糸球体性血尿	非糸球体性血尿
1）一次性糸球体疾患 IgA腎症，急性腎炎，慢性糸球体腎炎，急速進行性糸球体腎炎	**1）炎症性** 腎盂腎炎，膀胱炎，前立腺炎，腎結核
2）二次性糸球体疾患 ANCA関連腎炎，Goodpasture症候群，ループス腎炎，紫斑病性腎炎	**2）結石異物** 腎結石，尿管結石，膀胱結石
3）遺伝性糸球体疾患 Alport症候群，菲薄基底膜病	**3）腫　瘍** 腎癌，尿管癌，膀胱癌，前立腺癌
	4）血管病変など ナットクラッカー現象，腎梗塞，腎動静脈血栓症，腎動静脈奇形
	5）その他 多発性嚢胞腎，遊走腎，水腎症，外傷

表3　血尿を来す疾患

比較項目	糸球体性血尿	非糸球体性血尿
色（肉眼的血尿）	暗赤色 or コーラ色	赤色 or ピンク色
凝血塊	認めない	認めることがある
蛋白尿	500mg/日以上のことが多い	500mg/日以下
赤血球形態	変形率が高い	正常
赤血球円柱	認めることが多い	認めない

表4　糸球体性血尿と非糸球体性血尿の鑑別

血尿単独例の診かた

血尿は蛋白尿に比べ高頻度に認められる．特に女性での陽性率が高く，加齢とともに陽性率の上昇が認められる．一般に肉眼的血尿を認めた場合には，泌尿器科的検索を優先すべきである．血尿を呈する疾患を**表3**に示す．

1．血尿の定義

尿沈渣中の赤血球5個以上/HPFが血尿と定義される．尿中変形赤血球の陽性率が高い場合は糸球体疾患が示唆される．尿試験紙法では尿中に出現した赤血球（溶血剤を含む試験紙に触れることにより溶血した赤血球）のヘモグロビンを感知している．この反応はヘモグロビンの他，ミオグロビンでも陽性になる．したがって，腎・泌尿器疾患以外の溶血性貧血や筋肉融解症候群などでも陽性になるが，この場合，尿に赤血球は出現しない．

2．血尿患者の診療の進め方

まずは尿中に血液が混じている部位の診断で，おおまかに糸球体性血尿なのか，非糸球体性血尿なのかの鑑別を行う（**表4**）．赤血球円柱・白血球円柱・顆粒円柱などの病的円柱や高い赤血球変形率を認めれば，糸球体腎炎，尿細管・間質性腎炎などの腎実質性疾患を考える．尿中白血球の増加や細菌尿を認める場合は，細菌の定量培養を行う．腫瘍の診断には，超音波検査をはじめとする画像診断と細胞診，さらには膀胱鏡検査などが必要となる．

突発的な肉眼的血尿はナットクラッカー現象，

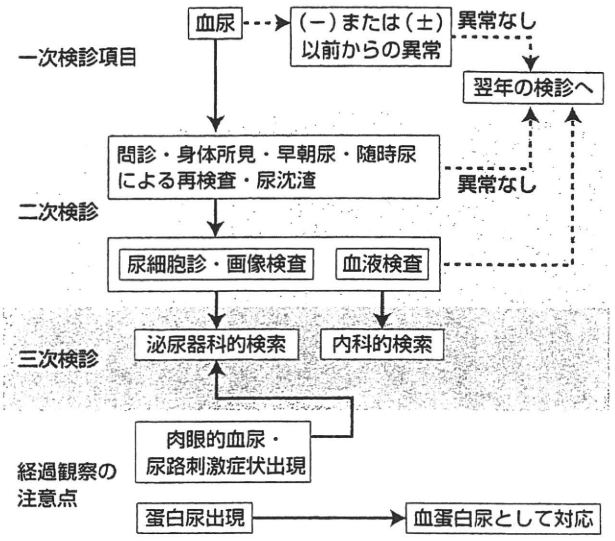

図2　検尿異常(血尿)へのアプローチ

動静脈瘻などの可能性を考慮し，画像検査を中心とした検索を進める．肉眼的血尿のある場合は，泌尿器科専門医の診療が必要である(図2)[1]．

一般に血尿単独患者の診療に当たっては，将来腎不全へと進行する腎疾患の早期発見を目的とした場合，血尿単独例の大半は腎機能障害を来すことが稀なため，初めて検尿異常を指摘された段階で画像検査を含めた精密検査を行い，その後は原則的に蛋白尿出現までは検診で経過観察することが可能である．しかし，泌尿器科的疾患の初期徴候であることは否定できず，経過中に尿路刺激症状や肉眼的血尿等が出現した時には必ず医療機関を受診するよう，十分に指導することを忘れてはならない．特に，尿路系悪性腫瘍は高齢男性に多く，過去の報告でも無症候性血尿例で高率に尿路悪性腫瘍が見出されたとの報告もあることから，十分な注意が必要である．また，経過中約10％の患者で尿蛋白陽性となることが知られており[2]，尿蛋白が陽性となった場合，血蛋白尿としての対応が必要である．

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★★ ワンポイントアドバイス ★★★★★

★微量アルブミン尿

糖尿病性腎症の早期など，試験紙法で陽性となる顕性蛋白尿が出現する以前に尿中アルブミン排泄量が増加していることが知られている．一般に尿試験紙法で尿蛋白陰性で，尿中アルブミン排泄量30～300mg/日の場合，あるいは尿中アルブミンとクレアチニンを同時に測定しアルブミンクレアチニン比として評価し，30mg/g・Cr以上を呈する場合を微量アルブミン尿陽性としている．

微量アルブミン尿は早期腎障害のマーカーとなる他，心血管イベントの独立した危険因子である．糖尿病患者の診療においては，腎障害の早期発見のために，定期的に(3カ月に1回程度)尿中アルブミン排泄量を評価することが望まれる．海外では高血圧患者においても腎障害の早期発見マーカーとして微量アルブミン尿の測定が進められている．

日本人をはじめアジア民族では，白人に比べ尿蛋白の陽性率が高く[3]，糖尿病以外の疾患に対し微量アルブミンでの評価を加えると，欧米の成績に比べ数倍の陽性率となることが知られている[4]．わが国での糖尿病以外の疾患での微量アルブミン尿の扱いについては，今後のさらなる検討が必要である．

特集　腎疾患：診断と治療の進歩

トピックス

I. 診断へのアプローチ
1. 検尿異常

森戸　直記　　山縣　邦弘

要　旨

末期腎不全による透析患者の世界的な増加から慢性腎臓病（chronic kidney disease，CKD）の疾患概念が提唱され，その早期発見と治療が早急な課題となっている．CKDの定義の一項目としての腎障害は，事実上検尿異常のなかでも蛋白尿の存在と同義語であり，蛋白尿は腎機能低下の危険因子であるだけでなく心血管疾患の発症の危険因子である．尿検査は簡便で安価であり，検尿異常の存在とその異常の種類（蛋白尿単独，血蛋白尿など），尿蛋白排泄量やその経過は，腎臓病の原因を知る上での基本的アプローチとしてきわめて重要である．

〔日内会誌　97：913～920，2008〕

Key words：検尿，蛋白尿，血尿，慢性腎臓病

はじめに

わが国の2006年の新規透析導入患者は3万6千人，総透析患者数は26万人にまでおよび，毎年約1万人もの透析患者の増加がある．透析患者の増加は歯止めがかからない状況でそれに関わる医療費は年間1兆円を超えており，腎臓病患者の腎不全への進行を抑制することは医療経済的にも重要な課題となっている．これまでの疫学調査から蛋白尿の存在は最も重要な腎機能低下の危険因子であり，末期腎不全に至る可能性が高くなるとされている．近年の治療法の進歩により，腎疾患の早期発見で末期腎不全への進行抑制が可能となってきていることから，腎疾患の早期発見とその対策の必要性が認識されてきている．また，腎機能障害のあるものは末期腎不全に至る以前に心血管疾患（cardiovascular disease，CVD）で死亡する例が圧倒的に多いというショッキングな事実も明らかになり，世界的な透析患者の増加も相まって，2006年にはKDIGO（Kidney Disease-Improving Global Outcomes）が世界的な課題としてCKD対策の重要性を提唱している[1]（CKDは腎障害あるいは糸球体濾過量（GFR）60ml/min/1.73m^{2}未満が3カ月以上持続する場合と定義されている）．腎機能が正常のものでも微量アルブミン尿を含む蛋白尿の合併はstage Iとして分類され，蛋白尿陽性であることは腎機能低下の危険因子であることと共にCVDのイベント発症と死亡の危険因子である．

蛋白尿，血尿のいずれも呈さず腎不全に至る腎疾患は少数であることから，検尿は腎不全予備軍の発見に有効であるとともにCVDイベント高リスク者の洗い出しに有効で簡便な検査である．本稿では，検尿異常（蛋白尿，血尿）とそ

