症例の解説

腎機能の評価では、一昨年の健診においてSCr 0・9㎎／dℓで、尿所見異常なし。一応は基準値以下であるが、日本人用推算式による推算糸球体濾過量（eGFR）は46・4㎖／分／1・73㎡となり、CKDステージ3（GFR中等度低下：30～59㎖／分／1・73㎡）に入る。

当院受診時のeGFRは、23・0㎖／分／1・73㎡と、さらにステージ4（GFR高度低下：15～29㎖／分／1・73㎡）に低下していた。特に、ごく最近に食欲不振、全身倦怠感などの症状が出現していることから、比較的急性の腎機能低下の増悪が予測される。

基礎にあるCKDの原疾患としては、尿所見に大きな異常はないことから糸球体疾患は否定的である。長期の高血圧歴があり、超音波検査による両腎の皮質の委縮と表面の不整（楔状の変化）から、腎硬化症が疑われる。しかし、最近の比較的急性の腎機能低下は、消炎鎮痛薬（NSAIDs）による薬剤性腎障害の関与も否定できない。理学的に脱水の所見（舌の乾燥、皮膚ツルゴールの低下）、BUN／Cr比の上昇（40／1・7＞10）からは、腎前性腎機能低下の要素が考えられる。また、血清Ca値は血清Albで補正すると〔補正Ca値：血清Ca値10・2＋（4・0－血清Alb値3・0）〕11・2㎎／dℓの高Ca血症が存在する。高Ca血症による尿細管障害（尿濃縮力障害）に起因する多尿、間質障害によって脱水を来し、腎機能低下を増悪している可能性もある。

高Ca血症の原因は、腎機能低下時のビタミンD製剤の相対的な過剰投与の可能性が高いので、尿中Ca排泄量、血清iPTH値、血清PTHrP値などは測定せず、ビタミンD製剤を中止して、経過を見ることにした。脱水の補正、腎機能低下・増悪の病因解明のため、入院治療とした。

また、Friedewaldの式（LDL-C＝TC－HDL-C－0.2×TG）で計算したLDL-Cは、118㎎／dℓとCKD診療ガイドにおける目標値以下であるが、non-HDL-C（TC－HDL-C）は154㎎／dℓと若干高値である。食事療法（減塩食、低蛋白食、動物性脂肪制限）と降圧薬としてのARB（抗炎症作用が報告）の効果を期待して、3カ月経過観察とした。

経過

生理食塩水を基本とした補液による脱水の補正を行ったところ、食欲不振や全身倦怠感も消失し、1週間後にはSCr 0・9㎎／dℓ、K 4・0mEq／ℓ、Ca 8・9㎎／dℓと低下した。一方、血圧は徐々に上昇し、150／80mmHg程度となり、携帯型自動血圧計（ABPM）によると、午前7時ごろがピークで160／90mmHg程度と高値であった。

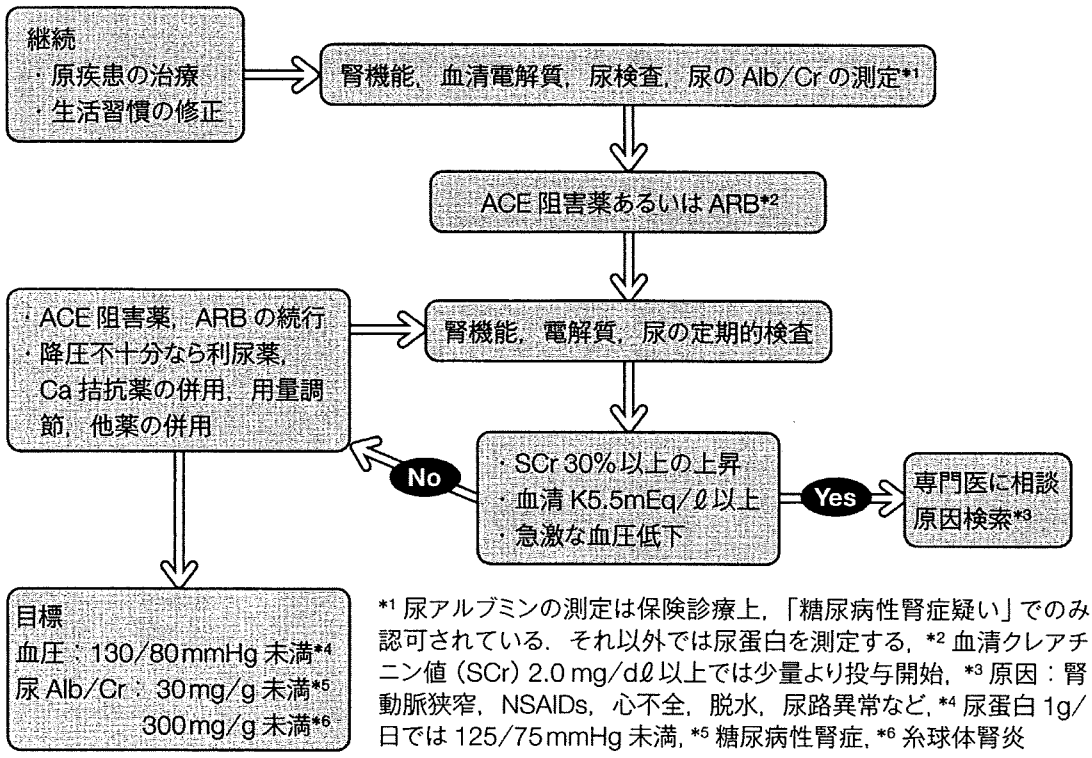
塩分制限（6g／日）とARBを追加して、退院時には早朝（起床時）血圧は130／70mmHgと改善された。ARBの追加後にはSCrは1・0㎎／dℓへ若干上昇したが、それ以上の増悪や高K血症は認めず、2週間後に退院とした。また両膝痛が強く、消炎鎮痛薬の再開を希望していたため、湿布による治療を基本とし、NSAIDsは症状の強い時のみの頓服として再開、ビタミンD製剤も0・25㎍／日に減量して再開した。その後高K血症、高Ca血症は出現していない。

3カ月後、TC 176㎎／dℓ、HDL-C 42㎎／dℓ、TG 148㎎／dℓ（non-HDL-C 134㎎／dℓ）、UA 7・2㎎／dℓとほぼ目標値（130㎎／dℓ）を達成し、食事療法も遵守されていると判断し、治療継続とした。

病態の解説

本症例のように、高血圧合併のCKD（腎硬化症）では、CKDと診断されたら、随時血圧で130／80mmHg、蛋白尿1g／日以上で125／75mmHg未満（家庭血圧では、それぞれ5mmHg低い血圧）を降圧目標に、生活習慣改善と同時にRAS阻害薬を中心とする降圧薬投与を開始するとされる。RAS阻害薬開始当初は急性腎不全、高K血症に注意し、降圧目標を達成するまで、Ca拮抗薬、利尿薬を随時追加する。

治療効果は、蛋白尿（アルブミン尿）、腎機能（eGFR）と血糖、脂質、禁煙状況や大血管障害検査指標（頸動脈超音波によるIMT、



*1 尿アルブミンの測定は保険診療上，「糖尿病性腎症疑い」でのみ認可されている．それ以外では尿蛋白を測定する，*2 血清クレアチニン値（SCr）2.0 mg/dℓ以上では少量より投与開始，*3 原因：腎動脈狭窄，NSAIDs，心不全，脱水，尿路異常など，*4 尿蛋白 1g/日では 125/75mmHg 未満，*5 糖尿病性腎症，*6 糸球体腎炎

図1　CKDを合併する高血圧の治療計画

PWV／CAVIなど）で評価する。

本症例では、SCrが一般的な基準値以下であったことから、CKDとしての認識がなく、Ca拮抗薬によって随時血圧は、高血圧の基準値である140／90 mmHgであり低いことで満足されていた。また、高齢のCKD患者では注意を要する腎毒性の可能性のある薬剤（NSAIDs）の投与量や、活性型ビタミンD製剤による高Ca血症への注意が疎かになったと考えられる。すなわち、高血圧患者では常にCKDの合併に留意し、検尿とeGFRによる早期発見の重要性が再認識された症例である（**図1**）。

冠動脈危険因子の管理に関しては、本症例では血糖は基準値内で喫煙癖はなく、軽度の脂質代謝異常（高TG血症）があるのみである。日本動脈硬化学会の「動脈硬化性疾患予防ガイドライン（2007年版）」では、動脈硬化惹起性（悪玉）のLDL-CをTCに代わる主な治療指標としている。LDL-C値は、TGが400㎎／dℓ未満の場合は、Friedewaldの式による推算値が用いられてきた。脂質異常症を伴う腎疾患患者は、少なくとも「動脈硬化性疾患予防ガイドライン」におけるカテゴリーⅢの脂質管理目標値（LDL-C120㎎／dℓ未満、HDL-C40㎎／dℓ以上、TG150㎎／dℓ未満）を目標とすべきと考えられる。

一方、CKDのリポ蛋白代謝異常の特徴はVLDL、IDL、レムナントリポ蛋白、small dense LDLなどTGを多く含む動脈硬化惹起性の異常なリポ蛋白の増加を反映するTGの上昇とHDL-Cの低下であり、これらは炎症や低栄養との関連が示唆されている。non-HDL-Cは、これらのリポ蛋白代謝異常を反映し、心血管イベント・予後の判定に対する有用性が示唆されている[1]。CKDに対する日本における基準値は明記されてはいないが、米国のガイドライン（K／DOQI）では、130㎎／dℓ未満とされ、低下作用が証明されている薬物はHMG-CoA還元酵素阻害薬（スタチン）である。

