ポリン・タクロリムス），アミロライド（トリテレン®），ST合剤（バクタ®），ペンタミジン（ベナンバックス®），ナファモスタット（フサン®），ACE阻害薬，アンジオテンシン受容体拮抗薬（ARB），アルドステロン拮抗薬などがある。薬剤の使用や食事内容を検討するとともに原因の鑑別を進めるために，血清の電解質（Mg・Caを含む），BUN，Crtn，浸透圧，末血，血液ガス，尿のpH，浸透圧，Crtn，電解質（Mg・Caを含む）を検討する。まず検討することは，①偽性高K血症の有無，②腎不全の有無，③アシドーシスの有無である。偽性高K血症は採血中，採血後にK濃度が上昇する病態で，原因は採血時の過剰駆血，検体放置，血小板増多，白血球増多，赤血球膜異常，呼吸性アルカローシスである。診断は大腿静脈のような大静脈や動脈からのヘパリン加採血による血漿K濃度の測定が正常であることからなされる。

(2) ステップ2

尿K測定を行い，尿K 40 mEq/日（または/gCrtn）以上かどうかを検討する。尿K 40 mEq/日（または/gCrtn）以上の場合は，Kの摂取過剰または組織崩壊の存在，またはKの再分布異常の存在を疑う。Kの摂取過剰または組織崩壊による高K血症の原因としては，輸血，横紋筋融解，腫瘍崩壊があげられる。Kの再分布異常としては高浸透圧（マンニトールや高血糖）による細胞内からの遊離，透析患者の絶食（インスリンの低下に伴う），薬剤〔シクロスポリン，イソフロレン，ニコランジル（シグマート®），ジゴキシン，フッ素中毒（Na/K ATPase阻害による），β-blocker，サクシン麻酔〕などがあげられるが，基本的に問診やルーチンの採血項目から概ね予想がつくことが多い。

(3) ステップ3

尿K排泄が40 mEq/日以下の場合は尿NaとTTKGを評価する。尿Naが25 mEq/L以下では塩分欠乏が高K血症の一因であるといえる。TTKGはTranstubular K Gradientの略で，集合管におけるK分泌能を示す指標＝アルドステロンが集合管できちんと働いているか否かの指標である。ただし尿Naが25 mEq/L以上で尿浸透圧＞血清浸透圧の場合にのみ測定の意義がある。具体的には以下の式で計算される。

$$TTKG = \{(尿K) \times (血清浸透圧)\} / \{(血清K) \times (尿浸透圧)\}$$

K：1 mg/dL = 0.26 mEq/L (0.26 mmol/L)

正常はTTKG 7～9であり，TTKG 9以上はK分泌亢進＝集合管でのアルドステロン系の機能亢進を，TTKG 6以下（2以下になることが多い）はK分泌低下＝集合管でのアルドステロン系の機能低下を示す。尿K排泄が40 mEq/日以下でTTKGが7以上の場合は遠位尿細管以降への尿流量の低下（脱水や腎不全

のため）が原因である。尿K排泄が40 mEq/日以下でETTKGが6以下の場合は集合管でのアルドステロン系の機能低下を示し，腎性の高K血症を疑う。この場合，レニン，アルドステロンの測定から，3つのタイプ（低アルドステロン型・低レニン低アルドステロン型・尿細管機能障害型）の鑑別が概ね可能である。フロリネフ負荷テストに対するTTKGの反応をみると，鑑別はより明確になる。このような腎性の高K血症では，アルドステロン系の作用低下状態のために4型尿細管性アシドーシスを合併する場合が多い。

4. カルシウム（Ca）

1）Caの制御機構

Caもほかの電解質と同様に，摂取と排泄（主に尿中）のバランスにより体内量が規定される。NaやKと異なる点は，体内総Caの99%は骨や歯など硬組織に存在しており，必要に応じて組織から遊離してくることである。つまり，食餌Ca摂取と腸管からの吸収，骨への取り込み・放出，腎臓でのCaの排泄・再吸収と，Ca代謝の司令塔である副甲状腺の4つの臓器の異常が組み合わさることでCa異常は顕在化することとなる。血清Ca濃度を実際に制御するのは，血清イオン化Ca濃度それ自体，副甲状腺で分泌される副甲状腺ホルモン（PTH：parathyroid hormone），腎臓で活性化されるビタミンDである。血清Ca値を評価する際の注意点は，血清中のCaはイオン化型と蛋白結合型の形で存在しているが，生理活性に関与するのはイオン化Ca濃度であるという点である。通常の血清Ca濃度は総Ca濃度を測定しているので，評価する際には補正Ca濃度を計算する。補正Ca濃度は血清Ca濃度を血清アルブミン値で補正した値であり，アルブミン値が4 mg/dL以下の場合，以下の式で計算される。

$$\text{補正 Ca：mg/dL} = (\text{Ca：mg/dL}) + \{4.0 - (\text{Alb：mg/dL})\}$$

この補正式は便宜上のものであり，例えばCaとアルブミンの結合はアシドーシスでは低下，アルカローシスでは増加するが，この補正式では考慮されていない。血清Ca値異常を疑うときは補正Caの計算のみでなく，可能な限りヘパリン採血全血を用いたイオン化Caも測定しておくことが望ましい。

