。日本の糖尿病患者や高血圧患者もそれほど太っていません。また，保健指導の在り方は，これらの点も踏まえて，科学的に検討する必要があると思います。

もう 1 つ，厚生労働省「腎疾患重症化予防のための戦略研究」(FROM-J) が，筑波大学の山縣邦弘先生をリーダーにして，全国 15 拠点で行われています。目的は，CKD 診療について，かかりつけ医と腎臓専門医との連携による効率的医療体制の模索です。これには，3 つの段階があります。第 1 段階が健診からかかりつけ医受診までで，かかりつけの医師が CKD を診断して医療の土俵に乗せるかの問題です。第 2 段階はかかりつけ医が CKD を腎専門医に紹介すべきかの判断をすること，次に紹介しない CKD 患者の原疾患である生活習慣病などの管理をすることです。また，腎専門医から逆紹介を受けた患者の管理も重要です。第 3 段階が，かかりつけ医から紹介されて，専門医が CKD の原疾患を診断して，治療方針を立て治療する段階です。安定した患者は，かかりつけ医に逆紹介することも重要です。これらの 3 段階をどう連携させ整備するかということで，制度をどのように設計していくか，考えていく必要があります。

伊藤　以前，仙台市で産婦人科の先生方の集まりに行き，二次性高血圧の発見について講演したことがあります。産婦人科の先生方には，非常に参考になったそうです。内科以外の他科の領域の先生方には，CKD の情報がどの程度伝わっているのか，少々疑問に思っています。

渡辺　実は，CKD 診療ガイドが最も役立ったのは整形外科領域なのだという話もあります。腎機能が悪い人に NSAIDs を使用している場合に，薬剤の使い方に留意するようになったという意味です。つまり，医療連携システムには他科の先生も含まれ，診療ガイドはその媒介として重要です。

井関　あれは非専門医へのガイドですから，目的はかなり達したというわけです。

伊藤　アンケートで，CKD について最も知らなかったのが大学病院の医者だということがわかりました。大学病院全体でみると，腎臓に関連する科以外はなじみがないようです。

井関　私どもも戦略研究に参加していますが，基幹病院がある医師会では CKD の紹介率が悪いのです。特定健診などを契機とした専門機関への紹介率が一番低いのは大学があるところでした。

渡辺　大学があまりにも縦割りになりすぎています。その是正には，CKD の問題はまさに良い機会になります。CKD は，概念的に腎臓病，心臓病や脳血管障害が関連し，いわば全身の病態なのです。もう 1 つ大事なのは，そういうことを大学や専門病院の医師が認識することです。

さらに，われわれが教育を受けたころには腎臓病は治らないと教えられましたが，それが30年後も尾を引いています。今，そういう誤解を払拭しておかないと，30年後まで，将来かなり尾を引くことになると思います。教育体制が大事だと思います。

伊藤　そうですね。多くの人に共通する情報をできるだけ広範囲に正確に伝えられるシステムを作っておかないといけません。

斎藤　心・腎連関という言葉ができたので，カテーテルを使用している先生が，造影剤の使い方を以前よりは気をつけておられます。そういう意味で，言葉ができるのは良いことです。

■CKD患者の血圧管理

伊藤　CKDの管理で不十分だと思うことに，高血圧患者への対応があります。そのあたり，いかがでしょうか。

井関　日本では，男性の糖尿病患者は女性の2倍です。40代～60代の男性は，仕事をしていますので，高血圧の管理があまりなされていません。未治療者は，男性が圧倒的に多いです。肥満もありますが，糖尿病も管理されているのかなと思います。

渡辺　喫煙率も高いですね。

井関　啓発情報なども，男性には届きにくいようです。

伊藤　次の対策で重要なことは，生活習慣の是正ですね。特に塩分の問題は，キャンペーンをしても，なかなか思うようにいかないです。

渡辺　減塩，肥満，喫煙などの問題は，やはりマスコミによる啓発が重要かもしれませんね。

■CKDの概念の普及・啓発

伊藤　CKD対策全般に関し，今後の課題をお話しくださいますか。

渡辺　課題を大きく2つに分けると，1つは健診，保険制度などの社会システムの問題，もう1つは高血圧，糖尿病，喫煙などの生活習慣改善啓発の問題があります。コスト面から考えると，この両面でコメディカルの人にいかに活躍してもらうかが重要な鍵になります。そのためには，コメディカルの活動の達成度を評価して，なんらかのかたちのインセンティブをつけることが大事だと思います。それが，大きな視野からみれば，医療費の削減につながるのではないかと思います。腎臓疾患の関連では，CKD対策指導料といったものが，保険制度上，いつも削られています。指導の際には，糖尿病と同様，コメディカルの人が中心になる必要があります。そういう意味で，戦略研究で栄養ケアステーションが各地にできていますので，広がっていくとよいと考えています。一方，メタボリックシンドロームが国民に理解されたように，なんらかのかたちで，CKDの概念を刷り込んでいくことが重要で，口コミもかなり大事かなという気がしています。

斎藤　市民講座を行うと，参加者は高齢の人が多いのです。日本は，40代の若い人が集まりにくい社会なのでしょう。だから，そこを変えないといけません。

伊藤　昔，ヘンリー・フォード病院の車庫を出たところに，「あなたの健康はわれわれの財産だ」と書いてありました。米国では，勤めている人たちのヘルスケアをきちんと行うシステムが構築されています。日本は徐々に，それを切り捨てるような方向にいき始めていますね。それは，いろいろな意味で逆にコストを上げてしまうという懸念があります。たとえば，正規雇用の社員から派遣社員になってしまい，責任がなくなっています。構造的に問題だと思います。健診で疾患発見された人は，きちんと受診して治療しないかぎり働かせないなどの対策も重要です。すると，血圧は下げられる。糖尿病や肥満までは無理かもしれないが，血圧を下げただけでも相当効果があると思います。特に，40代，50代の未治療の人たちには必要です。

渡辺　もう1つ，研究予算の問題もあります。

米国と異なり，臨床研究，治験を含めて日本の研究は，企業からの支援に依存していることが多いです。ただ最近は，戦略研究などの大型の公的研究が出てきたので，少しは改善されてきています。要は，直接的な経済利益とは関係がない，真に国民の福祉向上につながる研究に予算をつけることが大きく影響すると思います。

斎藤　やはり経済的なことを考えて，実現可能な方法を研究しないといけないと思います。多くの費用が必要なことを実施することは，国民全員には不可能です。たとえば尿検査も，デップスティックはよいが，アルブミン尿の検出は保険でカバーされていないので，実地医家の先生には測定しにくい現状があります。現状の手持ちの道具を，いかに上手に使用するか，費用負担が少ない方法を研究することも必要だと思います。

井関　もう１つ問題なのは，血尿です。アジア人には腎炎が多いので，血尿をなんとかKDIGO の CKD の概念中に含めようと検討しています。血尿がある人は蛋白尿が出やすいこともわかっています。腎炎は別個の問題だという気がします。

斎藤　日本高血圧学会の高血圧治療ガイドラインには，血尿＋尿蛋白は生検の対象となっています。

渡辺　日本腎臓学会と日本泌尿器学会合同で，血尿に関するガイドラインが作られていて，今度改訂作業に入ります。どのように，腎生検など，特殊検査にもっていくかの指針は今でも一応作ってあります。