本症例では、Friedewaldの式で計算したLDL-Cは118㎎／

表1　高齢者に多い腎疾患

	一次性	二次性	泌尿器科疾患
糸球体疾患	膜性腎症 微小変化型ネフローゼ症候群 巣状分節性糸球体硬化症 IgA腎症	高血圧性腎症（腎硬化症） 糖尿病性腎症 顕微鏡的多発血管炎 （ANCA関連血管炎） 腎アミロイドーシス C型肝炎ウイルス関連腎症	
尿細管間質疾患	慢性間質性腎炎	骨髄腫腎 痛風腎 虚血性腎症 薬剤性腎障害	前立腺肥大 （腎後性腎不全） 多発性嚢胞腎 尿路結石 腎尿路悪性腫瘍

（文献[2]より）

dℓと目標値以下であるが、non-HDL-Cは154mg／dℓと若干高値である。スタチンの保険適用は高（LDL）コレステロール血症であり、本症例は適用でない。一方、食事療法（減塩食、高カロリー・低蛋白食、動物性脂肪制限）やRAS阻害薬、チアゾリジンには抗炎症作用が報告されており、病態改善が期待でき、事実本症例でも効果的であった。

◆原疾患別の治療

CKDは、原疾患としては一次性、二次性の多数の腎疾患からなる疾患群である。末期腎不全や心血管イベントの予防では共通点があるが、CKD発症予防や治療は原疾患に特異的な面が多く、その的確な診断が重要である。本症例のような高齢者では、若年者とは腎疾患の発症頻度が異なる点を考慮すべきである（**表1**）。本症例では、長期にわたる高血圧歴、超音波検査による両腎の皮質の委縮と表面の不整（楔状の変化）から、臨床的に腎硬化症と診断した。

腎疾患の確定診断には、原則として腎生検による組織学的検査が必要である。しかし、本症例のように腎機能低下や腎萎縮が進んだ場合は、得られる情報も期待できず、治療方針を立てるのにも役立たないので、腎生検の適応はないと考えられる。

本症例の原疾患と考えられる腎硬化症、腎機能の増悪に関与したと考えられるNSAIDs、高Ca血症による腎障害の病態について概説する。

①腎硬化症

腎の細動脈硬化を基礎病変とするが、広義には高血圧による腎の大血管障害による腎障害（虚血性腎症）も含む。長期の高血圧歴が腎機能低下や尿異常所見に先行する。尿蛋白は陰性か軽度（0・5g／g・Cr以下、定性では±程度）、尿沈渣には異常を認めないことが多い。顕著な尿の異常所見を認める場合には、他の腎疾患の合併を疑い腎生検を含む診断法を考慮すべきである。同時に高血圧性の眼底変化や心肥大を伴うことが多い。

病理学的には、小葉間動脈や輸入細動脈は内膜肥厚による内腔の狭小化を呈する。その結果、尿細管間質の委縮、さらに糸球体の虚血性硬化や残存糸球体の肥大を起こす。腎動脈主幹部やその分枝は、粥状硬化や石灰化による虚血性腎症では楔状の腎表面の委縮を特徴とする[3]。

治療は、前述のように厳密な24時間にわたる血圧管理が根本で、第一選択薬は蛋白尿（アルブミン尿）抑制作用を持つRAS阻害薬である。高齢者に多い動脈硬化による両側の腎動脈狭窄などでは、RAS阻害薬の使用で急性腎不全や高K血症が発症することがあるので、処方後は2～4週以内にSCr、K値を確認すべきである[4]。動脈硬化の併存はほとんどの症例で認め、他のCKD以上に、脂質管理、禁煙や肥満の是正などの血管保護的な治療が重要である。

②NSAIDsによる腎障害

薬剤性腎障害の原因としては、

抗菌薬、NSAIDs、抗腫瘍薬、抗リウマチ薬の順に頻度が高いが、NSAIDsは非処方薬（ＯＴＣ薬）としても使用され、使用頻度が高く連用される傾向があり、最も注意が必要である。

NSAIDsはシクロオキシゲナーゼ（ＣＯＸ）を阻害し、アラキドン酸からのプロスタグランジン（ＰＧ）産生を低下させる作用により、鎮痛・解熱作用を示す。腎臓での主たるＰＧ作用は、血管拡張による腎血流増加や尿細管作用による利尿効果である。特に、脱水、腎不全（ＣＫＤ）、心不全や肝硬変などによる腎循環血漿量の減少時には、ＰＧが腎血流量維持（腎保護）に重要である。このような病態におけるNSAIDsの使用は、腎血流量減少によって腎機能障害を惹起する可能性がある。また、NSAIDsによる尿細管間質性腎炎の可能性もあり、臨床経過や尿沈渣による膿尿、好酸球尿、Gaシンチグラムや必要に応じた腎生検による組織学的検査などで鑑別する必要がある。

一般に、NSAIDsのＣＯＸ阻害作用は容量依存性であり、ＣＫＤ患者で使用する際は、低用量とし、連用は避けるべきである。血行動態作用によるNSAIDsの腎障害は、早期ならば薬剤中止で可逆的に回復する[5]。急性尿細管間質性腎炎では、副腎皮質ステロイド薬の使用を検討する。本症例では、薬剤の中止と脱水の是正で腎機能は可逆的に回復している。

③高Ca血症による腎障害

高Ca血症は、ある程度高値となると、尿の濃縮障害による多尿、食欲不振から脱水となり、脱水が高Caを悪化させる悪循環に陥る。脱水による腎前性腎不全だけでなく、ある程度高度な高Ca血症（12～15㎎／dℓ）では、直接の腎血管収縮による可逆的な腎障害[6]や微小な結石による尿細管閉塞を惹起する。特に、ＣＫＤなどの腎血流低下状態では高Ca腎障害を生じやすい。

治療は、脱水補正・Ca利尿を目的とする補液やビスホスホネート製剤の使用であるが、緊急時には血液透析が必要な場合もある。本症例と異なり高Ca血症の原因薬剤の使用が確認できない場合は、原発性副甲状腺機能亢進症、多発性骨髄腫や他の悪性腫瘍、サルコイドーシスなどの肉芽腫性疾患などとの鑑別が必要である。

総括

本症例は、高齢者の高血圧患者で、健診では検尿異常が顕著でなく、SCrも基準値内（正常高値）であったためＣＫＤと診断されなかった。降圧目標、第一選択薬の面で「高血圧治療ガイドライン」に沿った治療が行われず、薬剤投与の際の腎障害に対する留意が不足したと考えられる。この点で、高血圧患者におけるＣＫＤの早期発見のための定期的な検尿とeGFRによる腎機能評価の重要性が再認識された。

ＣＫＤの治療には原疾患の診断が重要である。検尿は、診断の第一歩であるが、ＣＫＤでも尿所見がないか軽微なことが珍しくない。特に本症例のように、高齢者では加齢による腎機能低下に加えて、腎硬化症、虚血性腎症（血管性腎障害）・薬剤性腎障害（尿細管間質性腎障害）が多い。そのほかに泌尿器科疾患による腎後性腎不全などの頻度が高い。

また、ＣＫＤでは薬剤の処方に当たって、腎排泄性の薬物では腎機能に応じた変更が必要である。本症例のように、本来肝排泄性の薬物でも腎毒性の可能性が予測されるものは、特に高齢者では可能な限り少量の使用を心掛け、腎機能や電解質の経過観察が必要である。また、ＣＫＤの治療の目的は、腎保護のみならず、心血管イベントの予防であるので、高血圧、糖代謝異常、脂質代謝異常、喫煙対策が必須であり、ＣＫＤにおけるそれらの病態の特徴と治療目標値を理解して対処すべきと考える。

●文　献●

1) Nishizawa Y, et al : Kidney Int 63 (Suppl 84) : S117, 2003. 2)日本腎臓学会誌：CKD診療ガイド，東京医学社，東京，2007. 3) Harvey JM, et al : Lancet 340 (8833) : 1435, 1992. 4) Madhavan S, et al : Lancet 345 (8952) : 749, 1995. 5) Huerta C, et al : Am J Kidney Dis 45 (3) : 531, 2005. 6) Lins LE : Acta Med Scand 203 (4) : 309, 1978.