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の予後，検尿異常のメカニズムとその出現，原疾患との関連について述べたい．

1．尿異常の頻度

健診や日常診療においては，主に試験紙法によって蛋白尿，血尿の有無がスクリーニングされている．茨城県での住民健診受診者123,764人（男性41,012人　女性82,752人）のうち検尿異常を認めたのは，蛋白尿のみ陽性は男性638人（1.6%），女性521人（0.6%），蛋白尿＋血尿陽性は男性248人(0.6%)，女性399人(0.5%)，血尿のみ陽性は男性3,424人(8.3%)女性15,443人（18.7%）であった[2]．他の前向きコホート研究で登録時の蛋白尿の頻度をみると，沖縄県(Isekiら2003年）の対象106,177人で5.3%，山形県(Kontaら2006年)の2,321例で4.4%であった．

血尿は，男性と比較し女性に多くみられる．茨城県日立地域の職域健診（対象56,269人）の解析では，男女をあわせた集計になるが，血尿の頻度は20歳代で0.94%，30歳代で1.68%，40歳代で3.95%，50歳代で3.64%，60歳以上で3.94%であり，40歳代までは加齢に伴って増加した[3]．他の前向き研究で登録時の血尿の頻度をみると，沖縄県（Isekiら1996年）の対象107,192人で男性3.5%，女性12.3%であった．

茨城県の職域健診（対象56,269人）で検尿異常のあった805人（蛋白尿のみ陽性例177人，血尿・蛋白尿陽性例150人，血尿のみ陽性例478人)に対する二次検査を行った[2]．蛋白尿のみ陽性例では糖尿病性腎症，多発性嚢胞腎，尿路結石をそれぞれ1%～2%認めた．経過中に65%が慢性腎炎症候群と診断され腎生検施行例では，IgA腎症53.4%，非IgA増殖性糸球体腎炎15.1%，膜性腎症11.0%，微小変化8.2%，巣状糸球体硬化症5.5%であった．

一方，蛋白尿＋血尿例は二次検査で，尿路結石が4.7%，慢性前立腺炎が1.3%であった．さらに経過中に67.3%が慢性腎炎症候群と診断され腎生検施行例では，その84.4%がIgA腎症と診断された．

血尿単独例では，二次検査で尿路結石が9.4%，そのほか多発性嚢胞腎，慢性前立腺炎と診断された．検査に異常の認められなかった無症候性血尿の約半数が平均6.3年の経過観察中に尿所見が消失し，10.6%に新たに蛋白尿を認めた．この尿蛋白出現者に対する腎生検の結果は75.0%がIgA腎症であった．

2．蛋白尿の起こる疾患（表1）

蛋白尿の診断においてはまず生理的蛋白尿と病的蛋白尿の鑑別が重要である．随時尿で比較的少量の尿蛋白陽性であれば運動性や体位性蛋白尿の可能性があるため，早朝起床時と来院時の検尿をする．早朝起床時の尿蛋白が陰性で，来院時の随時尿のみ尿蛋白陽性の場合，生理的な労作性あるいは起立性蛋白尿が疑われる（図1）．

病的蛋白尿が疑われる場合，原因疾患の鑑別が必要になる．原因の部位によって腎前性，腎性，腎後性蛋白尿に分類される．腎性蛋白尿は，糸球体性と尿細管性に分類される．糸球体性蛋白尿は糸球体係蹄壁の異常によりその透過性が亢進して血中の蛋白が尿中に漏出する状態である．健常者では一日10kg以上もの血漿蛋白が糸球体を通過するが，尿蛋白排泄量は150mgを超えない．原尿（糸球体濾液）中の蛋白濃度は1～3mg/dlであるが，通常はほぼ100%が近位尿細管で再吸収されるため尿蛋白はみられない．しかし，ネフローゼ症候群では原尿中の蛋白が数十倍以上に増加し再吸収しきれないものが蛋白尿として認められる．糸球体係蹄壁には分子の荷電で蛋白の漏出を制限するcharge barrierと分子の大きさにより制限するsize barrierという障壁があり，これらの破綻が蛋白尿をきたす．糸球体基底膜に存在するヘパラン硫酸プロテオグリカンが陰性に荷電しておりcharge barrierの本

表 1．蛋白尿の起こる疾患

生理的蛋白尿
起立性蛋白尿
激しい運動後，発熱時など
病的蛋白尿
1．腎前性蛋白尿　Bence Jones 蛋白：骨髄腫 など
ヘモグロビン尿：血色素尿症，溶血性貧血
ミオグロビン尿：挫滅症候群，行軍ミオグロビン尿症
2．腎性蛋白尿
糸球体性蛋白尿
・糸球体上皮細胞スリット膜の障害
先天性ネフローゼ症候群，家族性巣状糸球体硬化症（nephrin，podocin，CD2AP，α-actini 4，laminin β2 の異常）
糖尿病性腎症，膜性腎症（nephrin の発現低下の報告）
・糸球体上皮細胞の障害
ミトコンドリア遺伝子異常による巣状糸球体硬化症
・糸球体基底膜障害による蛋白尿
Alport 症候群（Ⅳ型コラーゲン α 鎖の異常）
Goodpasture 症候群（抗糸球体基底膜抗体の存在）
・糸球体基底膜 charge barrier の障害
微小変化型ネフローゼ症候群
尿細管性蛋白尿　間質性腎炎，Fanconi 症候群，重金属中毒
3．腎後性蛋白尿
腎盂以下の炎症，結石，腫瘍

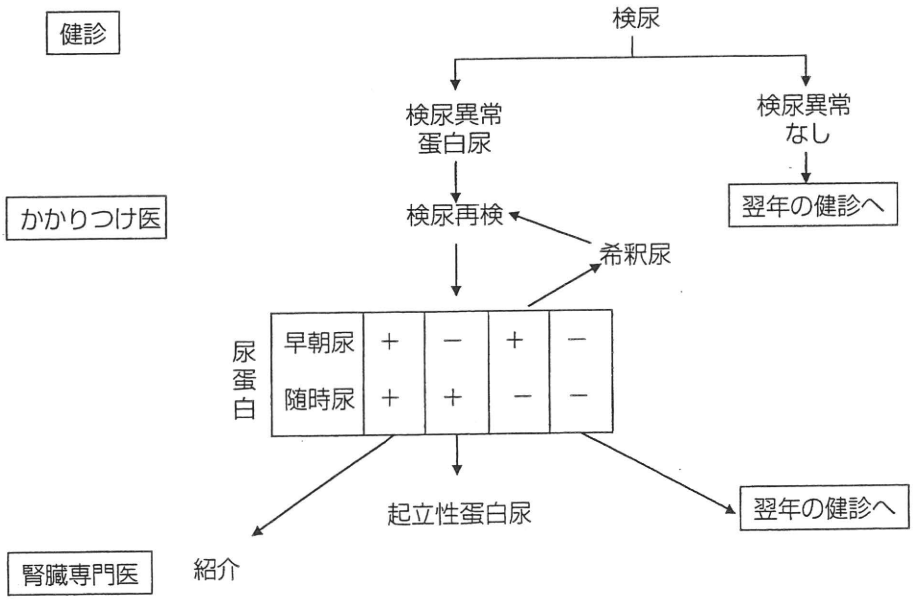

図 1．検尿異常（蛋白尿）へのアプローチ

体と考えられている．一方，糸球体上皮細胞（podocyte）足突起間を結合しているスリット膜のsize barrierとしての役割が明らかになってきており，スリット膜を構成しているpodocyte関連蛋白の異常が蛋白尿の出現に重要な役割を果たしているという報告も増えている[4]．糸球体障害部位別の糸球体性蛋白尿をきたす疾患を表1に掲げた．疾患による障害部位は単一でなく複合