腎機能評価の場合には，クレアチニンを使用した式には欠点もあるので，シスタチン C を使った推算式を検討すべきで，現在進んでいます。

井関　糖尿病性腎症は特に違います。糖尿病の人では eGFR はあまり正確ではありません。

伊藤　短期的には，今あるクレアチニンのほうがシスタチン C より安価ですから，どういう流れで最も経済効率良く，かつ見落としもせずに予後に結びつけられるかという研究が大事です。それと同時に，なんでも最初は高価なので，未来に向かっては，シスタチン C のほうが良いということにもなります。大量に行うようになれば，コストも下がります。基礎研究も重要です。

透析療法に関してはどうでしょうか。

井関　透析療法に関して画期的な進歩はありません。しかし，透析量の問題，CAPD（持続式携帯型腹膜透析）の低普及，併用療法（血液透析と CAPD）など，いろいろ課題があります。ナーシングホーム入所者に血液透析を導入すると，ADL（日常生活動作能力）はもちろん，治療意欲がどんどん落ちて，米国では死亡率が１年間で 60％と報告されています。以前から気になっていましたが，わが国でも老人ホーム，介護施設入所者では見逃されているケースが多いのではないかと思います。高齢者医療では腎機能にもう少し留意する必要があります。

渡辺　社会的な問題としては，移植をさらに推進しないといけません。

伊藤　腎臓領域には，最先端のバイオマーカーやメカニズムの研究から，社会的な移植医療まで，さまざまな問題が山積しています。その解決は，なかなか困難です。CKD に関しては，心血管疾患のリスクであると同時に，透析療法が必要になるなど，多数の不利な点があります。このことを，できるだけ多くの人に知ってもらうことが，われわれの努力の第一歩かなと思います。本日の座談会が少しでもそのお役に立てばと思います。どうもありがとうございました。

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Trends in the prevalence of chronic kidney disease and its risk factors in a general Japanese population: The Hisayama Study

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Abstract

Background. Chronic kidney disease (CKD) is increasingly recognized as a leading public health issue. However, there are limited data assessing secular trends in the prevalence of CKD in general Asian communities.

Methods. We performed three repeated cross-sectional surveys of residents aged ≥40 years in 1974 [2118 subjects (participation rate, 81.2%)], 1988 [2741 subjects (80.9%)] and 2002 [3297 subjects (77.6%)] in a Japanese community. We compared the prevalence of CKD [one or both of proteinuria and estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2] and potential risk factors among the three surveys.

Results. The prevalence of CKD increased significantly with time in men (13.8% [95% confidence interval (95% CI), 11.4–16.2%] in 1974, 15.9% [95% CI, 13.6–18.2%] in 1988 and 22.1% [95% CI, 19.6–24.6%] in 2002; P for trend < 0.001), but not in women (14.3% [95% CI, 12.2–16.4%], 12.6% [95% CI, 10.9–14.3%] and 15.3% [95% CI, 13.4–17.2%]; P for trend = 0.97). The frequencies of individuals with CKD Stages 3–5 (eGFR < 60 mL/min/1.73 m^2) increased over the three decades in both sexes. Despite the widespread use of antihypertensive agents, the proportions of individuals with CKD who reached blood pressure of <130/80 mmHg were only 27.0% in men and 47.5% in women. The frequency of metabolic disorders including diabetes, hypercholesterolaemia and obesity increased over the three decades in both sexes.

Conclusions. The prevalence of CKD increased significantly in men, but not in women over the last three decades in a general Japanese population. Our findings support the requirement for a comprehensive treatment for hypertension and metabolic disorders to reduce the burden of CKD.

Keywords: chronic kidney disease; general population; hypertension; metabolic disorder; prevalence

Introduction

Chronic kidney disease (CKD), most commonly defined by a reduction in kidney function or the presence of proteinuria [1,2], is increasingly recognized as a leading public health issue. The number of patients with end-stage kidney disease has been expanding rapidly and is predicted to exceed 2 million worldwide by the year 2010 [3]. Furthermore, it has been established that CKD is a risk factor not only for progressive kidney failure, but also for cardiovascular morbidity and mortality [4–6].

Several cross-sectional studies have demonstrated that CKD affects 10–15% of the adult population in developed Western countries [7–9]. Recent epidemiological studies have suggested that CKD may be more prevalent in Asian countries than in developed Western countries [10,11]. Furthermore, it has been reported that the number of patients undergoing dialysis in Asian countries such as Malaysia and Japan has been increasing [12,13]. It is likely that the prevalence of CKD would increase over time as a consequence of the accumulation of risk factors such as hypertension, glucose intolerance, obesity and hypercholesterolaemia, probably owing to the westernization of the lifestyle in these Asian countries. However, there are limited data assessing secular trends in the prevalence of CKD in general Asian communities to date. A better understanding of the past and current prevalence of CKD and its potential risk factors may provide useful information for the development of management strategies for CKD.

The Hisayama Study is a community-based cohort study that has been underway since 1961, with a goal of estimating the effects of the remarkable lifestyle changes on the burden of cardiovascular diseases in Japan [14–17]. The aim of the present study is to assess trends in the prevalence of CKD and its risk factors over the last three decades and to examine their relationships.

Subjects and methods

Study population

The town of Hisayama is a suburban community adjacent to Fukuoka City, a metropolitan area on Kyushu Island in southern Japan. The population of the town has been stable for 50 years and was approximately 8000 in 2008. The age and occupational distributions of the Hisayama population are almost identical to those of Japan as a whole. Full commu-

nity surveys of the residents have been repeated from the initiation of the study to date. The study design and characteristics of the subject population have been described in detail elsewhere [14–18]. Briefly, four study cohorts composed of Hisayama residents aged ≥40 years were established in 1961, 1974, 1988 and 2002. For this study, we used data from the cross-sectional surveys conducted at baseline in the latter three cohorts, which included available data on serum creatinine and proteinuria. The full community surveys were conducted as follows. In 1974, we invited all 2629 residents in that age group in the town registry to participate in the survey by the assistance of the town office, and of those, 2135 (participation rate, 81.2%) consented to participate in the health examination. After excluding 17 subjects for whom blood samples were unavailable, 2118 subjects (911 men, 1207 women) were enrolled in this study. In the same manner, 2741 subjects from 2742 participants (participation rate, 80.9%) in 1988 and 3297 subjects from 3298 participants (participation rate, 77.6%) in 2002 were enrolled in the study. A total of 3059 (38%) subjects participated in two or more of the three surveys.