ポイント

①高齢者、特に本症例のごとく小柄な女性では、筋肉量が少なくSCrで腎機能を評価するのは困難である。尿所見の異常がない場合でもeGFRで評価することがCKDの早期発見に重要である。

②CKDの原疾患としては、尿所見の異常を伴わず、eGFRの低下がある場合には、脱水による腎前性腎不全、水腎症などの閉塞性腎障害（腎後性腎不全）が否定された場合、腎性腎不全としては血管性疾患または尿細管間質性腎障害の鑑別を行うべきである。

③高齢者では一般に腎血流量が低下しており、特にeGFR低下例や循環血漿量の低下した状態では、腎機能に応じた薬剤投与量、投与法の変更と、投与後の腎機能経過観察が必要である（「CKD診療ガイド」p88～102の「付表：腎機能低下時の薬剤投与量」を参照[2]）。本症例で使用していたNSAIDsや活性型ビタミンD製剤は、一般には腎排泄性ではないため腎機能低下時にも減量を必要としない薬剤とされる。

しかし本症例では、NSAIDsによる腎障害とビタミンD製剤による高Ca血症が尿濃縮力障害、多尿を惹起し、それによる脱水（腎前性腎機能低下）がさらに高Ca血症を増悪させる悪循環を呈した可能性がある。すなわち、腎毒性を有する薬剤（NSAIDsなど）は、常用量でも高齢のCKD患者では腎機能を増悪させる可能性がある。

高齢のCKD患者では、これらの薬剤を開始したら、腎機能や血清電解質（Ca、P、Na、K、Cl）の経過観察を要する。この時、血清Ca値の評価には、血清Albによる補正Ca値の算出が必要であることも留意すべきである。

④「高血圧治療ガイドライン」（JSH2009）では、CKD患者の随時血圧の降圧目標は130／80 mmHg未満（1日1g以上の蛋白尿の場合は、125／75 mmHg未満）であり、降圧薬としてはRAS阻害薬（ARB、ACE阻害薬）が第一選択薬となっている。

早朝高血圧や夜間高血圧はCKDを悪化させる因子であり、携帯型自動血圧計（ABPM）または起床時や就寝前の自己測定による家庭血圧が診断に重要である。

⑤CKDは、腎機能低下による末期腎不全のみならず、心血管イベントの危険因子であり、冠動脈危険因子の管理が同時に必要である。

本症例では、CKDの病因でもある高血圧のほかに、CKDに特徴的な脂質異常症が存在した。CKDにおける脂質異常症は、TGに富むリポ蛋白（VLDL、IDL、レムナントリポ蛋白やsmall dense LDL）の増加とHDL-Cの低下であり、管理指標としてはnon-HDL-Cが有用である[1]。

昨日の常識

慢性腎臓病対策は，末期腎不全（透析導入）の回避が目的

今日の常識

慢性腎臓病（CKD）対策は，心血管イベント予防も目的

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はじめに

昨日まで，われわれは診察室で尿異常（タンパク尿，血尿）や，軽度の腎機能低下を認めるのみで自覚症状に乏しい腎疾患患者に治療の必要性を説くとき，「透析にならないように…」というフレーズを必ずといっていいほど使ってきたのではないだろうか．もちろん，それは今日においてもなお必要といってよいだろう．しかし今日からは，さらに「心筋梗塞や，脳梗塞などの心血管病（CVD）を予防するために…」というフレーズを加えるのを忘れないようにしたい．

1 CKDとは

昨日と今日を境する新しい疾患概念が，CKD（chronic kidney disease：慢性腎臓病）である．**CKDとは，①腎障害を示唆する所見（検尿異常，画像異常，血液異常，病理所見など）の存在，②糸球体濾過値（GFR）が60mL/分/1.73m^{2}未満の，片方または両方が3ヵ月以上持続することにより診断され，原疾患は問わない．**

近年，透析・移植を要する末期腎不全（ESRD）患者が世界的に著しく増加し，医療経済を圧迫していることや，CKD患者ではCVDの併発が多いことを示す証拠が数多く示されたことなどを背景に，2002年にアメリカのnational kidney foundation, kidney disease outcomes quality initiative（K-DOQI）work groupのガイドライン[1]が提示されるに至り，改めてCKDがCVDの危険因子であることが脚光を浴びることになった．

2 CKDはCVDの危険因子である

図はアメリカ一般住民においてCKD患者を5年間観察し，予後を調査したものである[2]．GFR60～89mL/分/1.73m^2（CKDステージ2）の軽度の腎機能低下群では，観察期間中の死亡率は，むしろ透析・移植が必要なESRDに至る確率よりはるかに高く，尿タンパク陽性群では陰性群と比較して，死亡率がさらに高い．CKDが進行したGFR 30～59mL/分/1.73m^2（CKDステージ3），GFR 15～29mL/分/1.73m^2（CKDステージ4）の各群においても，この傾向は同様で，CKDの進行に伴い死亡率は明らかに増加する．この死因の多くはCVDが占めると推定されており，CKDがCVDの高リスク群であることを明確に認識させられる重要な成績の一つである．

前述のK-DOQIガイドラインでは，システマ

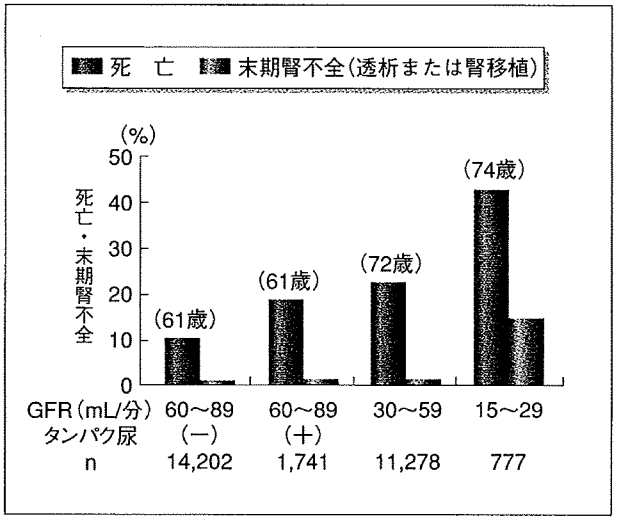

図　腎機能別に見た死亡と末期腎不全（透析または腎移植）発症率（アメリカの成績）
（　）内は平均年齢　（文献2）より改変）

ティックレビューにより，**腎機能低下はCVDあるいは全死亡の危険因子であり，タンパク尿およびアルブミン尿はCVDの発症の危険因子である**と結論した．また，個別研究では，アメリカのHMO保険(Kaiser Permanente)加入者を対象とした疫学調査で，腎機能低下とともに総死亡，CVDイベント発症，総入院の相対危険度は増加すること[3]，オランダの一般住民を対象とした観察研究で，尿アルブミン排泄量増加に伴い，CVDによる死亡率は直線的に増加することが示されている[4]．

欧米とは疾病構造の異なるわが国においても，近年の一般住民コホートにおける疫学研究で，タンパク尿群で全死亡[5]，CVDによる死亡[5,6]，腎機能低下群で全死亡[5,6]，CVDによる死亡[5]，冠動脈疾患[7]，脳血管障害[5,7]発症の相対危険度が有意に高値であることが示された．

3 CKDにおけるCVDイベントの予防のための戦略—基本的考え方—

前述の疫学的研究から，因果関係は別として，CKDがCVDの危険因子であることは確実である．治療戦略の基本は，いうまでもなく原疾患に特異的な治療である．これに加え，生活習慣を背景にCKDの患者に併存する，CVDの古典的危険因子(高血圧，糖尿病，脂質異常症，喫煙など)の適切な管理を早期より積極的に行うとともに，CKDの進行に伴い顕在化する，いわゆるCKD関連非古典的危険因子(GFR低下，タンパク尿，レニン—アンジオテンシン系(RAS)活性化，体液過剰，Ca・P代謝異常，貧血，低栄養，炎症，酸化ストレス，尿毒症性物質，電解質異常など)を意識したリスク管理を行うことが重要となる．

RAS阻害薬による大規模介入研究と，その付加的観察研究により，**治療介入によるタンパク尿・アルブミン尿の減少の程度は，CVD発症の抑制と相関がある**ことが，今日広く知られている．

おわりに

わが国のCKDステージ3以上の頻度は10.6%[8]である．**CKDは今日のコモンディジーズであり，わが国においてもCVDの発症リスクを高め，健康を脅かす重要な症候群である**という認識が重要である．今日，CKD対策としてかかりつけ医が専門医やコ・メディカルスタッフと密接に連携しながら，早期より心血管リスク管理にかかわることが求められる時代となったといえる．

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ORIGINAL ARTICLE

Geographic difference in the prevalence of chronic kidney disease among Japanese screened subjects: Ibaraki versus Okinawa

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Abstract
Background In Japan, there is a geographic difference in the prevalence of end-stage renal disease (ESRD). Few epidemiologic studies, however, have compared the prevalence of chronic kidney disease (CKD) among different geographic areas. Other than genetic factors, socioeconomic conditions and lifestyle are targets for modification.
Methods We examined the prevalence of CKD among two large community-based screened populations, 40 years of age and older, in Japan: Ibaraki ($N = 187,863$) and Okinawa ($N = 83,150$). Prevalence of CKD was defined as an estimated glomerular filtration rate (eGFR) of less than 60 ml/min/1.73 m^2 using the coefficient modified abbreviated Modification of Diet in Renal Disease (aMDRD) study equation using a standardized serum creatinine value. CKD prevalence was compared among screenees with (+) or without (−) hypertension (systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg) and hyperglycemia (plasma glucose ≥ 126 mg/dl).
Results Both male and female participants in Okinawa had a significantly lower prevalence of hypertension (−)/hyperglycemia (−) than did patients in Ibaraki. The prevalence of CKD in Okinawa was higher than that in Ibaraki among screenees with hypertension (−)/hyperglycemia (−), and highest among screenees with hypertension (+)/hyperglycemia (−).
Conclusion The regional difference in CKD prevalence may underlie the variation in ESRD prevalence observed in Japan.

Keywords Chronic kidney disease · Glomerular filtration rate · Prevalence · Screening

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Introduction

The prevalence of end-stage renal disease (ESRD) is linearly increasing and is as high as 2,000 per million people in Japan [1]. The geographic difference in the prevalence of ESRD in Japan is well known; Okinawa has the highest ESRD population, whereas the ESRD population in Ibaraki is smaller than the National average [1]. This trend might be explained by either a high prevalence of chronic kidney disease (CKD), a faster progression of CKD, or both. The north-south gradient in the incidence and prevalence of certain diseases, such as stroke and hypertension are also well known in Japan [2]. Populations in northern Japan have a higher salt intake and other dietary habits also vary [3]. People in Okinawa tend to be more obese and have a

higher prevalence of metabolic syndrome, which causes CKD [4, 5]. The prevalence of CKD may reflect the health and functional status of the community, such as the proportion of the population with diabetes and hypertension, as well as differences in muscle mass, diet, and lifestyle.