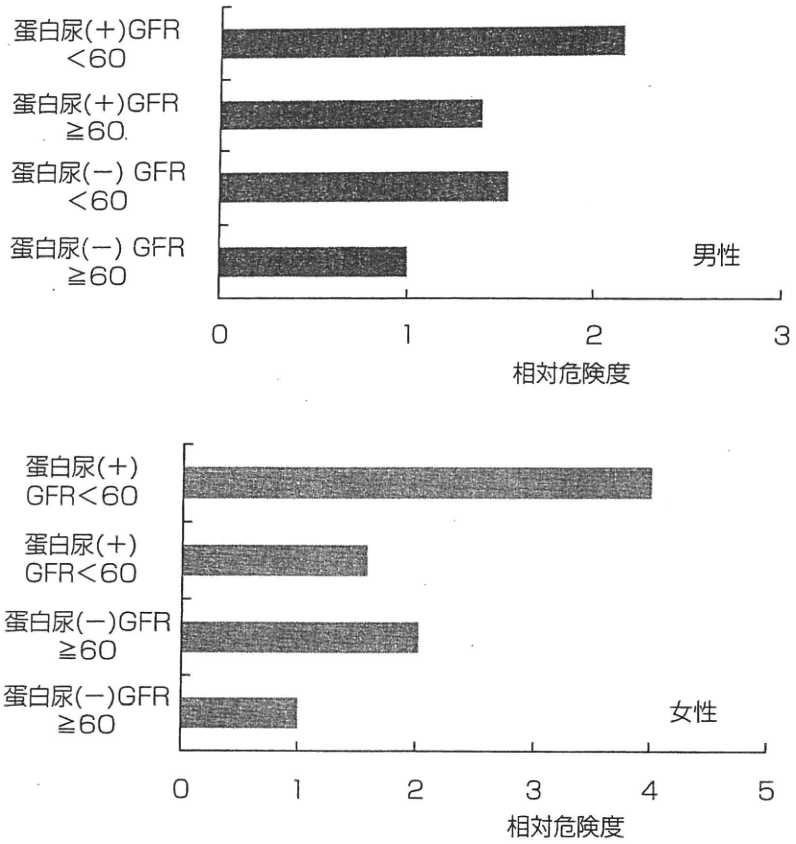

図3. 蛋白尿の有無による心血管死の相対危険度
蛋白尿の存在により心血管死の危険が増加する.
(文献9より改変引用)

蛋白尿の程度は腎機能予後と直結していることが知られている[10]. 血尿陽性例で腎機能悪化をみたものはすべて経過中に蛋白尿を認めていた.

血尿単独例は中年以降の女性で陽性率が極めて高く, その大半は腎機能障害をきたすことがまれである. 一方, 高齢男性では, 無症候性血尿においても高率に尿路悪性腫瘍が見いだされたとの報告も散見されることから十分な注意が必要である.

初めて血尿を指摘された段階において画像検査を含めた精密検査により尿路異常の有無を検索し, 異常がなければその後は原則的に蛋白尿出現までは健診での経過観察でよい. しかし, 初回の画像のみでは泌尿器科的疾患の初期徴候であることを否定できない. したがって, 経過中に尿路刺激症状や肉眼的血尿などが出現したときには必ず医療機関を受診するように指導し, 40歳以上の無症候性血尿では尿路悪性腫瘍の可能性が高くなるので注意する. 血尿単独陽性例が, 経過観察中蛋白尿も陽性となった場合には腎臓専門医への紹介と腎生検を含めた精査が必要と考えられる[8].

6. 二次性疾患の尿異常の特徴(糖尿病性腎症, パラプロテイン腎症)

糖尿病性腎症の最も早期の診断マーカーは微量アルブミン尿の出現であり, ACE-I(アンジオテンシン変換酵素阻害薬)やARB(アンジオテンシンII受容体拮抗薬)の使用と厳格な血糖管理で抑制あるいは消失可能である. 試験紙法による尿蛋白が陰性であっても, 糖尿病, 高血圧などを有している場合には, 微量アルブミン尿の測定が勧められる(高血圧は保険適応外). 漫然

表2. 血尿をきたす疾患

1. 糸球体性血尿
   - 一次性糸球体疾患
     - IgA 腎症，急性腎炎，慢性糸球体腎炎，急速進行性糸球体腎炎
   - 二次性糸球体疾患
     - ANCA 関連腎炎，Goodpasture 症候群，ループス腎炎，紫斑病性腎炎
   - 遺伝性糸球体疾患
     - Alport 症候群，菲薄基底膜病
2. 非糸球体性血尿
   - 炎症性
     - 腎盂腎炎，膀胱炎，前立腺炎，腎結核
   - 結石異物
     - 腎結石，尿管結石，膀胱結石
   - 腫瘍
     - 腎癌，尿管癌，膀胱癌，前立腺癌
   - 血管病変など
     - ナットクラッカー現象，腎梗塞，腎動静脈血栓症，腎動静脈奇形
   - その他
     - 多発性嚢胞腎，遊走腎，水腎症，外傷

と通常の試験紙検査を行っていると早期発見治療の機会を逸してしまい，顕性蛋白尿を呈するようになってからでは腎不全進行の抑制をするのは極めて困難である．尿アルブミン定量は高血圧性腎障害（腎硬化症）やメタボリックシンドロームに伴うCKDにおいても早期診断に有用で，アルブミン尿は心血管病の独立した危険因子であることも明らかとなっていることから，糖尿病性腎症以外のCKD診療においても尿アルブミン測定が保険で認められることが望まれている．微量アルブミン尿を認める早期腎症では，尿中アルブミン，尿中トランスフェリン，尿中IV型コラーゲンなどの測定を定期的に行い（保険診療上3カ月おき）腎障害の進行がないかを評価する．

また，試験紙法では蛋白誤差法を用いているため，陰性に荷電しているアルブミンの検出には適しているものの，多発性骨髄腫や原発性マクログロブリン血症に認められるBence Jones蛋白などの荷電の少ない蛋白の検出には向かない．よって，試験紙法で蛋白疑陽性の場合でも必要に応じてピロガロールレッド法などの比色法による蛋白総量定量を評価する必要がある．

おわりに

検尿によるスクリーニングは末期腎不全患者の減少のみならず，心血管イベントの抑制という点からも重要である．2007年日本腎臓学会が中心となり，「CKD診療ガイド」[8]が作成された．ACE-IやARBなどの尿蛋白減少や腎保護作用が明らかになり，CKDの早期発見により透析患者の減少，CVDイベントの抑制が期待される．検尿異常（蛋白尿，血尿）を認めた際はCKD診療ガイドなどを参考に適切な対応が求められる．

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Original Article

Slower Decline of Glomerular Filtration Rate in the Japanese General Population: A Longitudinal 10-Year Follow-Up Study

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The prevalence of stage 3 to 5 chronic kidney disease (CKD) in Japan (18.7%) is considerably higher than that in the United States (4.5%). This study investigated in the Japanese general population whether this higher prevalence of CKD might reflect to a progressive decline of renal function, and in turn to the increased risk of end-stage renal disease. A decline in renal function over 10 years was examined in 120,727 individuals aged 40 years or older who participated in the annual health examination program of the two periods over 10 years, 1988–1993 and 1998–2003. Renal function was assessed with estimated glomerular filtration rate (GFR) using the abbreviated Modification of Diet in Renal Disease (MDRD) Study equation modified by a Japanese coefficient. The rate of GFR decline in the participants was 0.36 mL/min/1.73 m^2/year on average. In the male population aged 50–79, the mean rate of GFR decline was significantly higher in the presence of hypertension than in its absence. The rate of GFR decline was more than two times higher in participants with proteinuria than in those without proteinuria in both sexes. The rate was significantly higher in participants with an initial GFR <50 mL/min/1.73 m^2 among the groups younger than age 70 and in participants with an initial GFR <40 mL/min/1.73 m^2 in the group with age 70–79. Based on the slow rate of GFR decline, we concluded that the decline in renal function progresses slowly in the Japanese general population. Hypertension, proteinuria and lower GFR were found to be significant risk factors for a faster decline of GFR. (*Hypertens Res* 2008; 31: 433–441)

***Key Words*: glomerular filtration rate, Modification of Diet in Renal Disease, equation, Japanese**

Introduction

A current epidemic of chronic kidney disease (CKD) is a major health problem worldwide. In Japan, the number of new patients with end-stage renal disease (ESRD) has been increasing during the last three decades. In 2005, a total of 36,063 ESRD patients were introduced to dialysis therapy, most of whom were elderly (mean age of 66) (*1*).

Previously, we have confirmed that an accurate glomerular

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Table 1. Study Participants

Prefecture of health-check program	Period of 10-year comparison	Sex	*n*	Total program participants (%)
Okinawa	1993 and 2003	Male	11,324	38
		Female	18,349	42
Ibaraki	1993 and 2003	Male	25,262	38
		Female	60,723	45
Hokkaido	1991 and 2001	Male	395	46
		Female	572	49
Tokyo	1992 and 2001	Male	1,928	26
		Female	622	24
Fukuoka	1988 and 1998	Male	605	N/A
		Female	951	N/A
Total		Male	39,510	
		Female	81,217	
		Total	120,727	

N/A, not available.

filtration rate (GFR) is estimated from serum creatinine value for Japanese using the abbreviated Modification of Diet in Renal Disease (MDRD) Study equation modified by a Japanese-coefficient (*2*). When CKD was defined by GFR <60 mL/min/1.73 m^2 (CKD stage 3), prevalence of CKD in the Japanese general population was predicted to be 18.7% (about 19 million) based on a nationwide epidemiological study in 527,594 individuals aged 20 years and older (211,034 males and 316,560 females) who participated in a community-based, company-based or hospital-based annual health examination program conducted in 2000–2004 (*3*).