2）低Ca血症

補正Ca濃度8.5 mg/dL以下またはイオン化Ca濃度1.05 mmol/L（= 2.1mEq/L）以下の場合をいう。症状は神経（いらいら，うつ，認知能力の低下）および神経

筋症状（筋痙攣，指のしびれ感，気管攣縮，喉頭攣縮）が主であり，重篤な場合は緊急治療の適応である。所見としては心電図異常（QT 短縮，不整脈），Chvosteck 兆候（外耳孔前部の顔面神経幹を叩くと顔面筋が収縮），Trousseau 兆候（収縮期圧以上のマンシェット駆血 3 分以上で助産婦の手が誘発）を認める。長期間の低 Ca 血症では皮膚乾燥，脱毛，つめや歯の脆弱化，大脳基底核と皮質の石灰化，骨病変（くる病＝小児の成長障害，骨軟化症＝大人の易骨折）を生じる。ガドリニウム系造影剤の使用後に検査上低 Ca になる（実際は違う）ことがあり，偽性低 Ca 血症と呼ぶ。

3）低 Ca 血症の治療

(1) ステップ 1

神経および神経筋症状を認める緊急時は，心電図モニター下に 10 mL の 8.5% グルコン酸 Ca を 5 ～ 10 分で経静脈投与，効果が不十分な場合はさらに 10 mL を追加投与し，その後，維持療法として，補正 Ca 濃度，できればイオン化 Ca 濃度のモニター下に過剰投与に注意しながら 10 mL の 8.5% グルコン酸 Ca 投与を 4 ～ 6 時間おきに繰り返す。グルコン酸 Ca の持続投与を行うこともある。低 Ca 血症の補正時には，低 Mg と高 P の補正が非常に重要である。高 P 血症を合併した低 Ca 血症は，腎不全で認められる場合がほとんどであるが，Ca 投与により Ca × P 積が上昇しリン酸 Ca が析出する危険があるので，血液透析や P 吸着剤で管理するほうが無難である。低 Mg 血症合併時は，Mg の補給を行わないと Ca の補正は成功しない。具体的には 20 mL の 10% $MgSO_4$ を血圧・心電図モニター下に 10 ～ 20 分かけて静脈投与する。

(2) ステップ 2

軽度の低 Ca 血症は内服で十分管理可能である。Ca 製剤（乳酸 Ca または炭酸 Ca を 1.5 g/日程度から開始し増量），活性化ビタミン D 製剤〔1 α $(OH)_2D_3$ 0.25 ～ 0.5μg/日または 1,25 $(OH)_2D_3$ 0.25μg/日〕，サイアザイド系利尿薬（フルイトラン 1 ～ 2 mg/日，尿 Ca 排泄低下作用あり）を組み合わせて，補正 Ca 値は正常下限，異所性石灰化を防ぐため補正 Ca × P 値 55 以下，腎石灰化や尿路結石を防ぐためスポット尿で尿 Ca（mg/dL）/尿 Crtn（mg/dL）を計算し，比が 0.25 以下になるように管理する。低 Mg 血症に対しては酸化 Mg 0.3 g/日程度から開始し，下痢に注意しながら投与量を調整する。腎不全に合併した高 P 血症を認めた場合は緊急時には血液透析を考慮し，時間的な余裕があれば P 吸着薬（炭酸 Ca 1.5 g/日程度より開始）の使用や食事療法（P 制限）を行う。

4）低 Ca 血症の鑑別診断（表 5）

(1) ステップ 1

緊急補正の必要性の有無を検討し対応する。必ず補正カルシウムの計算と，可能であればイオン化 Ca 値の評価を行う。低 Ca 血症をきたす原因薬剤の使用の有無，アシドーシスの有無，腎機能，低 Mg 血症の有無をチェックする。低 Ca 血症をきたす原因薬剤として，高 Ca の治療薬（89 頁 高 Ca 血症の治療の項参照），クエン酸（輸血内），抗ウイルス薬（フォスカルネット），フッ素中毒，抗真菌薬（ペンタミジン・ケトコナゾール），抗癌薬（アスパラギナーゼ・シスプラチン・ドキソルビシン）などがある。