We compared the prevalence of CKD between two large community-based screening registries available in two target prefectures (Ibaraki and Okinawa). To define CKD, we applied the newly developed and modified abbreviated Modification of Diet in Renal Disease (MDRD) study equation as it provides the most accurate formula for this purpose [6]. Determining the factors related to the regional difference in CKD prevalence might be useful for preventing ESRD. The present study is the first to demonstrate a regional difference in CKD prevalence in Japan.

Methods

The Japanese Society of Nephrology has organized an epidemiology work group and has collected data to estimate CKD population in Japan [7, 8]. The authors are participating with the epidemiology work group. Among the community-based screening programs, we selected two cohorts because the details of these subjects were previously reported and the method of serum creatinine measurement was verified. Okinawa, 128°E 27°N, is in the southern-most part of Japan, and Ibaraki, 140°E 36°N, is in northern Japan. Screening was performed during April 2005 to March 2006. Hypertension was defined as 140/90 mmHg and over and hyperglycemia was defined as fasting plasma glucose 126 mg/dl and over.

Community-based screening registry

(Okinawa) Details of the screening in Okinawa were published previously [9, 10]. For this study, we used the 2005 Okinawa General Health Maintenance Association (OGHMA) registry, and analyzed data for those aged 40 years and over at the time of screening. There were 83,150 screenees, 13.0% of the target population of 0.64 million in 2005 (Total 1.36 million).

(Ibaraki) Details of the screening in Ibaraki were published previously [11–13]. For this study, we used the 2005 registry, and analyzed data for those aged 40 years and over at the time of screening. There were 187,863 screenees, 11.6% of the target population of 1.62 million in 2005 (Total 2.98 million). The central laboratory measured creatinine using an autoanalyzer (Hitachi 7170). Data were provided after written agreement by the research committee for each registry.

GFR estimation

GFR was estimated using the coefficient modified MDRD study equation after obtaining the standardized serum creatinine (SCr) from the Cleveland Clinic. Serum creatinine (C-SCr) was calibrated using the following formula: for Okinawa, C-SCr = 1.03557343 × SCr + 0.00736639; for Ibaraki, C-SCr = 1.01758277 × SCr − 0.0643799. Both laboratories measure SCr using an enzymatic method. We confirmed the accuracy of creatinine measurement using a calibration panel composed of 42 serum samples, whose values were determined by the Cleveland Clinic (kindly provided by Dr. Van Lente at the Cleveland Clinic). eGFR (ml/min/1.73 m^2) = 175 × $Age^{-0.203}$ × $S\text{-}Cr^{-1.154}$ × (if female × 0.742) × (if Japanese × 0.741). Performance of the IDMS aMDRD equation for evaluating Japanese CKD patients was recently published [6].

Statistical analyses

Data are expressed as means ± standard deviation (SD). The st CKD was defined as eGFR <60 ml/min/1.73 m^2 [6]. A statistical significance of differences in the characteristics among participants was examined using non-paired *t* test, the Wald chi-square test, and Wilcoxson test (categorical variables). Multivariate logistic analyses were performed using SAS (Version 8.2, SAS Institute Inc., Cary, NC). A *P* value of less than 0.05 was considered statistically significant.

Results

The demographics of the screened cohorts were different between the two community-based registries: 35.6% of the participants in Ibaraki and 42.6% of those in Okinawa were men. Therefore, the mean (SD) glomerular filtration rate (GFR) levels are summarized for each age-class for both men and women among the total number of screenees (Table 1). The mean GFR levels were significantly higher in Okinawa than in Ibaraki, except in those age 80 and over among both sexes. Prevalence of CKD in Ibaraki (Okinawa) was 18.1% (15.3%) in men and 16.0% (13.9%) in women, respectively. However, the fraction of screenees were different between the two cohorts. In Ibaraki (Okinawa), it was 8.9% (23.3%) in age 40–49, 18.7% (24.9%) in age 50–59, 35.1% (23.9%) in age 60–69, 30.6% (21.9%) in age 70–79, and 6.7% (6.0%) in age 80 and over in men. In women, that was 14.4% (21.2%) in age 40–49, 27.1% (25.1%) in age 50–59, 31.7% (23.9%) in age 60–69, 22.3% (22.1%) in age 70–79, and 4.5% (7.8%) in age 80 and over.

The proportion of screenees without either hypertension or high plasma glucose was significantly smaller in

Table 1 Comparison of GFR among screened subjects in Okinawa and Ibaraki: total screened

	Ibaraki	Okinawa	*P* value
Men			
40–49	76.8 (13.3), *N* = 5,961	78.4 (14.7), *N* = 8,238	<0.0001
50–59	74.8 (14.4), *N* = 12,485	75.6 (15.4), *N* = 8,810	<0.001
60–69	69.6 (14.3), *N* = 23,515	70.4 (15.1), *N* = 8,476	<0.0001
70–79	65.8 (14.8), *N* = 20,513	66.5 (15.5), *N* = 7,757	<0.001
80 and over	61.6 (15.6), *N* = 4,463	60.6 (15.9), *N* = 2,112	<0.05
Women			
40–49	80.7 (15.6), *N* = 17,388	86.1 (16.5), *N* = 10,120	<0.0001
50–59	77.1 (15.5), *N* = 32,798	80.8 (16.5), *N* = 11,991	<0.0001
60–69	72.8 (15.4), *N* = 38,309	74.7 (15.7), *N* = 11,401	<0.0001
70–79	67.8 (15.3), *N* = 27,008	68.7 (16.2), *N* = 10,541	<0.0001
80 and over	62.1 (15.7), *N* = 5,423	62.1 (19.3), *N* = 3,704	NS

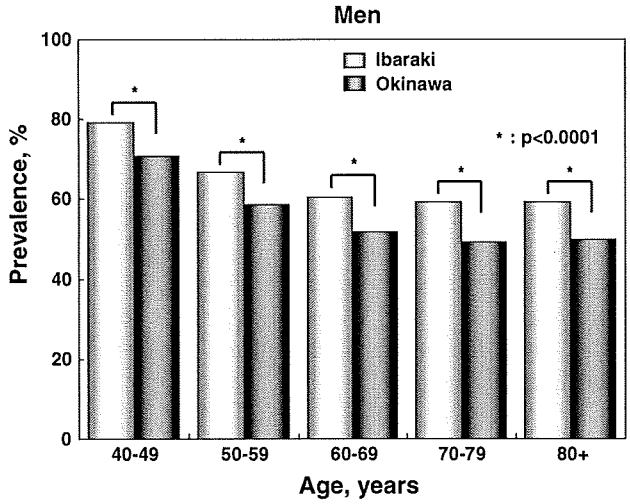

Fig. 1 Prevalence of screenees without hypertension or hyperglycemia in Okinawa and Ibaraki (men)

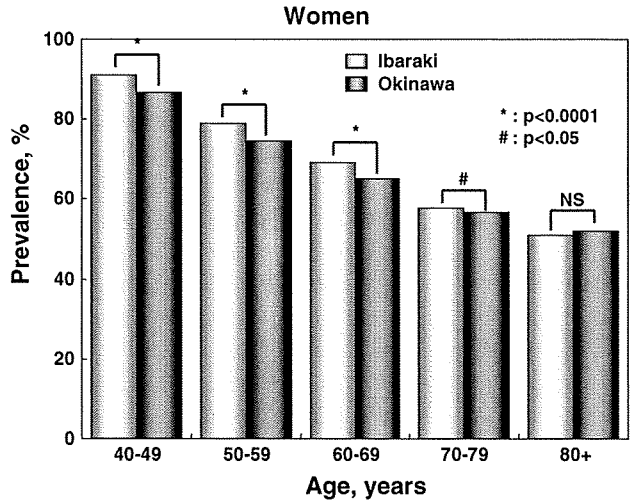

Fig. 2 Prevalence of screenees without hypertension or hyperglycemia in Okinawa and Ibaraki (women). *NS* not significant

Okinawa than in Ibaraki among men (Fig. 1) and women (Fig. 2) of all age-groups. Overall prevalence of hypertension and hyperglycemia in Okinawa was 29.9% and 10.4%: 35.5% and 14.2% in men, 26.2% and 7.6% in women, and that of Ibaraki was 27.9% and 5.1%: 31.9% and 8.4% in men, 25.9% and 3.4% in women. Among those 40–79 years of age, the prevalence of CKD of eGFR <45 ml/min/1.73 m^2, was higher in Okinawa than in Ibaraki in those with normal blood pressure and normal glucose levels, high plasma glucose, hypertension, and the total screened populations in men (Fig. 3). In each sex, the prevalence of CKD of eGFR <45 ml/min/1.73 m^2, was compared with Okinawa and Ibaraki (Fig. 4). The prevalence of CKD of eGFR <45 ml/min/1.73 m^2 among those with age 80 years and over in Okinawa (Ibaraki) was 12.6% (10.1%) in men ($P < 0.05$) and 13.0% (11.4%) in women ($P < 0.001$), respectively.