The prevalence of CKD is higher in Japanese population (19%) than in both Norwegian population of Nord-Trondelag county and US population (both about 10%). The prevalences of stage 3 and 4 CKD (GFR: 60–31 and 30–15 mL/min/1.73 m^2) were also higher in the Japanese general population than in populations of the countries the above (for Japan: 18.5% and 0.20% in 2000–2004 (*3*); for the US: 3.7% and 0.13% in 1999–2000 (*4*); and for Nord-Trondelag county, Norway: 4.2% and 0.16% in 1995–1997 (*5*), respectively). Eriksen *et al.* (*6*) reported in a longitudinal study that the mean change in the estimated rate of GFR decline over 10 years was 1.03 mL/min/1.73 m^2/year, and the renal function declined progressively in a relatively small population of patients in a hospital of Tromso, Norway. We predicted that the large Japanese population with lower GFR may have progressive decline in the renal function. In that case, we may have a large number of ESRD patients in Japan in the near future. Thus, the present study investigated the rate of decline in GFR in the Japanese general population over a period of 10 years using the data on serum creatinine, blood pressure and urinalysis of participants aged 40 years and older of the annual Japanese health examination program. The rate of GFR decline was estimated from a set of serum creatinine values obtained 10 years apart in 120,727 participants of the Japanese health examination program which was conducted over two periods, 1988–1993 and 1998–2003, in five prefectures.

Hypertension and proteinuria was evaluated as risk factors for accelerated decline of renal function in the study population, since these conditions are known to exacerbate CKD progression to end-stage renal disease.

Methods

Study Population

In this study, we obtained the data on 290,268 individuals (107,145 males and, 183,123 females) aged 40 years and older who participated in the annual health examination program of 5 different prefectures of Japan (Hokkaido, Ibaraki, Tokyo, Fukuoka, and Okinawa) during the period between 1988 and 1993 (Table 1). Of those, 120,727 adult participants (41% of the total; 39,510 males and 81,217 females) who had two serum creatinine values measured at an interval of 10 years were included in the present study. When proteinuria was defined as a urinary protein level of 1+ or more (about ≥30 mg/dL) in the dipstick test using a spontaneously and freshly voided urine sample, 2,054 patients (1.7%) had proteinuria among 117,865 participants whose urinary protein was measured. When hypertension was defined as a mean blood pressure of 106 mmHg or more measured in the sitting position, 16,722 patients (13.9%) had hypertension among 120,727 participants whose blood pressure was measured. All the participants were kept anonymous and the study was conducted according to the Japanese law of privacy protection.

Calibration of Serum Creatinine Values

Although the Jaffe method was generally used for creatinine assay before 2000, the enzymatic method is currently used in many laboratories in Japan. In the present study, creatinine was measured by the Jaffe method in the earlier annual health

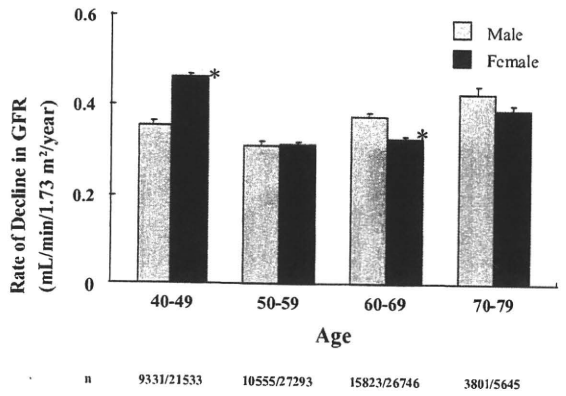


Fig. 1. *Difference in the rate of decline in GFR between male and female participants in each age group. The rates of decline in GFR were calculated from 39,510 males and 81,217 females. Data are shown as the means±SEM. *$p<0.001$ vs. male.*

examination program and was measured by the enzymatic method in the later program. The mean creatinine values of the general population measured by the Jaffe method were higher than those obtained by the enzymatic method, but the degree of difference between the two measurements was roughly constant across the age groups. We previously conducted a nationwide epidemiological study to predict the prevalence of CKD in the Japanese general population, based on a survey of participants in an annual health examination program run by community, company and hospital (*3*). The serum creatinine values of each laboratory were calibrated in the central laboratory. To use the surveyed serum creatinine values from different laboratories in different years in the present study, the values were aligned to the gender-specific and age-specific mean creatinine values in the previous study noted above and calibrated to the values of the central laboratory measured by the Jaffe method. We calculated the mean creatinine value for the subjects with age ranging from 40 to 79 years in each laboratory by either method. The mean difference in creatinine values was corrected in each laboratory on a year- and gender-basis.

GFR Estimation with the Japanese-Coefficient–Modified MDRD Study Equation

The GFR of each participant was calculated from the serum creatinine value (S-Cr) and the age using the Japanese-coefficient–modified MDRD Study equation as follows.

$$\text{GFR (mL/min/1.73 m}^2) = 0.881 \times 186 \times \text{Age}^{-0.203} \times \text{S-Cr}^{-1.154} \text{ (if female} \times 0.742)$$

The rate of GFR decline over 10 years were calculated for each group of participants with initial GFR of five categories (30–39, 40–49, 50–59, 60–69, >70 mL/min/1.73 m^2). When analyzed using two successive measurements, the values will, on average, tend to be closer to the mean on the second measurement (the so-called regression effect). When we compared the rate of GFR decline in one GFR category with that in another GFR category, the regression effect on the rate of GFR decline was corrected by the following equation:

$$\text{Corrected rate of decline in GFR} = \text{GFR}_2 - \text{GFR}_1 + (1 - b) \times (\text{GFR}_1 - \text{mean GFR}_1)$$

Where GFR_1 is the initial GFR value of the subject, GFR_2 is the final GFR value of the subject, mean GFR_1 is the mean of the initial GFR values in the study population, and b is the slope of the regression line in the study population (with final GFR on the Y axis and initial GFR on the X axis).

Statistics

Data were expressed as the number of participants or percentage (%) of the study population. The rate of GFR decline was expressed as the mean±SEM. The rates of GFR decline were compared among three or more cases by Scheffé's multiple comparison method after analysis of variance (ANOVA) or between two cases by Student's t-test. Values of $p<0.05$ were considered statistically significant.

Results

Prevalence of CKD (GFR <60 mL/min/1.73 m^2) in Participants in the Annual Health Examination Program

Among the 120,727 participants (39,510 males and 81,217 females), 42.72%, 35.91%, 17.80%, 3.29%, 0.26% and 0.01% had initial values of GFR >70, 69–60, 59–50, 49–40, 39–30, and <30 mL/min/1.73 m^2, respectively. In the study population, the prevalence of CKD stage 3 was 21.34% of the total participants and that of CKD stage 4 and 5 together was 0.01% of the total participants.

Mean Rate of Decline in GFR

The rates of GFR decline over 10 years were similar among the age groups: 0.35, 0.31, 0.37, and 0.42 mL/min/1.73 m^2/year in males, and 0.41, 0.31, 0.32 and 0.39 mL/min/1.73 m^2/year in females for the age groups of 40–49, 50–59, 60–69 and 70–79 years, respectively (Fig. 1). The overall rate of GFR decline in the study population was 0.36 mL/min/1.73 m^2/year.

Rate of GFR Decline in Hypertensive Patients

Hypertension occurred in 17.8% of males and 11.9% of females in the study population. In the presence of hypertension, GFR declined with significantly higher rate; the rate was higher in the group ≥106 mmHg than in the group <96

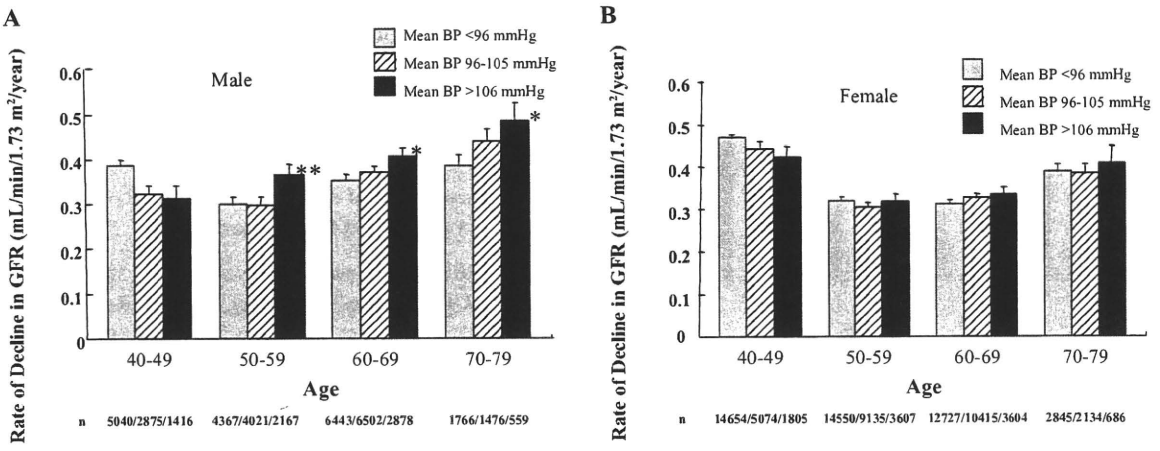


Fig. 2. *A: Difference in the rate of decline in GFR in male participants with a mean blood pressure of below 96 mmHg, 96 to 105 mmHg, or above 105 mmHg in each age group (n=39,510). B: Difference in the rate of decline in GFR in female participants with a mean blood pressure of below 96 mmHg, 96 to 105 mmHg, or above 105 mmHg in each age group (n=81,217). Data are shown as the means±SEM. *p<0.05, **p<0.01 vs. BP <96 mmHg.*

mmHg in the male groups aged 50 years and older (Fig. 2A). In female, the rate of GFR decline was slightly higher but not significantly in hypertensive patients than in normotensive participants in the age groups older than 60 years (Fig. 2B).