Definition of CKD

Details of the measurement of risk factors in each survey were described previously [15,16,18,19]. Freshly voided urine samples were tested by the dipstick method in all surveys. Proteinuria was defined as 1+ or more. Serum creatinine was measured by the non-compensated Jaffé method in 1974 and 1988 and the enzymatic method in 2002. Serum samples were assayed using a Technicon autoanalyser (Technicon Instruments, Tarrytown, NY) in 1974, a TBA-80S autoanalyser (Toshiba Inc., Tokyo, Japan) in 1988 and an AU-800 autoanalyser (Olympus Corporation, Tokyo, Japan) in 2002. The difference between the serum creatinine levels by the Jaffé method and those by the enzymatic method was calibrated by using 98 serum samples standardized by CRC Corporation (Fukuoka, Japan). The range of creatinine levels in the samples was 0.5 to 15.2 mg/dl by the Jaffé method. The conversion equation was estimated by using a simple linear regression model. The correlation coefficient of this equation was 0.996. The Jaffé method value was converted to an enzymatic method value by using the following equation:

$$\text{Serum creatinine (enzymatic method [mg/dl])} = 0.9754 \times \text{serum creatinine(Jaff amethod[mg/dl])} - 0.2802.$$

The estimated glomerular filtration rate (eGFR) was calculated using the isotope dilution mass spectrometry–traceable creatinine-based four-variable Modification of Diet in Renal Disease (MDRD) Study equation with the Japanese Society of Nephrology Chronic Kidney Disease Initiatives coefficient of 0.741 [20]. eGFR was derived using the following equation:

$$\text{eGFR}(\text{mL/min/1.73 m}^2) = 0.741 \times 175 \times \text{serum creatinine(enzymatic method[mg/dl])}^{-1.154} \times \text{age(years)}^{-0.203} \times 0.742(\text{if female})$$

CKD was defined as either the presence of proteinuria or eGFR < 60 mL/min/1.73 m^2. The clinical stages of CKD were classified according to the recommendations of the National Kidney Foundation Kidney Disease Outcomes Quality Initiative guidelines [1]: Stage 1 or 2 (eGFR ≥ 60 mL/min/1.73 m^2 and the presence of proteinuria), Stage 3 (eGFR 30–59 mL/min/1.73 m^2) and Stage 4 or 5 (eGFR < 30 mL/min/1.73 m^2).

Risk factors

In each survey, blood pressures were measured three times in a sitting position after at least 5 min of rest, and the mean of the three measurements was used for the analysis. Hypertension was defined as a mean systolic blood pressure ≥140 mmHg or a mean diastolic blood pressure ≥90 mmHg or a current use of antihypertensive agents. Subjects with hypertension were classified as treated or untreated based on whether or not they were currently using antihypertensive agents. Diabetes was defined by fasting glucose concentrations ≥126 mg/dl (7.0 mmol/L) or postprandial glucose concentrations ≥200 mg/dl (11.1 mmol/L) in addition to medical history of diabetes in 1974 and by those methods and a 75-g oral glucose tolerance test in 1988 and 2002. Diabetes was regarded as treated when the subject was under therapy with insulin or hypoglycaemic agents in 1988 and 2002, but the designation of treated or untreated diabetes was not made in 1974 due to an absence of information on treatment status. Serum total cholesterol levels were determined by the Zurkowski method in 1974 and by the enzymatic method in 1988 and 2002. Hypercholesterolaemia was defined as serum total cholesterol ≥220 mg/dl (5.7 mmol/L) or current use of a lipid-modifying agent. Treated hypercholesterolaemia was defined as current use of lipid-modifying agents only in 2002 because information on anti-lipidaemic agents was not available in 1974 and 1988. Body height and weight were measured in light clothing without shoes, and the body mass index (in kilogrammes per square metre) was calculated. Obesity was defined as a body mass index ≥25 kg/m^2. Metabolic syndrome was defined by using criteria recommended in a joint interim statement of five major scientific organizations [21]. Information on medical history, medical treatment, alcohol intake and smoking habits was obtained through a standard questionnaire by trained interviewers. Alcohol intake and smoking habits were classified as either current habitual use or not.

Statistical analysis

The prevalences of CKD and each risk factor were adjusted for the age distribution of the world standard population in 1998 by using the direct method. The age-adjusted mean values of risk factors were calculated using the analysis of covariance method with age included as a continuous variable. Trends in the prevalence or mean values of each factor across survey years were assessed by fitting the logistic or linear regression model with evenly spaced numeric codes for the survey year, respectively. The age-adjusted relative risk (RR) and its 95% confidence interval (95% CI) for CKD were estimated by using Poisson regression analysis [22]. The SAS software package, release 9.2 (SAS Institute, Cary, NC), was used to perform all statistical analyses. A two-tailed value of $P < 0.05$ was considered statistically significant.

Results

We compared the age-adjusted prevalence and mean values of risk factors among the three surveys by sex, as shown in Table 1. The prevalence of hypertension was constant in men, but decreased in women from 1974 to 2002. The prevalence of treated hypertension increased over time, whereas the prevalence of untreated hypertension decreased in both sexes. Consequently, mean blood pressure levels decreased over the last three decades. The frequencies of diabetes, hypercholesterolaemia, obesity, metabolic syndrome and alcohol intake increased with time, whereas the frequency of smoking habits decreased in both sexes. The prevalence of diabetes, especially untreated diabetes, increased with time in both sexes.

Figure 1 presents the age-adjusted prevalence of CKD in the three surveys by sex. The age-adjusted prevalence of CKD increased significantly with time in men (13.8% in 1974, 15.9% in 1988 and 22.1% in 2002; P for trend < 0.001), but not in women (14.3%, 12.6% and 15.3%, respectively; P for trend = 0.9). The prevalence of CKD Stages 3–5 increased 3-fold over time in men (4.8%, 9.4% and 15.7%; P for trend < 0.001) and doubled in women (5.8%, 9.9% and 11.7%; P for trend < 0.001). Conversely, the prevalence of CKD Stages 1–2 decreased to two-thirds in men (9.0%, 6.5% and 6.4%; P for trend = 0.02) and by half in women (8.5%, 2.7% and 3.4%; P for trend < 0.001). Similar trends in the prevalence of CKD across the three surveys were also observed in middle-aged and elderly populations in either sex (Figure 2). There was a comparable relationship for the prevalence of

Table 1. Age-adjusted prevalence and mean values of risk factors in 1974, 1988 and 2002 by sex

	Men				Women			
	1974 $n = 911$	1988 $n = 1165$	2002 $n = 1414$	P for trend	1974 $n = 1207$	1988 $n = 1576$	2002 $n = 1883$	P for trend
Age, years	56 ± 11	59 ± 12	61 ± 12	<0.001	57 ± 12	60 ± 12	62 ± 13	<0.001
Systolic blood pressure, mmHg	139 ± 21	136 ± 21	134 ± 21	<0.01	141 ± 21	134 ± 21	129 ± 21	<0.01
Diastolic blood pressure, mmHg	79 ± 12	81 ± 12	81 ± 12	<0.01	78 ± 12	76 ± 12	76 ± 12	<0.01
Hypertension, %	42.0 (39.0–46.0)	44.4 (40.6–48.2)	42.5 (39.0–46.0)	0.90	42.0 (38.4–45.6)	34.7 (31.9–37.5)	31.3 (28.9–33.7)	<0.001
Treated, %	9.2 (7.2–11.2)	13.8 (11.7–15.9)	19.4 (17.2–21.6)	<0.001	7.9 (6.4–9.4)	13.3 (11.6–15.0)	16.8 (15.1–18.5)	<0.001
Untreated, %	32.8 (29.1–36.5)	30.6 (27.4–33.8)	23.1 (20.4–25.8)	<0.001	34.1 (30.9–37.3)	21.3 (19.0–23.6)	14.5 (12.7–16.3)	<0.001
Diabetes mellitus, %	2.5 (1.5–3.5)	14.3 (12.1–16.5)	20.6 (18.2–23.0)	<0.001	2.0 (1.2–2.8)	9.0 (7.6–10.4)	11.5 (10.0–13.0)	<0.001
Treated, %	–	2.7 (1.8–3.6)	5.6 (4.4–6.8)	<0.001	–	2.6 (1.8–3.4)	2.8 (2.1–3.5)	0.23
Untreated, %		11.5 (9.5–13.5)	14.9 (12.8–17.0)	0.002		6.4 (5.2–7.6)	8.7 (7.3–10.1)	0.01
Hypercholesterolaemia, %	12.4 (10.1–14.7)	27.1 (24.0–30.2)	26.9 (23.9–29.9)	<0.001	20.3 (17.8–22.8)	41.4 (38.2–44.6)	41.0 (38.0–44.0)	<0.001
Treated, %	–	–	6.3 (5.0–7.6)	–	–	–	8.9 (7.7–10.1)	–
Untreated, %			20.6 (17.9–23.3)	–			32.1 (29.3–34.9)	–
Obesity, %	11.3 (9.1–13.5)	24.4 (21.4–27.4)	29.4 (26.2–32.6)	<0.001	21.3 (18.6–24.0)	23.9 (21.4–26.4)	23.8 (21.4–26.2)	0.004
Metabolic syndrome, %	–	8.1 (6.4–9.8)	13.4 (11.3–15.5)	<0.001	–	16.5 (14.5–18.5)	18.6 (16.7–20.5)	<0.01
Smoking habits, %	72.2 (66.6–77.8)	50.6 (46.4–54.8)	46.7 (42.6–50.8)	<0.001	10.2 (8.4–12.0)	6.9 (5.5–8.3)	8.6 (7.0–10.2)	0.002
Alcohol intake, %	63.6 (58.4–68.8)	61.9 (57.2–66.6)	71.2 (66.2–76.2)	<0.001	5.4 (4.1–6.7)	9.8 (8.1–11.5)	29.5 (26.6–32.4)	<0.001