(2) ステップ 2

Ca と PTH の関係を評価する（PTH の評価は intact PTH で評価する）。Ca が低いと PTH 分泌は刺激されるので，低 Ca 血症の場合には PTH 値が基準値範囲内であっても低めであれば軽度の副甲状腺機能低下症（先天性または後天性）の可能性を考慮する。

(3) ステップ 3

PTH が高値で高 P 血症（3.5 mg/dL 以上）の場合は，偽性副甲状腺機能低下症（PTH 受容体の機能異常）を，PTH が高値で低 P 血症（3.5 mg/dL 未満）の場合は，尿中 Ca 排泄と血清 25 $(OH)_2D_3$，血清 1,25 $(OH)_2D_3$ の評価を行い，ビタミン D 欠乏症〔血清 25 $(OH)_2D_3$ 低値〕，ビタミン D 依存性くる病〔VDDR-I：ビタミン D 合成酵素 1-α の異常，血清 25 $(OH)_2D_3$ 正常，血清 1,25 $(OH)_2D_3$ 低値〕，ビタミン D 抵抗性くる病〔VDDR-II：ビタミン D 受容体の異常，血清 1,25

表 5　低 Ca 血症の鑑別診断

- ステップ 1
  - 緊急性の有無→緊急治療
  - 問診（薬剤）
  - 偽性低 Ca 血症，アシドーシス，低アルブミンの有無
  - イオン化 Ca の測定
- ステップ 2
  - PTH，IP，腎機能の測定，Ca と PTH の関係を評価
- ステップ 3
  - PTH 低値→副甲状腺機能低下症
  - PTH 高値，高 P 血症（3.5mg/dL 以上）→偽性副甲状腺機能低下症
  - PTH 高値，低 P 血症（3.5mg/dL 未満）→尿中 Ca 排泄，1,25 および 25 ビタミン D 測定

$(OH)_2D_3$ 高値〕を鑑別する。

5）高 Ca 血症

補正 Ca 濃度 12 mg/dL 以上またはイオン化 Ca 濃度 1.35 mmol/L（=2.7 mEq/L）以上の場合をいう。高 Ca 血症の臨床症状は，血清 Ca 値の増加の程度と増加速度に依存する。血清 Ca は腎尿細管ヘンレの上行脚の Ca-sensing receptor（CaR）刺激を介して Ca 利尿を生ずる。この働きと PTH による Ca 吸収促進のバランスで高 Ca 血症が生じていることが多い。Ca 利尿が亢進した状況で水分摂取が不十分になると，脱水を生じ緊急治療の対象となる（高 Ca 血症性クライシス）。高 Ca 血症の臨床症状としては，精神異常，うつ，倦怠感，筋力低下，便秘，嘔気，嘔吐（まれに消化管潰瘍，膵炎），所見としては心電図異常（QT 短縮），尿路結石，腎石灰化（副甲状腺機能亢進症の 15 ～ 20%）などがある。早期の副甲状腺機能亢進症に伴う軽度の高 Ca 血症が心血管疾患発症のリスクとなることも報告されており，早期発見，治療の必要性が認識されつつある。

6）高 Ca 血症の治療

(1) ステップ 1

まず，高 Ca 血症性クライシスの有無を検討する。高 Ca 血症性クライシスは高 Ca 血症により悪心，嘔吐，高度脱水，乏尿，意識障害などを呈し，その結果さらに急激に高 Ca 血症が進行（15 mg/dL 以上）する状態をいい，輸液を中心とした緊急治療の適応である。具体的な治療法を以下に示す。

①生食 2,000 ～ 4,000 mL + フロセミド 40 mg/日，その後 3,000 ～ 6,000 mL/日で維持，脱水の補正度を検討しながらフロセミドを追加する。血清 Ca 濃度を上昇させるサイアザイド系利尿薬の使用は禁忌である。

②パミドロネート（アレディア®）30 ～ 45 mg またはインカドロネート（ビスフォナール®）10 mg またはアレンドロネート（テイロック®，オンクラスト®）10 mg を生理食塩水 500 ～ 1,000 mL で 4 時間以上かけて点滴静注，またはゾレドロネート（ゾメタ®）4 mg を生理食塩水 100 mL で 15 ～ 30 分かけて点滴静注。一回の投与で効果は 1 ～ 2 週間持続する。

③エルカトニン（エルシトニン®）40 単位 2 回/1 日筋注。破骨細胞の抑制。効果は早いが一過性なので，必ずビスホスネート製剤と併用する。

④プレドニゾロン 20 mg 静注。効果は遅い。

⑤血液透析（特に低 Ca ～無 Ca 透析液使用）。

(2) ステップ2

緊急性が低い場合，治療は原疾患によって決定される。ただし，脱水はほぼすべてのケースで合併しているので，飲水指導や必要なら補液を行う。高 Ca 血症に対してビスホスホネート製剤の投与は必ず経静脈投与を選択する。具体的な投与法はステップ1参照。