The Rate of Decline in GFR in Patients with Proteinuria

In the overall study population, proteinuria occurred in 2.6% of the males and 1.3% of the females. Patients with proteinuria had a twofold higher mean rate of GFR decline compared with patients without proteinuria in all the age groups in both males and females (Fig. 3), demonstrating that proteinuria accelerated the rate of a decline in renal function and was a strong risk factor for a decline in renal function.

The Impact of Initial GFR on the Rate of Decline in GFR

Initial GFR influenced the rate of GFR decline in both sexes. The lowest rate of GFR decline was in individuals with an initial GFR of 60–69 mL/min/1.73 m^2. In the age group of 40–49, the rates were 0.34±0.02 mL/min/1.73 m^2/year in males and 0.45±0.01 mL/min/1.73 m^2/year in females. When the rate was used as a reference point, the rate of GFR decline significantly increased in the group with an initial GFR of 30–39 mL/min/1.73 m^2 and was 10-fold higher (3.28±0.72 mL/min/year) in males and 4-fold higher (1.94±0.47 mL/min/year) in females (Fig. 4A). The mean rates were significantly higher in the groups with an initial GFR <50 mL/min/1.73 m^2.

In the age group of 50–59, the rate of GFR decline was higher in the group with an initial GFR of 30–39 mL/min/1.73 m^2, 3 times higher (0.91±0.43 mL/min/year) in male and 6 times higher (1.34±0.24 mL/min/year) in female, compared with the rate in the group of an initial GFR of 60–69 mL/min/1.73 m^2 (0.31±0.01 mL/min/1.73 m^2/year in males and 0.24±0.01 mL/min/1.73 m^2/year in female) (Fig. 4B). The mean rate of decline in GFR was greater in the group with an initial GFR <50 mL/min/1.73 m^2.

In the age group of 60–69, the rate of GFR decline increased with decreased initial GFR. The significant increase in the rate was 3 times higher in the group with initial value of GFR 30–39 mL/min/1.73 m^2 (0.98±0.18 mL/min/year) in male and 4 times higher (1.18±0.13 mL/min/year) in female compared with that in the group of GFR 60–69 mL/min/1.73 m^2 (0.31±0.01 mL/min/1.73 m^2/year in male and 0.26±0.01 mL/min/1.73 m^2/year in female) as shown in Fig. 4C. The mean rate of GFR decline was greater in those with an initial GFR of <50 mL/min/1.73 m^2.

In the age group of 70–79, the mean rate of GFR decline also increased along with the decreased initial GFR. The rate was higher (1.24±0.25 mL/min/year in males and 0.82±0.09 mL/min/year in females; both 3-fold increases) in those with an initial GFR of 30–39 mL/min/1.73 m^2 than in those with an initial GFR of 60–69 mL/min/1.73 m^2 (0.36±0.03 mL/min/1.73 m^2/year in males and 0.29±0.02 mL/min/1.73 m^2/year in females) (Fig. 4D). The GFR reduction rate was accelerated in those with an initial GFR of <40 mL/min/1.73 m^2.

A simulation of the GFR decline in relation to age is shown in Fig. 5. A significantly greater rate of GFR decline was observed in subjects with an initial GFR of <50 mL/min/1.73 m^2 in the age group of younger than 70 years and in those with an initial GFR <40 mL/min/1.73 m^2 in the age group of 70–79.

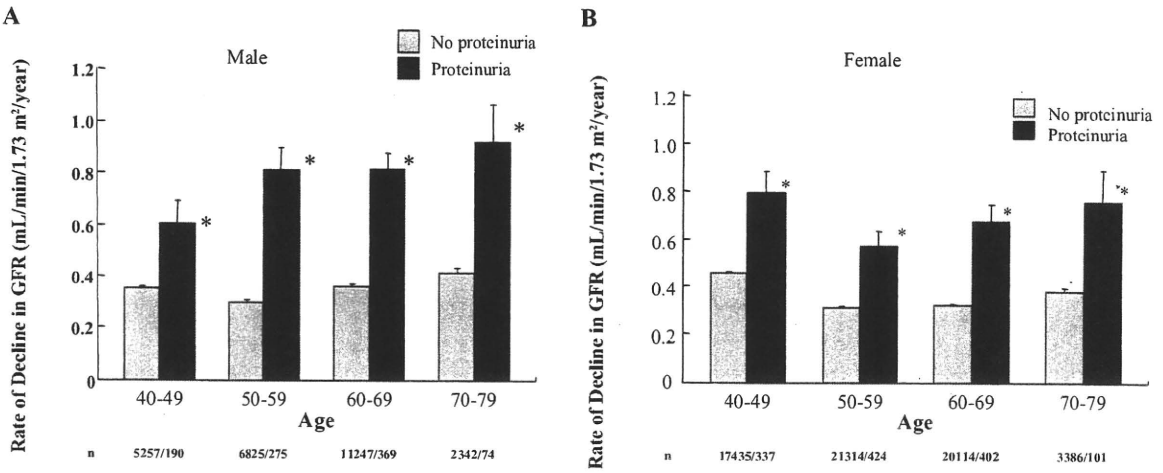


Fig. 3. *A: Effects of proteinuria on the rate of decline in GFR were evaluated in male participants with proteinuria (n = 985) or without proteinuria (n = 37,444). B: Effects of proteinuria on the rate of decline in GFR were evaluated in female participants with proteinuria (n = 1,069) or without proteinuria (n = 78,367). Data are shown as the means ± SEM. *p < 0.0001 vs. no proteinuria group.*

Discussion

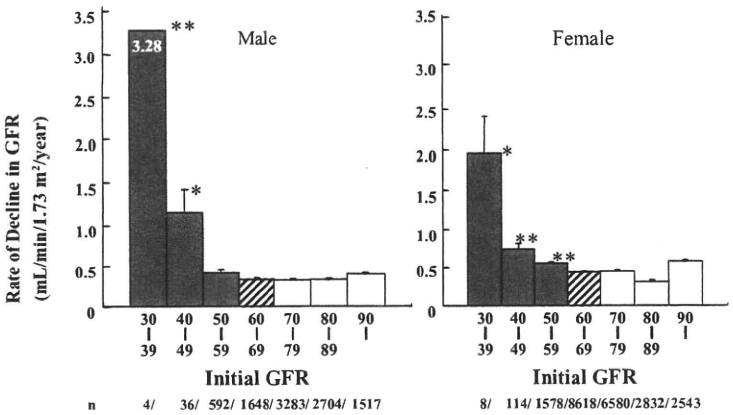
The rate of decline in GFR over 10 years in the Japanese general population was estimated in a large-scale longitudinal study of participants aged 40–79 years. The rate of GFR decline was found to be 0.36 mL/min/1.73 m^2/year. Accelerated GFR decline occurred in the presence of proteinuria in both sexes in any age, and in the presence of hypertension in men with age 50 and older in marginal extent. The rate of GFR decline over 10 years was affected by the initial GFR in different manner in different age groups. Accelerated decline in GFR occurred over the following 10 years when the initial GFR was < 50 mL/min/1.73 m^2 in the group with age younger than 70, while accelerated GFR decline occurred with the initial GFR < 40 mL/min/1.73 m^2 in the group with age 70–79.

The rate of GFR decline, 0.36 mL/min/1.73 m^2/year, in the present study was slower than the rates of 0.75–1.0 mL/min/1.73 m^2/year in the longitudinal studies of the United States (*7*) and Norway (*6*). GFR declined at a similar rate in males and females in any age groups. Iseki *et al.* (*8*) reported that the rate of GFR decline was 0.19 mL/min/1.73 m^2/years in Japanese in a longitudinal study of the screenings between 1983 and 1993, although the GFR was estimated by the original 4-variable MDRD Study equation without calibration of serum creatinine values.