Age is not age-adjusted. Values are means ± standard deviations or frequencies. Hypertension was defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or current use of antihypertensive agents. Diabetes mellitus was defined by fasting glucose concentrations ≥126 mg/dl (7.0 mmol/L) or postprandial glucose concentrations ≥200 mg/dl (11.1 mmol/L) in 1974 and by a 75-g oral glucose tolerance test in 1988 and 2002 in addition to a medical history of diabetes according to the recommendations of the American Diabetes Association. Hypercholesterolaemia was defined as serum total cholesterol ≥220 mg/dl (5.7 mmol/L) or current use of a lipid-modifying agent. Obesity was defined as body mass index ≥25 kg/m^2. Treated or untreated statuses were defined as the presence or absence of use of any medication for the treatment. Metabolic syndrome was defined by using criteria recommended in a joint interim statement of five major scientific organizations.

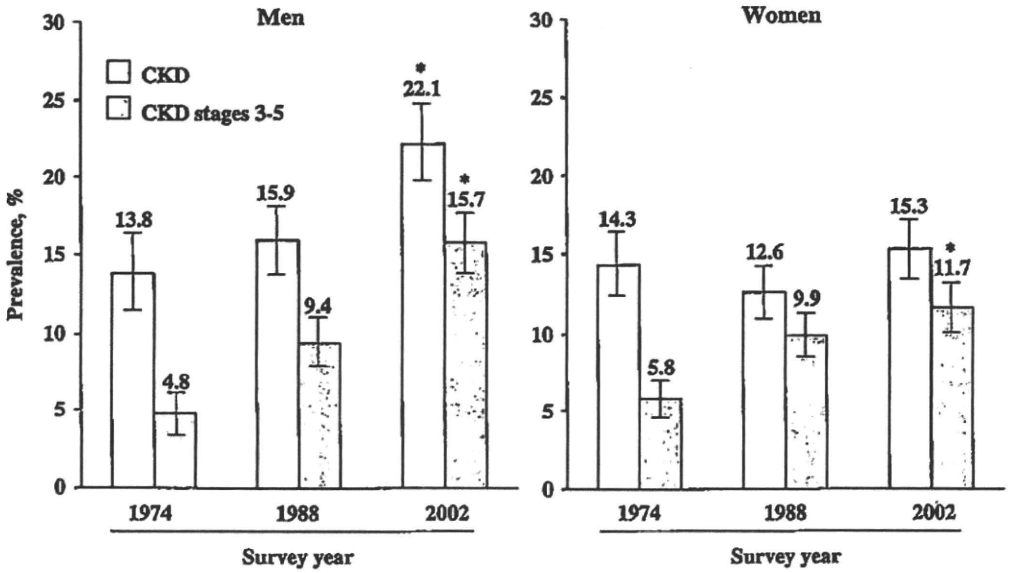


Fig. 1. Trends in the age-adjusted prevalence of CKD in 1974, 1988 and 2002 by sex.

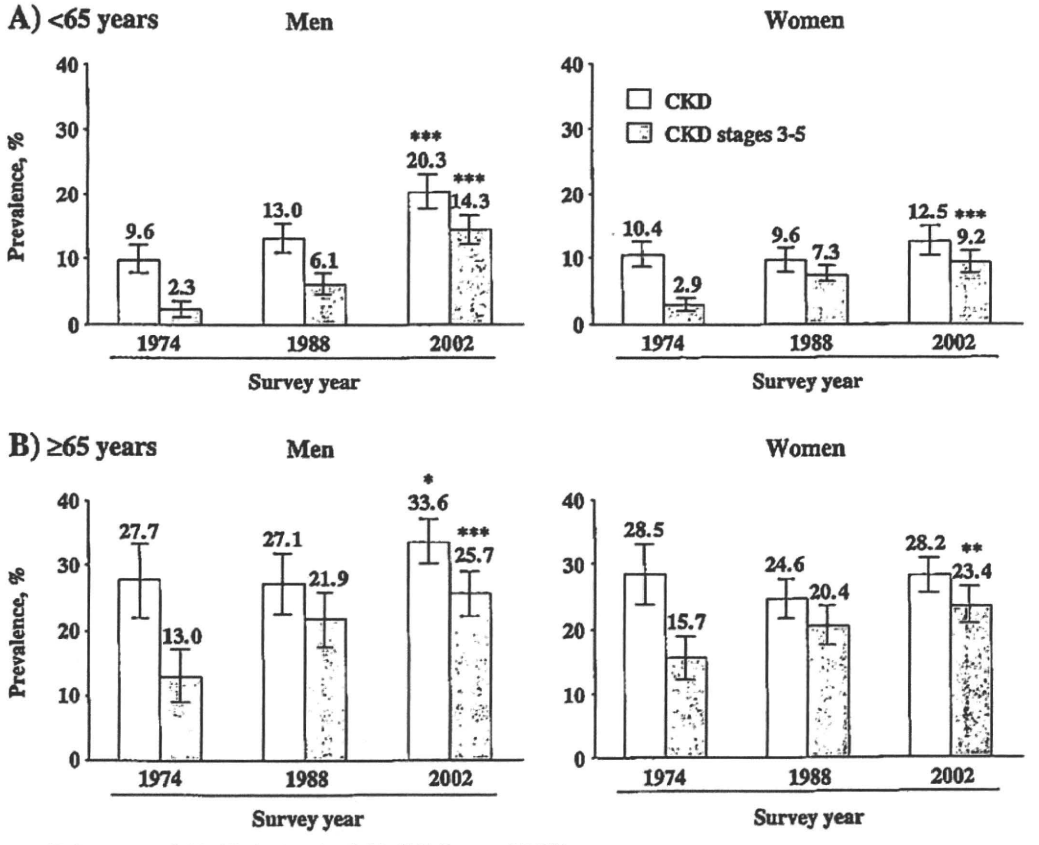
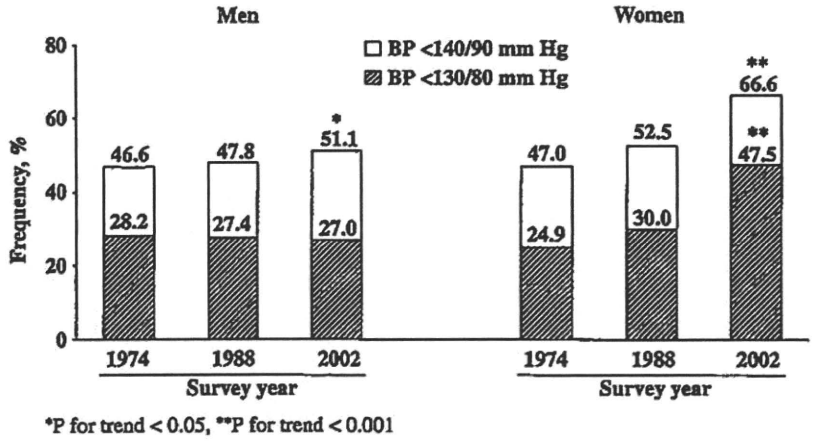