Similarly, mean GFR levels were high in Okinawa among those without either hypertension or high plasma glucose (Table 2). Compared to Ibaraki, the prevalence of low GFR (<45 ml/min/1.73 m^2) was significantly higher in Okinawa, particularly in those under 60 years of age (Table 3). Similar trends were observed among screenees without either hypertension or high plasma glucose (Table 4).

Discussion

We compared the CKD prevalence between two community-based screened cohorts using the standardized serum creatinine measurements and adopted a new, accurate GFR estimation formula for the screened Japanese populations. The strengths of the study include the large study population containing a comparable number of men and women

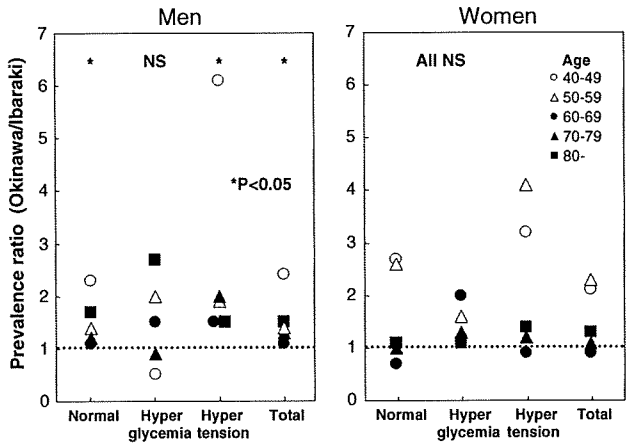

Fig. 3 Prevalence ratio of CKD, GFR <45 ml/min/1.73 m^2, in Okinawa and Ibaraki among screenees aged 40–79 years and those with age 80 years. Age-groups are 40–49 (*open circle*), 50–59 (*open triangle*), 60–69 (*filled circle*), 70–79 (*filled triangle*), and 80 and over (*open square*). In women, there was none with GFR <45 ml/min/1.73 m^2 among those with hyperglycemia age 40–49 years. $P < 0.05$ by the Wilcoxson test

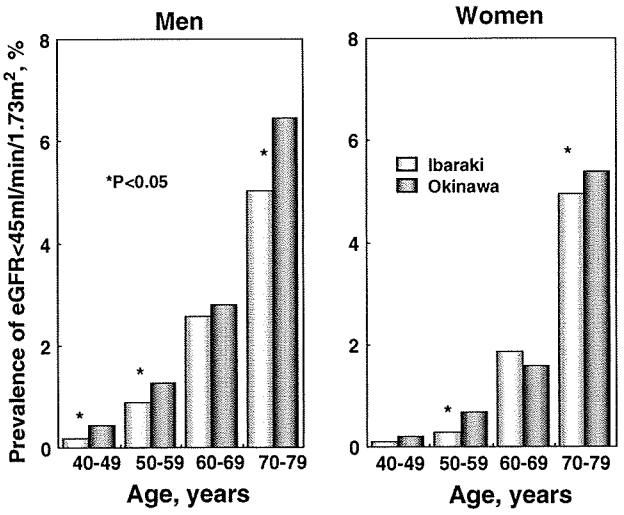

Fig. 4 Prevalence ratio of CKD, GFR <45 ml/min/1.73 m^2, by age in Okinawa and Ibaraki among screenees aged 40–79 years

and comparable age-groups, and the creatinine assays in each population were calibrated to standardized values. The key finding of the present study was that CKD prevalence was higher in Okinawa than in Ibaraki, even among groups of similar age and sex. As shown in Fig. 3, prevalence rate of GFR<45 ml/min/1.73 m^2 was higher in Okinawa, in particular age-class less than 60 years in both sexes. This may reflect the increase in obesity and metabolic syndrome in Okinawa. As a whole, mean levels of eGFR was higher in Okinawa (Table 1). This could be explained the two peaks of eGFR levels or wider distribution due to hyperfiltration related to obesity or hyperglycemia.

The findings of the present study may explain the high prevalence of ESRD in Okinawa [14]. According to the registry data of the Japanese Society for Dialysis Therapy, the prevalence of ESRD was 2,055 (Ibaraki), 2,704 (Okinawa), and 2,070 (Total) per million population in Japan in 2006 [1]. This number increased from the 2001 values of 1584 (Ibaraki), 2330 (Okinawa), and 1722 (Japan) per million population, respectively. The trend might also be explained by a rapid progression of CKD, insufficient therapy for CKD, or both.

Usami et al. [15] reported that the intake of angiotensin-converting enzyme inhibitors in Okinawa was lower than that in other parts of Japan, suggesting the insufficiency of CKD therapy in Okinawa. Because the income levels in Okinawa are the lowest in Japan, cheaper drugs are preferred. Other socioeconomically related conditions, such as a high smoking rate, a high motorization rate, and use of erythropoietin [16] may also be involved in the high prevalence of CKD.

The prevalence of CKD stages 3–5 differs among various ethnic groups. The CKD prevalence in Japan is one of the highest in the world [17–19]. The CKD prevalence might be explained by the age of the population in Japan, as more than 20% are 60 years and older. The prevalence of CKD is higher in those with hypertension and diabetes mellitus in the United States [20, 21]. In Okinawa, however, the prevalence of CKD was higher even in those without hypertension or hyperglycemia. GFR varies based on the presence of hyperglycemia, high protein intake, and obesity. Generally, Okinawan people are short in stature and have a higher prevalence of low birth weight than the national average [22]. A lower birth weight is associated with a lower nephron number and a significant risk of developing ESRD [23]. A low nephron number may result in the future development of hypertension and diabetes mellitus-related nephropathy [24]. Lifestyles have changed rapidly after the return of Okinawa to Japan in 1972, including a rapid increase in obesity.

In the present study, we applied the Japanese coefficient to improve the accuracy of the abbreviated MDRD equation to identify patients with stage 3 and 4 CKD. We used a coefficient of 0.741 obtained from the data of patients with a Cin <90 ml/min/1.73 m^2 as the Japanese coefficient with the IDMS traceable abbreviated MDRD (aMDRD) study equation. The equation provided a reasonably accurate GFR estimation in the range of less than 90 ml/min/1.73 m^2 [25]. This equation can be easily used by Japanese clinicians because the equation does not require that serum creatinine values be calibrated to the 1990 Cleveland Clinic values, where creatinine was measured using the non-compensated Jaffe method [26]. An accurate measurement of serum creatinine, however, is critical for use of IDMS aMDRD equation. In Japan, almost all clinical laboratories use the

Table 2 Comparison of GFR among screened subjects in Okinawa and Ibaraki: normal blood pressure and normal fasting plasma glucose

	Ibaraki	Okinawa	*P* value
Men			
40–49	76.5 (12.9), $N = 4,416$	77.9 (13.8), $N = 5,812$	<0.0001
50–59	74.4 (13.5), $N = 7,356$	74.9 (14.3), $N = 5,155$	NS
60–69	69.3 (13.6), $N = 12,093$	70.1 (14.2), $N = 4,364$	<0.01
70–79	65.7 (14.4), $N = 10,095$	66.7 (15.0), $N = 3,807$	<0.001
80 and over	61.4 (15.2), $N = 2,174$	61.2 (16.2), $N = 1,037$	NS
Women			
40–49	80.5 (15.3), $N = 15,428$	85.9 (16.1), $N = 8,765$	<0.0001
50–59	76.6 (15.0), $N = 24,392$	80.5 (16.1), $N = 8,921$	<0.0001
60–69	72.5 (15.0), $N = 24,103$	74.7 (15.1), $N = 7,419$	<0.0001
70–79	67.4 (14.9), $N = 13,801$	68.6 (15.5), $N = 5,946$	<0.0001
80 and over	61.9 (15.6), $N = 2,403$	62.1 (19.2), $N = 1,847$	NS

Table 3 Comparison of the prevalence of low GFR, <45 ml/min/1.73 m^2 and <60 ml/min/1.73 m^2 among screened subjects in Okinawa to those in Ibaraki (reference): total screened

	GFR <45	*P* value	GFR <60	*P* value
Men				
40–49	2.37	<0.01	0.93	NS
50–59	1.44	<0.01	1.42	<0.0001
60–69	1.10	NS	0.84	<0.0001
70–79	1.29	<0.0001	0.85	<0.0001
80 and over	1.50	<0.0001	1.06	<0.05
Total	1.04	NS	0.76	<0.0001
Women				
40–49	2.1	<0.05	0.65	<0.0001
50–59	2.34	<0.0001	1.40	<0.0001
60–69	0.86	NS	0.56	<0.0001
70–79	1.11	<0.05	0.76	<0.0001
80 and over	1.26	<0.0001	0.95	<0.05
Total	1.27	<0.0001	0.75	<0.0001

Table 4 Comparison of the prevalence of low GFR, <45 ml/min/1.73 m^2 and <60 ml/min/1.73 m^2 among screened subjects in Okinawa to those in Ibaraki (reference): normal blood pressure and normal fasting plasma glucose

	GFR < 45	*P* value	GFR < 60	*P* value
Men				
40–49	2.28	NS	0.86	<0.05
50–59	1.43	NS	1.47	<0.0001
60–69	1.08	NS	0.84	<0.0001
70–79	1.19	<0.05	0.84	<0.0001
80 and over	1.65	<0.0001	1.00	NS
Total	0.97	NS	0.73	<0.0001
Women				
40–49	2.72	<0.01	0.65	<0.0001
50–59	2.60	<0.0001	1.37	<0.0001
60–69	0.71	<0.01	0.53	<0.0001
70–79	1.01	NS	0.73	<0.0001
80 and over	1.14	NS	0.92	<0.05
Total	1.18	<0.001	0.72	<0.0001

enzymatic method to measure serum creatinine. The enzymatic method is more precise and accurate than the Jaffe method, which usually overestimates serum creatinine due to interference from the non-creatinine chromogen. Nevertheless, we further confirmed that the difference is still evident when using the original Japanese Society of Nephrology GFR estimation equation (S. Matsuo et al., personal observation).