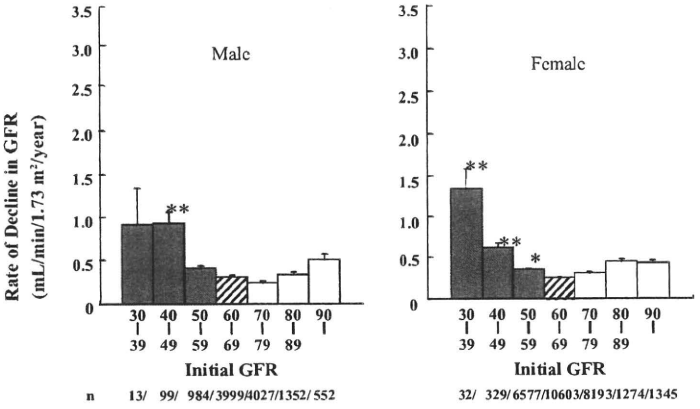
We found that hypertension and proteinuria affected the rate of decline in renal function. In the presence of hypertension, the GFR decline significantly accelerated only in male participants aged 50 years and older. Subjects with proteinuria had an approximately two-fold higher rate of GFR decline than those without proteinuria in both males and females of all age groups. In comparison with the group having an initial GFR of 60–69 mL/min/1.73 m^2, the groups with a lower initial GFR had a significantly higher rate of GFR decline in all age groups, suggesting that the lower the GFR the faster the decline of renal function. The initial GFR to produce significantly sharper decline in GFR was different in each age group; the GFR was < 50 mL/min/1.73 m^2 in the age groups 40–69, and it was < 40 mL/min/1.73 m^2 in the older group of age 70–79, suggesting that the decline in kidney function starts accelerating at a lower GFR in the elderly. In the present study, we demonstrated that a risk for fast decline in renal function starts at relatively higher initial GFR in younger patients than elderly patients. It is a particular importance that the findings were made in the present longitudinal study of 10-year follow-up with more than 120,000 participants who represented the Japanese general population. Figure 5 shows estimation of the GFR decline according to the aging.

In contrast to our findings, many studies have demonstrated that elderly subjects had a sharper decline in GFR than younger subjects. The mean rate of GFR decline was found to be 0.42 mL/min/1.73 m^2/year in males and 0.39 mL/min/1.73 m^2/year in females in the age group of 70–79 in Japanese, whereas the rate was higher approximately 1 mL/min/year in a normal elderly US population (*9–11*). The results of small study of the Baltimore Longitudinal Study on Aging also supported the findings, where an average GFR decline was 0.75 mL/min/year in men as evaluated with creatinine clearance (*7*). Similarly, in a longitudinal community-based study of a 2-year follow up of the elderly Canadians, Hemmelgarn *et al.* reported that the rate of GFR decline was 0.8 mL/min/1.73 m^2/year in women and 1.4 mL/min/1.73 m^2/year in men in age

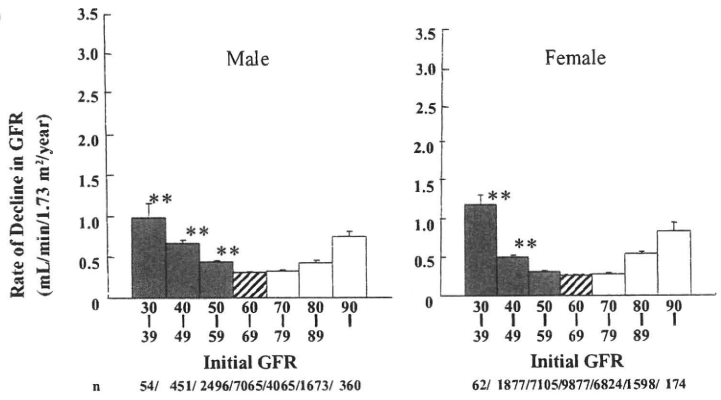
A: Age Group 40–49



B: Age Group 50–59



C: Age Group 60–69



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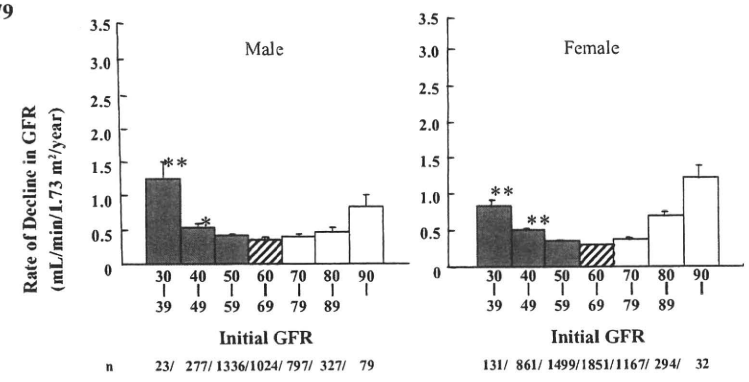

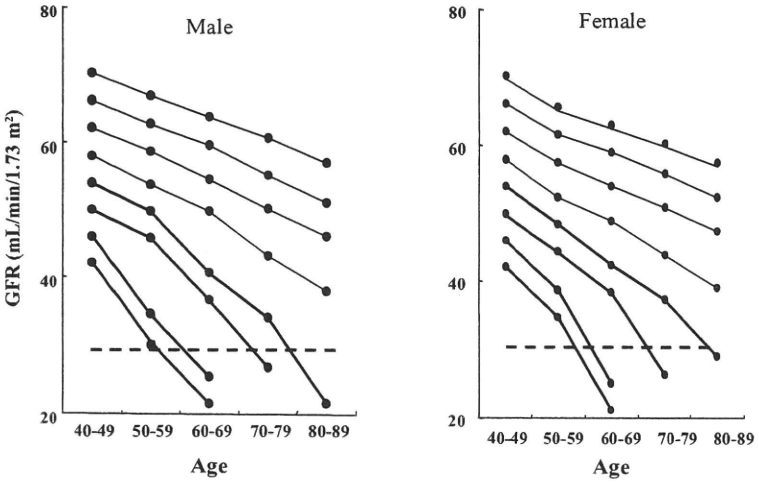

Fig. 5. *Estimation of the decline in GFR. The predicted GFR is illustrated in males and females. Thick solid lines show individuals who have an increased risk of sharp decline in GFR, potentially progressing to end-stage renal disease.*

group 66 years or older (about age 76 on average) without diabetes (*10*). However, these studies had critical disadvantages, because the study was conducted with a cross-sectional design (*9*) or with small number of subjects (*7*), and the loss of kidney function was analyzed using dichotomous outcomes (*10*) or evaluated based on creatinine clearance (*7*). Alternatively, GFR in the elderly individuals with longevity may slowly decline according to the aging, while the elderly with diseases may die early before the second measurement of serum creatinine 10 years later. A prospective study is required to answer the question.

In the present study, the highest rate of GFR decline was found among the subjects with an initial GFR of 30–39 mL/min/1.73 m^2. The maximal rate was much higher in the age group 40–49 than in the age groups 50 and older in both males and females. We may be underestimating the rate of GFR decline in study subjects with a lower initial GFR because some of the study subjects may already be introduced to renal replacement therapy by the time of the later health examination program of 10 years later and may be excluded from the study.

Furthermore, patients with CKD had a significantly slower decline of GFR in the Japanese cohort of our study than in the US cohort of a previous study; the rate of GFR decline in the MDRD Study was higher 7.8 mL/min/1.73 m^2/year (2.6 mL/min/1.73 m^2/4 months) in the patients with an average GFR of 38.6 mL/min/1.73 m^2, and 4.0 mL/min/1.73 m^2/year in the patients with the GFR of 18.5 mL/min/1.73 m^2 (*11*). In a 25-year follow-up study of a US population, Ishani *et al.* reported that men with high risk of heart disease and GFR <60 mL/min/1.73 m^2 but without kidney disease had significantly higher hazard ratio of 3.85 for a risk of ESRD (*12*). Taken together, these results indicate that a risk of progressive CKD and ESRD can be associated with different GFR values in different ethnic populations.