Fig. 2. Trends in the prevalence of CKD by age and sex.

CKD Stages 4–5, but the number of subjects with this stage of CKD was too small to assess reliably according to age or sex [eight subjects (0.4%) in 1974, seven subjects (0.3%) in 1988, 33 subjects (1.0%) in 2002 overall]. The number of subjects undergoing dialysis was zero in 1974, one in 1988 and 10 in 2002. The age-adjusted proportion of subjects with proteinuria did not change across the surveys in men (10.7% in 1974, 7.6% in 1988 and



*P for trend < 0.05, **P for trend < 0.001

Fig. 3. Age-adjusted frequencies of well-controlled blood pressure in subjects with CKD in 1974, 1988 and 2002 by sex.

Table 2. Age-adjusted prevalence of CKD according to hypertension status in 1974, 1988 and 2002 by sex

	Men				Women			
	1974	1988	2002	P for trend	1974	1988	2002	P for trend
Non-hypertension								
Prevalence (95% CI)[a], %	10.9 (7.6–14.2)	11.2 (8.5–13.9)	15.5 (12.7–18.3)		11.4 (8.4–14.4)	8.6 (6.6–10.6)	12.6 (10.5–14.7)	
RR (95% CI)[a]	1.00 (reference)	1.11 (0.76–1.61)	1.53 (1.09–2.17)	0.008	1.00 (reference)	0.79 (0.57–1.11)	1.13 (0.84–1.53)	0.20
Treated hypertension								
Prevalence (95% CI)[a], %	18.8 (10.7–26.9)	23.8 (16.7–30.9)	36.1 (23.7–48.5)		28.8 (15.8–41.8)	19.8 (13.3–26.3)	22.5 (10.8–34.2)	
RR (95% CI)[a]	1.00 (reference)	1.10 (0.70–1.77)	1.16 (0.78–1.81)	0.48	1.00 (reference)	0.79 (0.54–1.19)	0.72 (0.50–1.07)	0.11
Untreated hypertension								
Prevalence (95% CI)[a], %	16.6 (11.8–21.4)	17.5 (13.0–22.0)	28.8 (22.6–35.0)		15.8 (11.9–19.7)	16.7 (11.9–21.5)	19.8 (12.5–27.1)	
RR (95% CI)[a]	1.00 (reference)	1.00 (0.70–1.43)	1.65 (1.19–2.30)	0.001	1.00 (reference)	0.93 (0.69–1.27)	0.93 (0.68–1.28)	0.66

[a]Adjusted for age.

9.6% in 2002; P for trend = 0.65), but decreased significantly with time in women (10.2% in 1974, 3.8% in 1988 and 5.3% in 2002; P for trend < 0.001).

Next, we estimated the frequencies of well-controlled blood pressure in men and women with CKD in each of the three surveys (Figure 3). Among subjects with CKD, the proportion with blood pressure levels of <140/90 mmHg increased from 46.6% in 1974 to 51.1% in 2002 for men and from 47.0% to 66.6% for women, in parallel with the increment in the proportion of subjects taking antihypertensive agents. The frequency of blood pressure of <130/80 mmHg was <30% in men with CKD in all three surveys, whereas it increased from 24.9% in 1974 to 47.5% in 2002 in women. Among CKD subjects taking antihypertensive agents in 2002, 36.3% of men and 26.3% of women had a blood pressure level <140/90 mmHg, and only 11.1% and 12.8%, respectively, had a blood pressure level <130/80 mmHg. Table 2 shows the age-adjusted prevalence and RR of CKD by the status of hypertension treatment among the three surveys by sex. For men, the RR of presence of CKD increased with time in subjects with untreated hypertension (P for trend = 0.001), but not in subjects with treated hypertension (P for trend = 0.48). For women, there was no evidence of significant differences in the prevalence of CKD over time in any of the hypertension treatment statuses.

Finally, we assessed the relationship between metabolic syndrome and the risk of CKD in 1988 and 2002. Metabolic syndrome was associated with an increased risk of prevalent CKD in either sex (Figure 4). The strength of the relationship did not change over time for men (P for heterogeneity = 0.99), whereas it was attenuated significantly in 2002 compared with 1988 for women (P for heterogeneity = 0.01).

Discussion

In the present study, we demonstrated that the prevalence of CKD increased significantly in men, but not in women from the 1970s to the 2000s in a general Japanese population, whereas CKD Stages 3–5 increased progressively with time in both sexes. Importantly, more than half of

individuals with CKD did not reach the optimal target levels of blood pressure recommended by the current guidelines [23,24], despite an increment in the proportion of subjects taking antihypertensive agents over the last three decades. Furthermore, our findings implied that the recent increment in the number of subjects with metabolic disorders is linked to the increasing prevalence of CKD. These analyses, therefore, would seem to highlight the importance of the comprehensive management of metabolic disorders in addition to the strict control of blood pressure in order to reduce the burden of CKD in the general Japanese population.

The prevalences of CKD have been reported for several countries. The National Health and Nutrition Examination Surveys reported that the age-adjusted prevalence of CKD Stages 1–4 among subjects aged 20 years or older in the United States increased from 10.0% in 1988–1994 to 13.1% in 1999–2004 [8]. In Nord-Trondelag, Norway, the prevalence of CKD Stages 3–5 was 4.4% [9]. CKD may be more prevalent in Asian countries than in developed Western countries. A cross-sectional study conducted in 574 024 Japanese subjects over 20 years old demonstrated that the prevalence of CKD Stages 3–5 was 10.6 % in Japan [11]. Data from the screenings in Okinawa, Japan showed that the unadjusted prevalence of CKD Stages 3–5 among subjects aged 20 years or older increased between 1993 (10.4%) and 2003 (12.2%) in men, but decreased in women (19.5% in 1993, 17.4% in 2003), although the average serum creatinine levels increased in all age categories during this period in either sex [25]. An increasing trend in the prevalence of CKD in men was thus observed both in our study and Okinawa's study. The discrepancy observed in women between the two studies may have arisen from a self-selection bias caused by the low participation rate (<20%) in Okinawa's study, with subjects having an underlying disease (e.g. advanced kidney disease) being less likely to participate in the examination. Importantly, the prevalences of CKD in these studies were estimated on the basis of different eGFR equations, the direct comparison of which might be inappropriate. A nationwide examination will be needed to estimate the burden of CKD in Japan more reliably.