The strengths of the present study were as follows: (1) eGFR was calculated using the serum creatinine value after calibration and standardization, (2) both cohorts were large enough to compare by age and sex, (3) CKD prevalence was also evaluated using the two equations currently available in Japan.

There were some limitations of the present study: (1) Serum creatinine was not measured at a single laboratory, although assay methods of the participating laboratories were evaluated by standard samples from the Cleveland Clinic and the inter-laboratory coefficient of variation was very small (0.88%), (2) The formula for estimating GFR was developed using CKD patients; therefore, it is not applicable to a healthy population. In particular, underestimation is possible in those with an eGFR of more than 60 ml/min/1.73 m^2 [6]. Serum creatinine concentration is affected not only by GFR, but by various other factors as well, such as muscle mass, sex, race, diet, drugs, and tubular function. Ideally, the clearance of exogenous GFR markers, such as inulin, should be measured for GFR estimation, but the method is time-consuming and difficult and is not feasible for community-based screening. The Kidney Disease Improving Global Outcomes (KDIGO) group has initiated an action to improve clinical practice by

introducing GFR estimating equations that were developed for a large cohort of a variety of racial and other groups for international comparisons [27–29]. Asian populations, including the Japanese, generally have low muscle mass and low protein intake, which could impair the performance of the MDRD study equation, (3) Clinical information, such as inflammation, nutritional status, or drug treatment, was not included in the registry data.

In conclusion, the findings of the present study revealed that there are significant regional differences in CKD prevalence among screened subjects in Japan. Although, our results may need to be confirmed in other parts of Japan. Reasons for the difference in CKD prevalence remain speculative. Generally, people in Okinawa are short in stature and have a larger body mass index. Lifestyle habits, such as smoking, drinking, and exercise among people in Okinawa also differ from those in Ibaraki. The observed differences in ESRD prevalence might be at least partly due to the difference in the CKD prevalence. Further studies on CKD progression and background demographics in the two cohorts are warranted.

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Conflict of interest statement We have no conflict of interest.

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ORIGINAL ARTICLE

Prevalence of anemia according to stage of chronic kidney disease in a large screening cohort of Japanese

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Abstract
Background The prevalence of chronic kidney disease (CKD) is high in developed countries, including Japan. However, little is known about the prevalence of anemia according to the estimated glomerular filtration rate (eGFR) among Japanese.
Methods We studied screenees on the Okinawa General Health Maintenance Association (OGHMA) registry in 1993 ($N = 94,602$; 54,848 women and 39,754 men) who had both serum creatinine and hematocrit data. Anemia was defined as follows: hematocrit level <40% in men, <32% in women aged <50 years, and <35% in women aged ≥50 years. GFR was estimated using a new Japanese equation: eGFR (ml/min per 1.73 m^2) = 194 × serum creatinine$^{1.094}$ × age$^{0.287}$ × 0.739 (if female).
Results The prevalence of anemia clearly increased as CKD progressed below an eGFR of 60 ml/min per 1.73 m^2 in both genders. Logistic analysis adjusted with body mass index and older age (≥70 years) revealed that the odds ratio for complications of anemia was significantly increased below an eGFR of 45 ml/min per 1.73 m^2 in women and 90 ml/min per 1.73 m^2 in men. The association of lower kidney function with anemia was found to be more prevalent: adjusted odds ratio ≥2.0, from approximately 50 ml/min per 1.73 m^2.
Conclusion The present study suggested that there might be as many as 1,000,000 people with CKD stage 3–5 complicated with anemia in Japan.

Keywords Chronic kidney disease · Anemia

Introduction

Accumulating evidence has shown that even early-stage chronic kidney disease (CKD) is a risk factor for developing cardiovascular disease (CVD) [1–3]. In addition to traditional risk factors such as hypertension, anemia may be associated with CVD among general subjects [4]. Similarly, it has been reported that low hemoglobin, especially together with CKD, increases the risk of coronary heart disease (CHD), CHD-related death, and stroke [5–8]. Since anemia accelerates the progression of CKD and advanced CKD is likely to be complicated with anemia, the combination of anemia and CKD, which promote each other in a vicious circle, could result in an increased risk of CVD and vice versa, that is, cardio-renal anemia syndrome [9]. Therefore, it is critical to identify CKD patients complicated with anemia.

Recent studies have estimated that the incidence of mild kidney dysfunction is substantially high in the general population worldwide, though it varies across countries [10–13]. In the advanced stages of kidney failure, anemia is a common complication due to an inappropriately reduced endogenous erythropoietin production [14]. However, previous studies performed in the USA have found that even mild kidney dysfunction, with an estimated glomerular filtration rate (eGFR) of 60 ml/min per 1.73 m^2, had a

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significant impact on the occurrence of anemia [15, 16]. The study by Astor et al. [16] also demonstrated that there was a significant racial difference in the relationship between kidney function and anemia, with Japanese reported to have a much higher prevalence of CKD than US subjects [12, 17]. However, it is not yet known whether Japanese have a much higher prevalence of CKD complicated with anemia.

In this study, we investigated the prevalence of anemia according to CKD stage in a large community-based screening of Japanese subjects.

Methods

About OGHMA

Screening program: The Okinawa General Health Maintenance Association (OGHMA), a nonprofit organization founded in 1972 and currently under the direction of Drs. Ikemiya and Kinjo, conducts a large community-based annual health examination. Once each year, the staff, doctors, and nurses visit residences and workplaces throughout the prefecture to carry out health examinations. All subjects participate voluntarily in the screening. The OGHMA personnel provide mass screening, inform the participants of their results, and when necessary, recommend further evaluation or treatment. This process includes an interview concerning health status, a physical examination, and urine and blood tests. A nurse or doctor measures blood pressure using a standard mercury sphygmomanometer with the subject in sitting position. Dipstick testing for proteinuria, hematuria, and glucosuria (Ames Dipstick, Tokyo, Japan) is performed in spontaneously voided fresh urine. Proteinuria is defined as a dipstick urinalysis score of 1+ or more. Body mass index (BMI) is calculated as weight (kg) divided by the square of height (m). Computer-based data were available from April 1, 1993 through March 31, 1994 (n = 143,948) for the 1993 screening.

Participants

For the purposes of the present study, we examined OGHMA 1993 screenees who had both serum creatinine (SCr) and hematocrit data (N = 94,602; 54,848 women and 39,754 men). SCr was measured using a modified Jaffe's reaction in an autoanalyzer at the OGHMA laboratory.

Assessment of kidney function

Kidney function was evaluated by eGFR, which was calculated using the new Japanese equation: eGFR (ml/min per 1.73 m^2) = 194 × serum creatinine$^{1.094}$ × age$^{0.287}$ × 0.739 (if female) [18]. For calculating eGFR, we applied the value of SCr in enzymatic methods, which was calculated by the following equation: SCr (enzyme) = (SCr (Jaffe) − 0.194)/1.079 [19].

Definition of anemia, clinical data, and analysis

Anemia was defined according to the Japanese Society for Dialysis Therapy (JSDT) guidelines and the kidney disease outcomes quality initiative (K/DOQI) guidelines, which take both age and sex into account: men, <40%; women aged <50 years, <32%; and women aged ≥50 years, <35% [20, 21]. Diabetes mellitus (DM) was diagnosed when fasting plasma glucose levels were >126 mg/dl. Subjects who were already on chronic dialysis were excluded from the screening registry. To analyze the effect of kidney function on the prevalence and risk of anemia, subjects were divided into following six groups: less than 15 ml/min per 1.73 m^2, from 15 to 29 ml/min per 1.73 m^2, from 30 to 44 ml/min per 1.73 m^2, from 45 to 59 ml/min per 1.73 m^2, from 60 to 90 ml/min per 1.73 m^2, and more than 90 ml/min per 1.73 m^2.

According to the recently published JSDT Guideline for Renal Anemia in Chronic Kidney Disease, anemia was defined as <35% in women [22]. We also analyzed using this definition in women.

Statistics

Statistical significance of differences in characteristics across participants was examined using the t test (continuous variables), and the Wald chi-square test (categorical variables) was carried out. We compared values of hematocrit and prevalence of anemia between the different levels of clinical variables such as BMI, age, and eGFR by Scheffé's multiple comparison methods after analysis of variance (ANOVA). Multiple logistic analysis was done to examine the correlates of anemia by variables such as eGFR category, sex, older age (>70 years), and BMI category. Data are expressed as mean (standard deviation, SD). A P value of less than 0.05 was considered statistically significant.