In the present study, hypertension defined by a mean arterial blood pressure ≥106 mmHg was a marginal risk factor for faster decline in renal function in men but not in women. Similar observation was reported in the Multiple Risk Factor Intervention Trial (MRFIT) with a 16-year follow-up, where hypertension was a risk for developing ESRD in men in the US population (*13*). In a large community-based epidemiological study of 98,759 subjects with a 17-year follow-up in Okinawa, Japan, hypertension was the risk factor in both men and women (*14*). Furthermore, Yamagata *et al.* recently reported that hypertension defined by a blood pressure of 140/

Fig. 4. *The rate of decline in GFR was compared among the groups categorized with initial GFR. White columns indicate tentative values of decline rate because the individuals with higher initial eGFR were underestimated their GFR and may often be reduced the value in the second measurement by the effect of regression to the means. A: Rate of decline in GFR in age group 40–49 in males and females. The average GFR at age 40–49 was 77±10 mL/min/1.73 m^2 in male (n=9,331) and 74±11 mL/min/1.73 m^2 in females (n=21,533). B: Rate of decline in GFR in age group 50–59 in males and females. The average GFR at age 50–59 was 72±11 mL/min/1.73 m^2 in males (n=10,555) and 69±10 mL/min/1.73 m^2 in females (n=27,293). C: Rate of decline in GFR in age group 60–69 in males and females. The average GFR at age 60–69 was 77±10 mL/min/1.73 m^2 in males (n=15,823) and 74±11 mL/min/1.73 m^2 in females (n=26,746). D: Rate of decline in GFR in age group 70–79 in males and females. The average GFR at age 70–99 years old was 64±11 mL/min/1.73 m^2 in males (n=3,801) and 61±11 mL/min/1.73 m^2 in females (n=5,645). Data are shown as the means±SEM. *p<0.01, **p<0.001 vs. initial GFR 60–69 mL/min/1.73 m^2.*

90 mmHg or higher was an independent risk for developing CKD in a 10-year follow-up study of a general population in Japan (*15*). In a study of 504 African-American and 218 Caucasian men between 1976 and 1999, hypertension was a strong risk factor for early decline in kidney function; hypertensive patients (BP ≥160/95 mmHg) had a 5 times greater decline in GFR, (2.67 mL/min/1.73 m^2/year) compared with patients with blood pressure <140/90 mmHg (*16*).

The effect of hypertension on the rate in GFR decline in the elderly is controversial. In a longitudinal study, Eriksen *et al.* (*6*) showed that creatinine clearance declined more rapidly with age in hypertensive elderly than in normotensive elderly, where the rate of GFR decline was 0.92±0.32 mL/min/year in hypertensives, *vs.* 0.75±0.12 mL/min/year in normotensives. In contrast, another cross-sectional study reported that values of GFR measured by inulin clearance were not different between elderly hypertensives and elderly normotensives (*17*).

Being male has been reported to have a negative effect on the progression of CKD (*18*). Eriksen *et al.* reported that the rate of GFR decline was lower in female than in male patients with CKD 3 (male *vs.* female: 1.39 *vs.* 0.88 mL/min/1.73 m^2/year) (*6*).

In hypertensive males whose mean blood pressure were over 106 mmHg, GFR declined with significantly faster rate at age 50 and older, while the rate of GFR decline was not affected by the blood pressure at age 40–49. The systemic vascular lesion caused by hypertension may influence the rate of GFR decline after age 50 and older. A previous study reported that the mean common carotid intima-media thickness (IMT) increased in a linear manner with age in healthy subject, and the increase was more significant in the subjects with age 50 and older than in subjects with younger age (*19*). The carotid IMT was greater in patients with CKD than healthy controls at age 50 and older; however, the IMT in the patients was not different from that of healthy controls at age 40–49 (*20*). These results may support our results that the impact of hypertension on renal function may become apparent after age 50.

The prevalence of overt proteinuria was higher 2.6% in this study compared to 1.4% in the NHANES III in male (2.6% *vs.* 1.4%), but the incidence was similar between the two studies in female (1.3% *vs.* 1.5%) (*21*). In studies on diabetic patients, proteinuria including microalbuminuria has been shown to increase a risk for progression of renal disease (*22*). A higher risk for ESRD has also been demonstrated in patients with proteinuria in two large cohort studies with long-term follow-up. The hazard ratio of developing ESRD in patients with proteinuria was 3.1 in a sub-analysis of the MRFIT study with a 25-year follow-up of a total of 12,866 men, and was 3.09 in a study in Okinawa, Japan (*23*). Yamagata *et al.* also presented evidence that proteinuria is a risk factor for developing stage 3 CKD in the Japanese general population (*15*).

When creatinine is measured by the enzymatic method, estimated GFR (eGFR) is generally calculated by the isotope dilution mass spectrometry (IDMS)–traceable creatinine based 4-variable MDRD (IDMS-MDRD) Study equation (*24*). In the present study, we did not use the IDMS-MDRD Study equation with the Japanese Society of Nephrology–Chronic Kidney Disease Initiatives (JSN-CKDI) coefficient, although the modified equation is recommended for Japanese by the Japanese Society of Nephrology (*25*). The creatinine measurements in the participating laboratories were made by the Jaffe method in early 1990s, and some laboratories changed to the enzymatic method after 2000. Since most of the serum creatinine values in the present study were measured by Jaffe method, it was necessary to use the modified original MDRD Study equation with the Japanese coefficient which was created using values measured by the Jaffe method. The serum creatinine values measured by the enzymatic method were converted to the value obtained by the Jaffe method.

Our study has the advantages of large sample size and 10-year longitudinal follow-up. However, it also has several limitations. First, the data of this study were derived from health examination program run by community and hospital. Approximately 40% of the total participants of the first health examination program participated in the program 10 years later. Since a set of serum creatinine measurements over 10 years was required for evaluation of the rate of GFR decline, a survival bias may have been exist in the study. Additional bias may have arisen from patients with serious diseases who had already been examined in hospital visits and thus would not have participated in the health examination program. Second, although the two sets of creatinine values measured 10 years apart were measured in the same individuals in the same laboratories, the values of the serum creatinine may have drifted. We calibrated the value of serum creatinine for each laboratory based on the values in the central laboratory each year for either gender. Third, although we have adjusted the effect of regression to means, residual effects may be present. Fourth, systolic blood pressure is a stronger risk for ESRD than diastolic blood pressure (*13*).The risk of blood pressure should therefore be analyzed separately for systolic and diastolic blood pressure rather than by using the mean blood pressure. However, these data were not available in the present study.

In conclusion, the average rate of GFR decline in the Japanese general population was 0.36 mL/min/1.73 m^2/year, considerably slower compared with that of the Caucasian general population. Hypertension was a marginal risk factor for a faster decline in renal function in men, and proteinuria was a risk factor in both men and women. Patients younger than age 70 are at risk when they have GFR less than 50 mL/min/1.73 m^2, while patients aged 70–79 are at risk when their GFR is less than 40 mL/min/1.73 m^2. From the results, we are proposing the current definition for CKD, a GFR less than 60 mL/min/1.73 m^2, to be re-evaluated for the Japanese population.

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REVIEW ARTICLE

Chronic kidney disease perspectives in Japan and the importance of urinalysis screening

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Abstract There are racial differences in primary renal diseases for end-stage renal disease (ESRD) and the incidence and prevalence of cardiovascular disease (CVD). To reduce the number of patients with both ESRD and CVD, an effective screening method for CKD should be established. In Japan, screening with the urine dip-stick test for proteinuria has been used since 1972 targeting every child and worker and since 1983 for every resident over 40 years old. There are several reasons for continuing this screening program. First, the positive rate of proteinuria is high in the Japanese general population, especially subjects with neither hypertension nor diabetes. Most of these subjects have no symptoms, and the only sign of renal disease is asymptomatic urinary abnormalities. Second, the prevalence and incidence of glomerulonephritis, especially IgA nephropathy, are high in the Japanese and Asian races, and urinalysis is the only method for early detection of chronic glomerulonephritis. Third, 10-year survival of the ESRD patients due to glomerulonephritis was approximately twice that of ESRD patients due to diabetes and nephrosclerosis. Consequently, reducing the incidence of ESRD due to glomerulonephritis is one of the best ways to reduce the prevalence of ESRD. Furthermore, higher incidence of ESRD in Asian races than in Caucasians was reported. Proteinuria is known to be the best predictor for reducing renal function, and the urine dip-stick test for proteinuria is less expensive and is cost-effective. For an effective screening strategy to reduce the ESRD population in Japanese and Asians, universal screening with the urine dip-stick test for proteinuria could be one solution.

Keywords CKD · CVD · Screening · Proteinuria · Racial difference

Introduction

The estimated global maintenance dialysis population is just over 1.5 million patients [1]. The size of this population has

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been expanding at a rate of 7% per year. If current trends in end-stage renal disease (ESRD) prevalence continue, the ESRD population will exceed 2 million patients by the year 2010 [2]. At the end of 2005, patients with ESRD who required renal replacement therapy (RRT) were 257,765 in Japan. The prevalence of patients with ESRD was 1,797 per million population, and the incidence of patients with ESRD was 267 per million population in 2003 in Japan. Figure 1 shows yearly changes in the dialysis population from 1968 to the present in Japan (Fig. 1) [3]. Japan has the largest prevalence of ESRD patients in the world. Furthermore, Japan was the fourth in terms of ESRD incidence patients worldwide [4]. A health-related quality of life among dialysis patients was also poor [5], and life expectancy of the ESRD population is about half that of the general population in Japan [3]. The growing dialysis population is emerging not only to be a major global socio-economic problem, but also a public health problem.