In the present study, the prevalence of metabolic disorders, such as diabetes, hypercholesterolaemia and obesity, was found to have increased dramatically over the last three decades, probably due to the westernization of lifestyle in Japan [26]. In the 2002 survey, diabetes was significantly associated with the likelihood of CKD for both sexes. Diabetes is an especially serious problem in the prevention strategy for CKD because it has been the leading cause of end-stage renal disease since 1998 in Japan [13]. Likewise, hypercholesterolaemia and obesity have been shown to be independent risk factors for CKD [27,28]. Our findings showed a jump in the prevalence of metabolic disorder from 1974 to 1988 ahead of the increment in the prevalence in CKD, possibly suggesting a causal association of metabolic disorder with the risk of CKD. In this study, furthermore, metabolic syndrome, which is defined as the accumulation of three or more risk factors such as elevated blood pressure, glucose intolerance, central obesity and dyslipidemia, was associated with an increased risk of CKD. Our previous longitudinal study has demonstrated that individuals with metabolic syndrome have 2.1-fold greater risk than those without it [29]. It has also been reported that clusters of multiple metabolic disorders tended to cause CKD in the several epidemiological studies [30,31]. Therefore, it is reasonable to suppose that the increasing prevalence of metabolic disorders has contributed to the increasing trend in CKD, especially CKD Stages 3–5, in our subjects.

Hypertension is well-established as a powerful risk factor for not only cardiovascular disease, but also CKD [32]. In this study, blood pressure levels significantly declined in both sexes over the last three decades, probably because of the widespread use of antihypertensive medication. Nevertheless, about 70% of men with CKD and 50% of women with CKD did not reach the optimal blood pressure levels of <130/80 mmHg even in the latest survey. Several clinical trials have demonstrated that blood pressure lowering was beneficial for the prevention of progressive kidney disease [33,34] and cardiovascular disease in individuals with CKD [35–38]. A recent meta-analysis of Japanese cohort studies also revealed that lower blood pressure level is linearly associated with a lower risk of cardiovascular disease and death in subjects with CKD [39]. These findings, therefore, suggest that blood pressure should be controlled more strictly in individuals with CKD, using the recommendations in the current guidelines [23,24].

Our study showed that the prevalence of CKD Stages 1–2 decreased over the last three decades in both sexes. Importantly, the frequency of women with CKD Stages 1–2 was halved over time, and therefore, the overall prevalence of CKD did not change. In the 2002 survey, blood pressure was well-controlled in women, compared with men (Table 1). It has been established that blood pressure-lowering therapy, particularly the use of renin–angiotensin system inhibitors, reduces the risk of the development of proteinuria and subsequent kidney dysfunction [40–45]. Furthermore, the relationship between metabolic syndrome and the likelihood of CKD for women tended to be attenuated from the 1988 survey to the 2002 survey, possibly due to early interventions, including lifestyle modification or medications against metabolic disorder. Thus, our findings imply that optimal management of blood pressure and metabolic disorder may reduce the prevalence of CKD in women in the next decade.

Several limitations of our study should be noted. First, it is well-known that eGFR values calculated using the MDRD study equation with a single measure of serum creatinine are not fully accurate. In addition, measurement of serum creatinine was not repeated after an interval of at least 3 months. Additionally, the values of serum creatinine were not calibrated using the values from the Cleveland Clinic, although they were calibrated across the three surveys. These matters may have caused some degree of misclassification of eGFR levels. Nevertheless, these limitations may have had little effect on our conclusions because the extent of misclassification of eGFR levels would be similar across the surveys. Second, the method for measuring serum cholesterol could not be calibrated across the surveys in this study. However, we believe that our findings with regard to the trend in the propor-

tion of hypercholesterolaemia over time are likely to be real because the proportion of obesity showed a similar pattern. Third, a 75-g oral glucose tolerance test was not performed in 1974. Thus, the prevalence of diabetes in 1974 was likely to be underestimated because the glucose tolerance test is a more sensitive method to diagnose diabetes. Fourth, the blood pressure levels were estimated with office blood pressure measurement, but not with home blood pressure monitoring, likely attenuating the accuracy of the information about blood pressure control. Fifth, we were unable to obtain information regarding the cause of CKD or the type of antihypertensive drugs, including renin–angiotensin system inhibitors. This information would have enabled a deeper understanding of our results. Finally, this is a cross-sectional study, and thus, the data are of limited use in inferring causality between risk factors and CKD.

Conclusion

In conclusion, the prevalence of CKD increased significantly in men, but not in women from the 1970s to the 2000s in a general Japanese population. Despite the popularization of antihypertensive medication, blood pressure was not sufficiently controlled over time to meet the optimal level recommended by the current guidelines for patients with CKD. Additionally, the increasing prevalence of metabolic disorders would be expected to play a role in the increasing trend in CKD. Our findings support the requirement for a comprehensive treatment for hypertension and metabolic disorders in order to reduce the burden of CKD.

Supplementary data

Supplementary data is available online at http://ndt.oxfordjournals.org.

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Conflicts of interest statement. None declared.

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Ethnic disparities in prevalence and impact of risk factors of chronic kidney disease

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Abstract

Background. There is substantial heterogeneity in literature regarding the epidemiology for chronic kidney disease (CKD) in different Asian populations. We aimed to assess the prevalence and risk factors of CKD in a multi-ethnic Asian population in Singapore.

Methods. We examined 4499 participants of Chinese, Malay and Indian ethnicity, aged 24–95 years, who

Association of Kidney Function With Coronary Atherosclerosis and Calcification in Autopsy Samples From Japanese Elders: The Hisayama Study

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Background: Chronic kidney disease (CKD) is associated with increased risk of coronary heart disease. However, information regarding the histopathologic characteristics of coronary atherosclerosis in individuals with CKD is scarce. This study investigated the relationship between CKD and severity of coronary atherosclerosis in population-based autopsy samples.

Study Design: Cross-sectional study.

Setting & Participants: 126 individuals randomly selected from 844 consecutive population-based autopsy samples.

Predictor: Estimated glomerular filtration rate (eGFR) calculated using the 6-variable Modification of Diet in Renal Disease (MDRD) Study equation.

Outcomes: Severity of atherosclerosis in 3 main coronary arteries, including atherosclerotic lesion types defined using the American Heart Association classification; stenosis rates; and coronary calcified lesions.

Measurements: The relationship between CKD and severity of coronary atherosclerosis was evaluated using generalized estimating equation methods.

Results: Frequencies of advanced atherosclerotic lesions increased gradually as eGFR decreased (33.6%, 41.7%, 52.3%, and 52.8% for eGFRs ≥60, 45-59, 30-44, and <30 mL/min/1.73 m^2, respectively; *P* for trend = 0.006). This relationship was substantially unchanged even after adjustment for potential confounding factors (ORs, 1.40 [95% CI, 0.76-2.55], 2.02 [95% CI, 0.99-4.15], and 3.02 [95% CI, 1.22-7.49] for eGFRs of 45-59, 30-44, and <30 mL/min/1.73 m^2, respectively). Frequencies of calcified lesions of coronary arteries also increased gradually with lower eGFRs (*P* for trend = 0.02). Hypertension and diabetes were associated with increased risk of advanced coronary atherosclerosis and calcification of coronary arteries in individuals with decreased eGFR.