Results

OGHMA population

Of total of 143,948 OGHMA subjects, 94,602 (65.7%: 54,848 women and 39,754 men) had measurements of both SCr and hematocrit levels. The clinical characteristics of the screened subjects according to gender are summarized in

Table 1 Characteristics of screened subjects in 1993 in Okinawa, Japan

Variable	All (N = 94,602)	Men (N = 39,754)	Women (N = 54,848)	P value
Age (years)	54.7 ± 15.3	53.5 ± 15.7	55.6 ± 14.9	<0.0001
BMI (kg/m^2)	24.0 ± 3.4	24.1 ± 3.2	23.9 ± 3.5	<0.0001
SBP (mmHg)	127.4 ± 17.7	129.4 ± 16.8	126.0 ± 18.1	<0.0001
DBP (mmHg)	76.6 ± 10.5	78.6 ± 10.4	75.1 ± 10.3	<0.0001
Urine protein (%)	3504 (3.8)	1774 (4.5)	1730 (3.3)	<0.0001
Hematocrit (%)	41.4 ± 4.1	44.5 ± 3.3	39.2 ± 3.0	<0.0001
Estimated GFR (ml/min per 1.73 m^2)	79.3 ± 20.1	79.8 ± 18.6	78.9 ± 21.1	<0.0001
Anemia (%)	5450 (5.8)	3056 (7.7)	2399 (4.4)	<0.0001
Serum creatinine (mg/dl)	0.98 ± 0.21	1.10 ± 0.20	0.89 ± 0.17	<0.0001
Diabetes (FPG ≥ 126 mg/dl)	3103 (4.8)	1711 (6)	1392 (3.8)	<0.0001
Hypertension	28312 (30.0)	13309 (33.6)	15003 (27.4)	<0.0001
Age (years)				
20–29	5423 (5.7)	2773 (7.0)	2650 (4.8)	
30–39	11802 (12.5)	5746 (14.5)	6056 (11.0)	
40–49	17612 (18.6)	7723 (19.4)	9889 (18.0)	
50–59	19996 (21.1)	7684 (19.3)	12312 (22.4)	
60–69	22446 (23.7)	9035 (22.7)	13411 (24.5)	
≥70	17323 (18.3)	6793 (18.3)	10530 (19.2)	
Estimated GFR (ml/min per 1.73 m^2)				
≥90	25258 (26.7)	10709 (26.9)	14549 (26.5)	
60–89	54042 (57.1)	24100 (60.6)	29942 (54.1)	
45–59	13287 (14.0)	4360 (11.0)	8927 (16.3)	
30–44	1829 (1.9)	524 (1.3)	1305 (2.4)	
15–29	151 (0.2)	47 (0.1)	104 (0.2)	
<15	35 (0.04)	14 (0.04)	21 (0.04)	

SBP systolic blood pressure, *DBP* diastolic blood pressure, *FPG* fasting plasma glucose

Table 1. The prevalence of subjects aged 60 years or older was approximately 40%, which included about 20% of subjects 70 years or older (both genders). Male subjects were younger overall, but had a higher prevalence of diabetes, hypertension, and proteinuria than did female subjects. The prevalence of eGFR less than 60 ml/min per 1.73 m^2 was about 16%. The distribution of eGFR according to gender is shown in Fig. 1. As expected, the prevalence of anemia in women increased from 4.4% to 7.3% when the JSDT anemia criteria were applied; consequently the overall prevalence was 7.4% in overall subjects.

Relationship between kidney function and hematocrit

Table 2 shows the mean hematocrit levels and prevalence of anemia according to BMI category, age category, and eGFR category for men and women. The lower the BMI category or the higher the age category, the lower the mean hematocrit level and the greater the prevalence of anemia. At age 70 years, the prevalence of anemia was clearly high. The mean hematocrit levels decreased and the prevalence of anemia increased as kidney function decreased below an

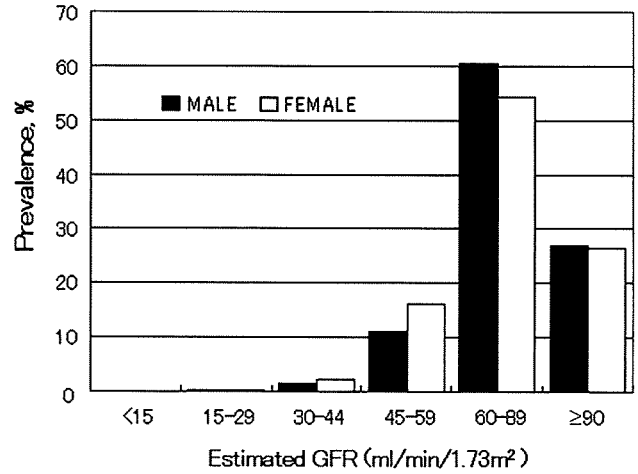

Fig. 1 Distribution of the estimated glomerular filtration rate in the cohort

eGFR of 60 ml/min per 1.73 m^2 among both men and women. In women, prevalence of anemia was 4.7% (age 20–29 years), 12.4% (age 30–39 years), 14% (age 40–49 years), 10.5% (eGFR ≥90 ml/min per 1.73 m^2), 5.7%

Table 2 Hematocrit levels and prevalence of anemia by clinical characteristics

	All ($N = 94,602$)			Men ($N = 39,754$)			Women ($N = 54,848$)		
	Number	Hematocrit (%)	Anemia, number (prevalence)	Number	Hematocrit (%)	Anemia, number (prevalence)	Number	Hematocrit (%)	Anemia, number (prevalence)
BMI (kg/m^2)									
≥26	24367	42.3 ± 4.0 (ref)	664 (2.7)	10422	45.5 ± 3.0 (ref)	317 (3.0)	13945	40.0 ± 2.8 (ref)	347(2.5)
24–26	20942	41.9 ± 4.0*	921 (4.4)	96651	44.9 ± 3.0*	489 (5.1)	11281	39.4 ± 2.9*	432 (3.8)
22–24	22287	41.3 ± 4.1*	1325 (5.9)	9645	44.4 ± 3.2*	726 (7.5)	12642	38.9 ± 2.9*	599(4.7)
<22	26241	40.3 ± 4.0*	2429 (9.3)	9754	43.4 ± 3.6*	1471(15.0)	16487	38.5 ± 3.0*	958(5.8)
ANOVA		$P < 0.0001$	$P < 0.0001$		$P < 0.0001$	$P < 0.0001$		$P < 0.0001$	$P < 0.0001$
Age (years)									
20–29	5423	42.8 ± 4.3 (ref)	53(1.0)	2773	46.1 ± 2.7 (ref)	32(1.2)	2650	39.4 ± 2.6 (ref)	21(0.8)
30–39	11802	41.9 ± 4.7*	294 (2.5)	5746	46.7 ± 2.8*	99 (1.7)	6056	38.3 ± 3.0*	195(3.2)
40–49	17612	41.3 ± 4.7*	671 (3.8)	7723	45.3 ± 2.9*	210 (2.7)	9889	38.2 ± 3.3*	461(4.7)
50–59	19996	41.6 ± 3.7*	811 (4.1)	7684	44.7 ± 3.0*	340 (4.4)	12312	39.7 ± 2.7#	471(3.8)
60–69	22446	41.5 ± 3.6*	1306 (5.8)	9035	44.0 ± 3.2*	833 (9.2)	13411	39.7 ± 2.7§	473(3.5)
≥70	17323	40.5 ± 3.8*	2320 (13.4)	6793	42.6 ± 3.8*	1542 (22.7)	10530	39.2 ± 3.1	778(7.4)
ANOVA		$P < 0.0001$	$P < 0.0001$		$P < 0.0001$	$P < 0.0001$		$P < 0.0001$	$P < 0.0001$
Estimated GFR (ml/min per 1.73 m^2)									
≥90	25258	41.4 ± 4.4 (ref)	1084 (4.3)	10709	45.0 ± 3.0 (ref)	459 (4.3)	14549	38.7 ± 3.1 (ref)	625 (4.3)
60–89	54042	41.7 ± 4.0*	2836 (5.3)	24100	44.6 ± 3.3*	1741 (7.2)	29942	39.4 ± 2.9*	29942 (3.7)
45–59	13287	40.8 ± 3.8*	1115 (8.4)	4360	43.6 ± 3.8*	642 (14.7)	8927	39.4 ± 2.9*	473 (5.3)
30–44	1829	39.6 ± 4.0*	331 (18.1)	524	41.9 ± 4.5*	174 (33.2)	1305	38.7 ± 3.4	157 (12.0)
15–29	151	37.4 ± 5.0*	60 (39.7)	47	39.2 ± 5.9*	27 (57.5)	104	36.6 ± 4.5*	33 (31.7)
<15	35	31.5 ± 4.9*	29 (82.9)	14	31.6 ± 4.8*	13 (92.9)	21	31.5 ± 5.0*	16(76.2)
ANOVA		$P < 0.0001$	$P < 0.0001$		$P < 0.0001$	$P < 0.0001$		$P < 0.0001$	$P < 0.0001$

* <0.0001, # <0.05, § <0.0005

(eGFR 60–89 ml/min per 1.73 m^2), 5.9% (eGFR 45–59 ml/min per 1.73 m^2), 12.3% (eGFR 30–44 ml/min per 1.73 m^2), 32.7% (eGFR 15–29 ml/min per 1.73 m^2), and 81.0% (eGFR <15 ml/min per 1.73 m^2) when JSDT anemia criteria were applied.