In 2002, the Kidney Disease Outcomes Quality Initiative (K/DOQI) of the National Kidney Foundation gave a definition and classification system for chronic kidney disease (CKD) [6]. The definition and classification of CKD were accepted by the international board of directors of Kidney Disease: Improving Global Outcomes [7]. CKD was defined in five stages based on the appearance of proteinuria and GFR levels. It was estimated that there are 19.2 million US adults with CKD; patients with early stage CKD had no symptoms, and the majority of individuals in early stage CKD were undiagnosed, even in developed countries [8, 9]. Furthermore, patients with CKD have an increased risk of not only ESRD, but poor cardiovascular outcomes and death [10–13]. A vast number of those with moderate CKD die before they develop more advanced CKD [14]. To reduce the number of patients with both ESRD and cardiovascular disease (CVD), effective screening and treatment methods for CKD should be established [7, 15, 16]. However, primary renal diseases for ESRD differ by race and area [17–20]. Also, the incidence and prevalence of CVD and its mortality differ by race and area [21, 22]. Consequently, the screening procedure for CKD requires different approaches depending on the patient's race, habitual, and socio-economical status. We should pay more attention to these differences to clarify a strategy for an effective screening procedure.

In Japan, an annual urinalysis screening program was introduced for every school child in 1973, for every working adult in 1972, and for every resident older than 40 years of age in 1982 under the auspices of local governments and the Ministry of Health, Labor and Welfare of Japan. Also, an annual measurement of serum creatinine was started in 1992 for every resident over 40 years of age [23, 24], although most countries do not perform universal urinalysis screening [25].

In this review, we will focus on our experiences with the Japanese urinalysis screening program and its achievement, problems, and reasons why it has continued until today. Furthermore, we will discuss our strategies for screening systems for CKD in Japan and in Asian populations, and future perspectives.

Racial and geographical differences in primary renal disease in Japan and other countries in terms of ESRD

At the end of 2005, patients with ESRD who required RRT were 257,765 in Japan. The incidence of patients with

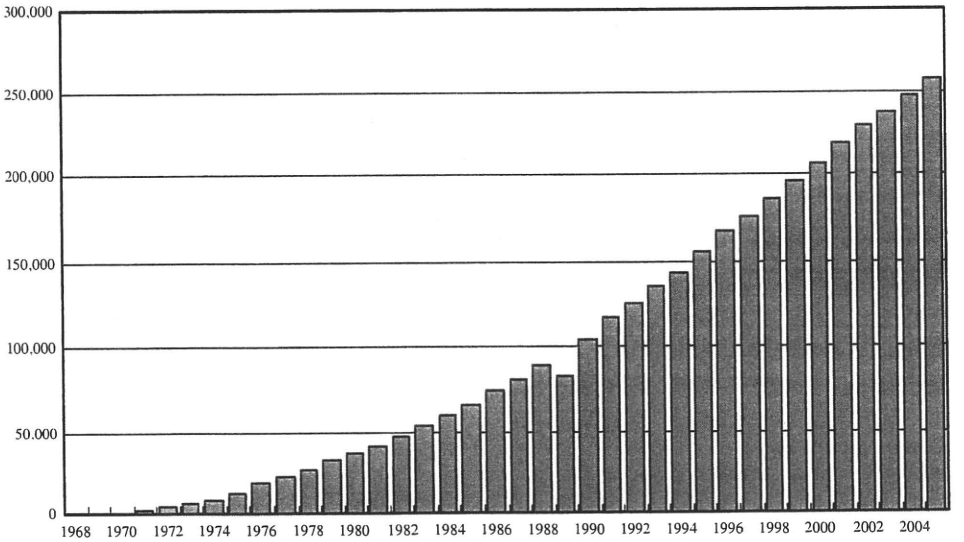

Fig. 1 Yearly changes of maintenance dialysis patients in Japan. A linear increase of maintenance dialysis patients was observed. (Data source: Japanese Society of Dialysis Therapy, registration data)

ESRD was 36,063 in Japan [3]. Figure 2 shows international comparisons of primary renal disease for those who started RRT for ESRD treatment [3, 4, 26–28]. Not only primary renal disease, but also the availability of ESRD treatment, along with age and population growth, race and the number of people with diabetes also vary between countries and areas [29, 30]. As shown in Fig. 2, while the proportion of diabetes was almost the same as in all countries, the proportion of nephrosclerosis and glomerulonephritis among countries was quite different. In Japan, glomerulonephritis was the most frequent primary renal disease for ESRD, actually accounting for more than 50% of patients entering the ESRD program in Japan from 1969 to 1996. In Taiwan, which has the highest incidence of ESRD patients in the world [4, 31], primary renal disease in patients with ESRD showed almost the same pattern as Japan.

Screening method for early detection of CKD

Most primary chronic glomerulonephritis is first manifested as asymptomatic proteinuria and/or hematuria [32, 33]. Figure 3 shows clinical manifestation of IgA nephropathy among 487 patients in Japan [34]. Approximately 68.2% of the patients with IgA nephropathy were discovered by asymptomatic proteinuria and/or hematuria [34]. For early detection of glomerulonephritis, urinalysis has been considered one of the best methods [35, 36]. The level of proteinuria is one of the strongest predictors for renal function deterioration [24, 37–41]. Consequently, to prevent an increase in the number of ESRD patients in Japan, a dipstick urine examination has been continued under the auspices of local governments and the Ministry of Health, Labor and Welfare of Japan since 1972 [23, 24]. However, in 1989 the US preventive service task force reported that routine dipstick urinalysis was not recommended for asymptomatic persons [25]. Although urinalysis screening may detect early glomerular diseases, the efficacy of early treatment of glomerulonephritis had not been studied in a randomized controlled trial at that time [25]. Furthermore, as shown in Fig. 2, about half of ESRD cases in the USA were due to hypertension or diabetes, which caused proteinuria after several years of exposure to hypertension and diabetes, and few cases of significant diseases had been detected with dipstick screening for hematuria and proteinuria after reviewing several population-based studies in both adults and children [25]. Also, most other countries did not recommend annual urinalysis screening for the same reasons [42].

Figure 4 shows yearly changes for the number of patients starting RRT in three major primary renal diseases

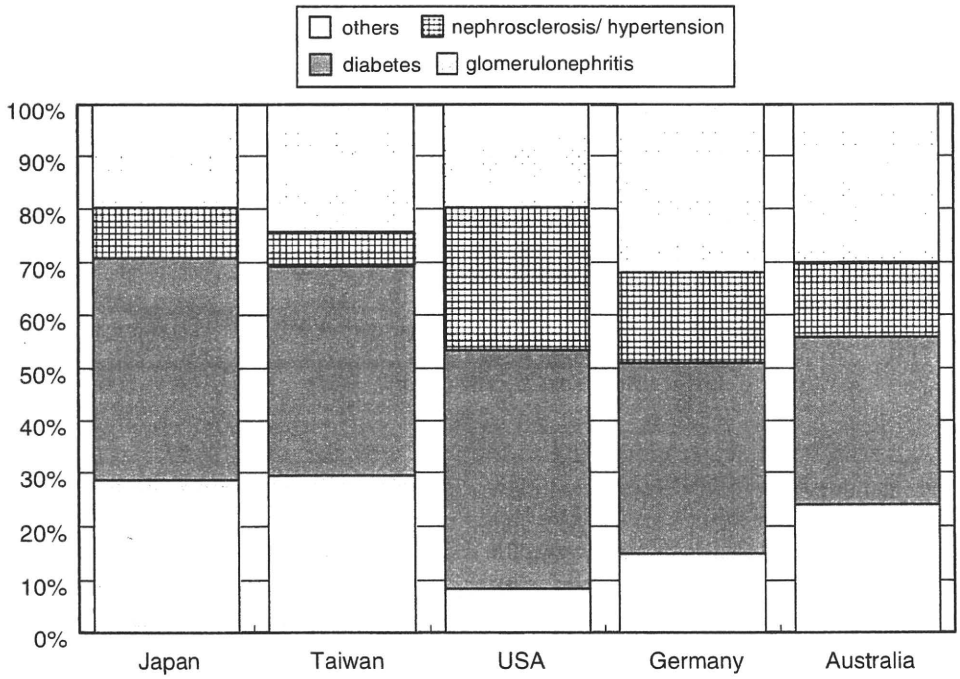

Fig. 2 Primary renal disease of new ESRD patients in several countries. Most countries showed diabetes as the most frequent cause of new ESRD. The proportion of nephrosclerosis and glomerulonephritis among those countries was quite different. In Asian countries, the proportion of glomerulonephritis was three to five times more than the proportion of nephrosclerosis as primary renal disease for ESRD. However, this tendency was not observed in the USA and European countries