Limitations: Cross-sectional study, absence of data for proteinuria, and extremely high proportion of aged people.

Conclusions: The autopsy findings presented here suggest that CKD is associated significantly with severity of coronary atherosclerosis. Patients with CKD should be considered a high-risk population for advanced coronary atherosclerosis.

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INDEX WORDS: Chronic kidney disease; coronary atherosclerosis; population risk; coronary artery stenosis; glomerular filtration rate; coronary disease.

Editorial, p. 1

Chronic kidney disease (CKD) is a significant public health problem, affecting 10%-15% of the adult general population in developed countries.[1-3] CKD is associated with increased risks of cardiovascular disease and death.[4-7] A higher incidence rate of myocardial infarction and excessive cardiac mortality have been documented repeat-

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edly in patients with CKD.[6-10] Cardiac failure is more common in patients with advanced CKD, showing a prevalence of ~40%.[11]

Several autopsy-based studies have shown a higher prevalence of arteriosclerotic lesions in individuals with CKD than in those without CKD.[12-14] Furthermore, patients with end-stage renal disease show more advanced atherosclerotic lesions with calcification in coronary arteries than the general population.[14] However, these studies were conducted in hospital-based populations, which are prone to underlying disease. Additionally, there are few studies investigating the histopathologic findings of coronary arteries in individuals with moderate stage of CKD.

The Hisayama Study is a prospective population-based study of cardiovascular disease risk factors in Japanese people[15] and is characterized by autopsy verification of the cause of death in ~80% of those who died.[16,17] The present study assessed the relationship between decreased kidney function and severity of coronary atherosclerosis in population-based autopsy samples.

METHODS

Study Population

The Hisayama Study was established in 1961 in the town of Hisayama, a suburban community adjacent to Fukuoka City in a metropolitan area of Kyushu Island in southern Japan. The population of Hisayama is ~7,000 and has been stable for 40 years. Full community surveys of residents have been repeated since 1961.[18] From January 1988 to November 2005, a total of 1,162 residents of Hisayama died; of these, 844 underwent autopsy examination. Individuals without health examination data within 3 years before death were excluded. The remaining 482 individuals were classified into 4 categories based on estimated glomerular filtration rate (eGFR): ≥60, 45-59, 30-44, and <30 mL/min/1.73 m^2 (data from the most recent health examination). Eighteen individuals had an eGFR < 30 mL/min/1.73 m^2. The individuals included in this study were randomly selected using a computer-generated random number from each category of eGFR level after matching for age at death and sex in a 1:2 ratio against individuals in the <30-mL/min/1.73 m^2 category. A final total of 126 individuals (49 men, 77 women) were enrolled in this study (Fig 1). The median period from the last health examination to death was 1.0 years (quartile [Q] 1 to 3, 0.0-2.0).

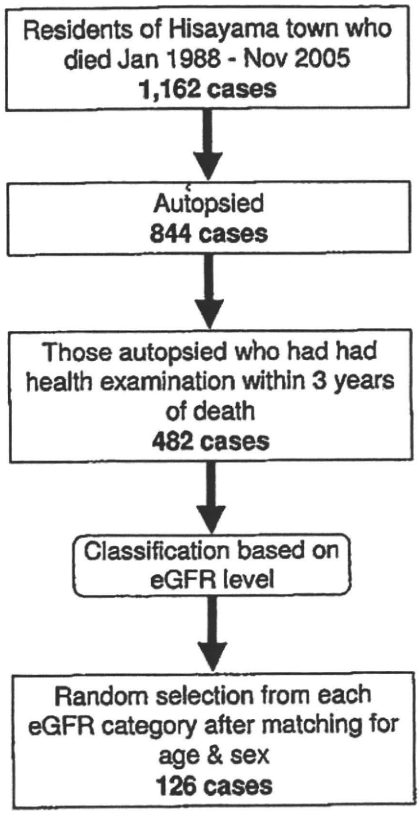

Figure 1. Flow diagram for study enrollment. Abbreviation: eGFR, estimated glomerular filtration rate.

Risk Factors

At each health examination, study participants undertook a self-administered questionnaire covering medical history, antihypertensive treatment, smoking habits, and alcohol intake. The completed questionnaire was checked by trained interviewers. Blood pressures were measured 3 times using a standard mercury sphygmomanometer at each examination, with mean values used for the analysis. Hypertension was defined as systolic blood pressure ≥ 140 mm Hg and/or diastolic blood pressure ≥ 90 mm Hg or use of antihypertensive agents. Blood samples were collected after overnight fasting. Serum creatinine was measured using the Jaffé method. Hemoglobin A_{1c} was measured using high-performance liquid chromatography. Diabetes mellitus was diagnosed as hemoglobin A_{1c} level ≥ 6.0%. Total cholesterol, high-density lipoprotein cholesterol, and triglyceride levels were determined enzymatically. Dyslipidemia was defined as total cholesterol concentration ≥ 220 mg/dL, high-density lipoprotein cholesterol concentration ≤ 40 mg/dL, or triglyceride concentration ≥ 150 mg/dL.

Definition of CKD

eGFR was estimated using the 6-variable Modification of Diet in Renal Disease (MDRD) Study equation,[19] and is given by the following equation (only 5 variables are shown because the multiplier for black race was not applicable to this population):

$$\text{eGFR (mL/min/1.73 m}^2) = 170 \times [\text{serum creatinine (mg/dL)}]^{-0.999}$$

$$\times [\text{age (years)}]^{-0.176} \times [\text{serum urea nitrogen (mg/dL)}]^{-0.170} \times [\text{serum albumin (g/dL)}]^{0.318} \times [0.762 \text{ if female}]$$

eGFR levels were classified into 4 categories: ≥60, 45-59, 30-44, and <30 mL/min/1.73 m^2, according to the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines.[20]

For sensitivity analyses, eGFR also was estimated using the 4-variable MDRD Study equation modified with the Japanese Society of Nephrology–Chronic Kidney Disease Initiative coefficient (ie, the JSN-CKDI equation)[21]:

$$\text{JSN-eGFR (mL/min/1.73 m}^2) = 0.808 \times 175 \times [\text{serum creatinine (enzymatic method [mg/dL])}]^{-1.154} \times [\text{age (years)}]^{-0.203} \times [0.742 \text{ if female}]$$

where the value of serum creatinine measured using the Jaffé method was converted to values for the enzymatic method by subtracting 0.207 mg/dL.[22]

Coronary Artery Morphological Examination

Heart tissue obtained at autopsy was immersed in 10% buffered formaldehyde for at least 24 hours, making sure to include the 3 main coronary arteries. The right coronary artery (segment 1), left anterior descending coronary artery (segment 6), and left circumflex coronary artery (segment 11) were dissected free from the surface of the heart, cut perpendicular to the long axis at 3-mm intervals, and embedded in paraffin. The segment of the vessel showing the most severe stenosis was selected for histological examination, excluding areas near the branching site. Three blocks were excluded because the segments of the coronary arteries were not adequately defined. In total, 375 blocks were obtained and all blocks for each individual were cut into 3-μm-thick serial sections in 1 sequence (1 block provided insufficient sample to estimate the extent of arterial stenosis). Sections from each block were serially subjected to hematoxylin and eosin, elastica–van Gieson, and Masson trichrome staining. Histological examinations were made without reference to the associated clinical information by 2 independent pathologists (T. Nakano and S.S. in blinded assessments).