Kidney function and the odds ratio of anemia

We performed multiple logistic analyses adjusted for older age (70 years and older) and BMI category to further assess the effect of decreased kidney function on anemia. Lower eGFR was found to be significantly associated with higher prevalence of anemia below eGFR of 90 ml/min per 1.73 m^2 in men and of 45 ml/min per 1.73 m^2 in women (Fig. 2). The odds ratios (ORs) of eGFR categories (ref, eGFR ≥90 ml/min per 1.73 m^2) overall, in men, and in women were as follows: eGFR 60–89 ml/min per 1.73 m^2: 1.150 (1.067–1.240, $P = 0.003$), 1.536 (1.374–1.717, $P < 0.0001$), and 0.857 (0.772–0.950, $P < 0.0001$); eGFR 45–59 ml/min per 1.73 m^2: 1.526 (1.385–1.681, $P < 0.0001$), 2.278 (1.979–2.622, $P < 0.0001$), and 1.076 (0.940–1.233, $P = 0.2885$); eGFR 30–44 ml/min per 1.73 m^2: 2.976 (2.564–3.454, $P < 0.0001$), 5.117 (4.072–6.431, $P < 0.0001$), and 2.265 (1.843–2.783, $P < 0.0001$); eGFR 15–29 ml/min per 1.73 m^2: 11.346 (7.909–16.276, $P < 0.0001$), 24.404 (12.710–46.857, $P < 0.0001$), and 8.234 (5.269–12.867, $P < 0.0001$); and eGFR ≤15 ml/min per 1.73 m^2: 104.250 (41.632–261.049, $P < 0.0001$), 288.024 (36.039–2301.922, $P < 0.0001$), and 65.386 (23.265–183.767, $P < 0.0001$). The OR of older age (over 70 years) was 2.772 (2.597–2.959, $P < 0.0001$) overall, 3.850 (3.531–4.198, $P < 0.0001$) in men, and 1.698 (1.530–1.884, $P < 0.0001$) in women. Additionally, the ORs of BMI categories (ref. BMI ≥26 kg/m^2) overall, in men, and in women were as follows: BMI 24–26 kg/m^2: 1.565 (1.412–1.735, $P < 0.0001$), 1.552 (1.339–1.798, $P < 0.0001$), and 1.580 (1.367–1.826, $P < 0.0001$); BMI 22–24 kg/m^2: 2.159 (1.960–2.377, $P < 0.0001$), 2.305 (2.007–2.648, $P < 0.0001$), and 1.959 (1.710–2.244, $P < 0.0001$); BMI <22 kg/m^2: 3.571 (3.264–3.907 $P < 0.0001$), 4.543 (3.991–5.171, $P < 0.0001$), and 2.466 (2.172–2.800, $P < 0.0001$).

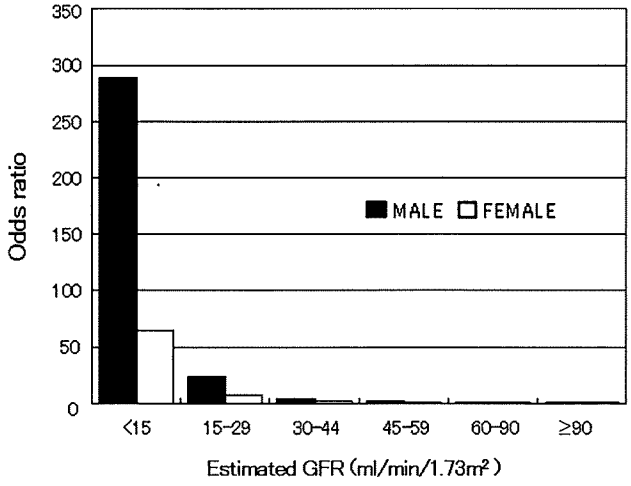

Fig. 2 Odds ratio of anemia by sex, adjusted for body mass index category and older age (>70 years) according to estimated glomerular filtration rate category in both sexes. Reference is eGFR ≥90 ml/min per 1.73 m^2

Prevalence of stage 3–5 CKD complicated with anemia

The result of the present study showed that 10% of subjects with stage 3–5 CKD were complicated with anemia. Since it has been estimated that there are 10,000,000 Japanese people with stage–3–5 CKD by using a new Japanese equation: eGFR (ml/min per 1.73 m^2) = 194 × serum creatinine$^{1.094}$ × age$^{0.287}$ × 0.739 (if female) [18], there could be as many as 1,000,000 Japanese people with stage 3–5 CKD complicated with anemia.

Discussion

Anemia is often associated with decreased eGFR. However, previous reports have suggested that the relationship between decreased kidney function and anemia varies across countries and races [15, 16, 23]. In the present study, which was conducted among a general Japanese population, the effect of decreased kidney function on anemia was significantly prevalent below eGFR of 90 ml/min per 1.73 m^2 in men and 45 ml/min per 1.73 m^2 in women.

As the previous study demonstrated [12], the distribution of eGFR among the general Japanese population is shifted to the lower side compared with that of the general US population [17]: the mean eGFR value was approximately 79 ml/min per 1.73 m^2 in our cohort, while it is reported to be 93 ml/min per 1.73 m^2 in the USA [17]. The higher incidence of aged subjects might be responsible for the lower eGFR value in Japan. Alternatively, the normal kidney function of the Japanese population might be fundamentally less than that of Caucasian populations due to the relatively smaller size of kidney and lower intake of protein. Regardless of its cause, a cutoff value of eGFR for clinical relevance is yet to be determined for the Japanese population. Some researchers have argued that it would be approximately 50 ml/min per 1.73 m^2 since the risk of end-stage renal disease (ESRD) increases significantly at this level [25]. In the present study, the OR of anemia increased to more than twice at eGFR values of less than approximately 50 ml/min per 1.73 m^2. According to the present study, the adjusted OR of stage 3 CKD for anemia in the Japanese general population has been shown to be around

two, which is similar to that in the general US population [16]. In terms of risk for complicating anemia, the clinical eGFR value in Japan might be similar to that of the general US population.

In the US population in the Third National Health and Nutrition Examination Survey (NHANES III), it was shown that African–Americans had a significantly higher OR (2.5) for anemia than Caucasians [16]. In another study from Italy conducted among patients whose mean age was about 75 years, the threshold of kidney function as a risk factor of anemia was found to be 30 ml/min per 1.73 m^2, which is lower than that of Japanese and US populations [24]. Although age might be responsible for the difference in the threshold level of kidney function in the Italian study, we found no such difference between subjects 70 years and older, and those under 70 years old (data not shown). Some factors, including differences in the definition of anemia and/or race, may affect this discrepancy.

In addition to racial differences, there might also be gender differences in the rate of complication with anemia at the same degree of kidney function. In the present study, men had a higher incidence and OR for anemia compared with women at eGFR values below 60 ml/min per 1.73 m^2; this is consistent with the previous report by Hsu et al. [25]. Differences in the cause of CKD between genders [26] and the effect of sex hormones on erythrogenesis might be responsible for this gender difference [27, 28].

The combination of anemia and CKD is reported to have a significant impact on survival compared with either anemia alone or CKD alone [29]. Since anemia has been identified not only as a nonclassical cardiovascular risk factor but also as a progressive factor in decreasing kidney function, anemia might play a significant role in the association between CKD and CVD. Accordingly, intervention for anemia could be an effective approach to prevent CVD in CKD subjects. However, large randomized intervention studies [30, 31] and a meta-analysis [32] have shown a slight but significant benefit of lower hemoglobin levels; it would thus be better to maintain these lower levels rather than attempt to improve outcome by achieving higher hemoglobin levels in CKD patients. Since the higher hemoglobin target group showed itself to have a higher risk of poorly controlled blood pressure [32], the clinical benefits of correction of anemia via an erythropoiesis-stimulating agent should be determined under strict control of blood pressure. Considering the substantial number of patients complicated with CVD and related death before starting hemodialysis therapy, intervention during ESRD might be too late to effectively prevent CVD. The incidence of anemia appears to increase from an eGFR of less than 60 ml/min per 1.73 m^2, as shown in previous studies [16] as well as in the present study. Therefore, intervention for anemia in the early stages of CKD could be an effective method of preventing CVD among CKD subjects.

In Japan, incidence of CKD is predicted to be much higher than that in the US population [12, 17]. Furthermore, it will increase since the number of elderly people is predicted to increase in Japan, at least during the next two decades. According to the present study, an association of kidney function with anemia was similar to that in the US population. Therefore, it is critical to screen CKD subjects for anemia.

The present study has a number of important limitations. First, we were unable to identify any causal association between decreased kidney function and anemia due to the cross-sectional design of the study. It was not clear how long-term CKD contributes to anemia at each CKD stage. We cannot exclude the possibility that other factors such as iron deficiency, malnutrition, and chronic disease might affect anemia. Second, one-third of the total cohort was excluded because of lack of data for Scr and Ht. It is possible that those with known kidney diseases and/or comorbid individuals are selected. However, the total number of subject is more than 90,000 and therefore it is subtle as a community-based cohort. Third, the results might vary according to the definition of anemia. The assessment of anemia by hematocrit may not be always precise and may be affected by volume status. Previous studies investigating the relationship between renal function and anemia have used the World Health Organization (WHO) criteria to define anemia [15, 16]. The WHO defines anemia as hemoglobin concentration of less than 12 g/dl for women and less than 13 g/dl for men. However, these criteria have physiological correlates in younger individuals. Therefore, it has been suggested that it might be inappropriate to apply these criteria to the present cohort, which included a substantially high number of older subjects [33]. Thus, it might be preferable to use the definition of anemia, which takes both age and sex into account [20, 21].

In conclusion, the threshold level of kidney function, below which there is an increased risk of more than twice for complicating anemia, was found to be an eGFR of approximately 50 ml/min per 1.73 m^2 in a general Japanese population. Therefore, there is expected to be a substantial number of CKD subjects with anemia who could have a higher risk for CVD as well as ESRD. Further information is needed to determine how and when intervention should be initiated in patients with both CKD and anemia.

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