Estimation of Atherosclerotic Lesions

Atherosclerotic lesions found in each section were classified into 6 types in accordance with the definitions proposed by the Committee on Vascular Lesions of the Council on Atherosclerosis, American Heart Association (AHA)[23]: type I (initial lesion), intimal thickening with isolated foam cells; type II (fatty-streak lesion), intimal thickening with intracellular lipid accumulation; type III (intermediate lesion), type II changes and small extracellular lipid pools; type IV (atheroma), type II changes and core of extracellular lipid; type V (fibroatheroma), lipid core and fibrotic layer to lesions, or mainly calcified, or mainly fibrotic; and type VI (complicated lesion), disrupted lesion with hematoma or hemorrhage or thrombotic deposits. The AHA classification defines advanced atherosclerotic lesions as types IV-VI.[23] Lesion calcification was assessed on hematoxylin and eosin-stained paraffin sections from all specimens.

Morphometry of Luminal Stenosis in the Coronary Artery

All arteries were analyzed quantitatively for stenosis rate using computerized planimetry according to Taylor et al.[24] Morphometry was performed using National Institutes of Health (NIH) Image software (version 1.63; NIH, Bethesda, MD). Elastica-van Gieson–stained sections were magnified and digitized to measure the luminal internal and external elastic lamina perimeters. Arterial areas were calculated from diameter values derived from the measured arterial perimeter (area = πr^2) to avoid artifacts from vessel shape distortion during processing. Plaque areas were calculated as the differences between internal elastic lamina and luminal area measurements. Percentage luminal stenosis was calculated as plaque area/internal elastic lamina area × 100.[24]

Statistical Analysis

The SAS software package for Windows, version 9.1 (SAS Institute Inc, Cary, NC) was used to perform statistical analyses. Trends in mean values or frequencies of variables across subgroups of eGFR level were tested using linear regression analysis or logistic regression analysis, respectively. Mean stenosis rates according to eGFR levels were calculated using a linear mixed model to account for correlation between vessels within a patient. Stenosis rates between vessels correlated fairly, with a correlation coefficient range of 0.21-0.32. This analysis was carried out using the procedure "MIXED" in SAS. Odds ratios (ORs) and their 95% confidence intervals (CIs) were estimated using the generalized estimating equation methods to deal with modeling the correlation among repeated outcomes within a patient.[25] Correlation coefficients for the probabilities of advanced atherosclerosis and calcified lesion between vessels ranged from 0.08-0.34 and 0.25-0.37, respectively. These analyses were performed using procedure "GENMOD" in SAS. Trends in relationships between eGFR levels and risk of outcomes were tested by adding the median value of eGFR for each category to the relevant model. Two-tailed $P < 0.05$ was defined as statistically significant.

RESULTS

Baseline Characteristics

Table 1 lists baseline clinical and demographic characteristics of individuals included in the study according to eGFR levels. Individuals with lower eGFRs had higher systolic blood pressure and calcium-phosphorus product and lower hematocrit values. Frequency of hyper-

Table 1. Laboratory Variables and Risk Factors According to Kidney Function

	eGFR (mL/min/1.73 m²)				*P* for Trend
	≥60	45-59	30-44	<30	
eGFR (mL/min/1.73 m²)	72 (68-85)	55 (51-58)	40 (37-43)	21 (19-25)	
No. of patients	36	36	36	18	
Age (y)	84 ± 6	85 ± 6	85 ± 8	85 ± 7	0.8
Men (%)	39	39	39	39	0.9
Serum creatinine (mg/dL)	0.9 (0.8-1.0)	1.1 (1.0-1.3)	1.5 (1.3-1.7)	2.5 (2.0-3.2)	<0.001
Serum urea nitrogen (mg/dL)	16 (12-18)	19 (16-24)	24 (19-27)	39 (29-46)	<0.001
Serum albumin (g/dL)	4.0 ± 0.4	4.0 ± 0.5	3.9 ± 0.5	3.7 ± 0.4	0.1
Systolic blood pressure (mm Hg)	141 ± 23	142 ± 29	143 ± 29	165 ± 29	0.01
Diastolic blood pressure (mm Hg)	73 ± 12	74 ± 14	75 ± 10	77 ± 13	0.2
Use of antihypertensive agent (%)	28	36	56	50	0.03
Hypertension (%)	61	58	78	94	0.006
Hemoglobin A_{1c} (%)	5.2 ± 0.8	5.7 ± 1.5	5.4 ± 0.8	5.4 ± 0.9	0.6
Diabetes (%)	11	22	19	22	0.3
Total cholesterol (mg/dL)	184 ± 37	190 ± 43	195 ± 53	186 ± 45	0.6
High-density lipoprotein cholesterol (mg/dL)	60 ± 17	52 ± 13	56 ± 17	53 ± 15	0.3
Triglycerides (mg/dL)	76 (65-102)	91 (81-124)	88 (68-123)	113 (70-167)	0.1
Calcium-phosphorus product (mg²/dL²)	29 ± 6	31 ± 5	31 ± 4	33 ± 5	0.005
Hematocrit (%)	37 ± 5	37 ± 6	35 ± 5	30 ± 6	<0.001
Smoking habit (%)	19	28	6	17	0.3
Alcoholic intake (%)	17	11	11	6	0.3
Median time from last health examination (y)	1.0 (0.5-2.0)	2.0 (0.5-2.0)	1.5 (0.5-3.0)	1.0 (0-2.0)	0.7
Causes of death					
Malignant neoplasms (%)	28	31	28	0	0.2
Heart diseases (%)	17	17	11	11	0.1
Cerebrovascular diseases (%)	17	11	3	11	0.4
Other diseases of circulatory system (%)	0	6	6	6	0.2
Infectious diseases (%)	17	19	33	22	0.5
Other causes (%)	19	6	8	33	0.08

Note: Values expressed as mean ± SD, frequency, or median (Q1-Q3). Hypertension was defined as blood pressure ≥ 140/90 mm Hg or use of antihypertensive agent. Diabetes was defined as hemoglobin A_{1c} level ≥ 6.0%. Trends were tested using linear regression analysis for continuous variables or logistic regression analysis for categorical variables. Conversion factors for units: eGFR in mL/min/1.73 m² to mL/s/1.73 m², ×0.0167; serum creatinine in mg/dL to μmol/dL, ×76.26; serum albumin in g/dL to g/L, ×10; serum urea nitrogen in mg/dL to mmol/L, ×0.357; total and high-density lipoprotein cholesterol in mg/dL to mmol/L, ×0.02586; triglycerides in mg/dL to mmol/L, ×0.01129.

Abbreviation: eGFR, estimated glomerular filtration rate.

tension and use of antihypertensive agents increased significantly with decreased eGFR. Mean values or frequencies of other potential risk factors were not statistically different among eGFR levels.

Relationship Between Kidney Function and Severity of Atherosclerotic Lesions

Figure 2 shows a typical coronary artery for subgroups of eGFR levels. Age- and sex-ad-