(3) ステップ3

血液腫瘍（多発性骨髄腫，ホジキン病）やビタミン D 代謝異常症（肉芽性疾患，ビタミン D 中毒）ではグルココルチコイド（プレドニゾロン 1 mg/kg/日 内服），PTHrP の分泌亢進時には 22-oxacalcitol（オキサロール®），原発性副甲状腺機能亢進症では cinacalcet（レグパラ®）による効果が期待できる。

7）高 Ca 血症の鑑別診断（表6）

高 Ca 血症の原因の大部分は原発性副甲状腺機能亢進症（45 ～ 50%）と悪性腫瘍関連疾患（45%）である。残りの 5 ～ 10%は多発性内分泌腫瘍（MEN），家族性低 Ca 尿性高 Ca 血症，薬剤，結節性疾患などを原因とするものである。

(1) ステップ1

緊急補正の必要性の有無を検討し対応する。必ず補正 Ca の計算と，可能であればイオン化 Ca 値の評価を行う。高 Ca 血症をきたす原因薬剤の使用の有無を検討し，アシドーシスの有無をチェックする。高 Ca 血症をきたす原因薬剤として，リチウム，ビタミン A 中毒，エストロゲン，抗エストロゲン，サイアザイド系利尿薬，テオフィリン，大量のミルクと制酸剤内服によるミルク・アルカリ症候群，ビタミン D 中毒などがある。薬剤で高 Ca 血症をきたした場合には，初期の原発性副甲状腺機能亢進症を合併している可能性に常に注意する。また，一般的に NSAIDs や脱水で薬剤性の高 Ca 血症が顕在化しやすい。

表6　高 Ca 血症の鑑別診断

- ステップ1
  - クライシスの有無→緊急治療
  - 問診（薬剤，無動）
  - 偽性高 Ca 血症，アシドーシス，低アルブミンの有無
  - イオン化 Ca の測定
- ステップ2
  - PTH の測定，Ca と PTH の関係を評価
- ステップ3
  - PTH 低値の場合，PTHrP と 1,25 ビタミン D を評価

(2) ステップ2

CaとPTHの関係を評価する（PTHはintact PTHで評価しておく）。Caが高いとPTH分泌は抑制されるので，高Ca血症の場合にはPTH値が基準値範囲内であっても高めであれば軽度の原発性副甲状腺機能亢進症の可能性があることに注意する。原発性副甲状腺機能亢進症は副甲状腺からのPTH異常産生のために高PTH，高Ca，低Pをきたす病態であり，高Ca血症の原因の約半分を占める。昔は線維性骨炎や腎石灰化で発見されることが多かったが，最近は軽度で間欠的な高Ca血症，PTH基準値内高めで発見されることも多い。

(3) ステップ3

PTH低値の場合，PTHrPと1,25ビタミンDを評価する。PTHrPは高Ca血症合併悪性腫瘍の80%で産生され，特に精巣，腎，乳，卵巣腫瘍やリンパ腫（HTLV-1・ノンホジキン）などで高頻度の産生を認める。また悪性腫瘍の骨転移や多発性骨髄腫では骨破壊に伴う高Ca血症を認める。腫瘤性疾患では，腫瘤がビタミンDを活性化するためビタミンDの内服や日光への曝露で高Caとなる。原因はサルコイドーシス，シリコン誘導性，真菌感染（カンジダ，コクシジオイデス），AIDSのカリニ肺炎，Wegener肉芽腫，結核などである。

おわりに

以上，本稿では水電解質異常症，特にその中でも水，Na，K，Ca制御機構と関連する疾患，および治療法を中心に述べた。これ以外に重要な電解質としてP，Mgがある。P，Mgの制御機構については近年新たな知見も得られ，非常に研究も活発な領域である。本稿で水電解質代謝異常に興味をもたれた方は，他書にてさらなる研鑽を積まれることをお勧めしたい。

（川田典孝，守山敏樹）

文　献

1) Brenner BM. The Kidney, 8th ed. Philadelphia：Saunders Elsevier, 2008.
2) Reilly RF, Perazella MA. Nephrology In 30 Days（佐藤武夫，吉田一成 監，30日で学ぶ腎臓病）．東京：メディカル・サイエンス・インターナショナル，2007.
3) 特集 水電解質と輸液．日腎会誌 2008；50：69-146.
4) 北岡建樹．よくわかる輸液療法のすべて．大阪：永井書店，2003.
5) 今井圓裕 編著．腎臓内科レジデントマニュアル．東京：診断と治療社，2000.

Clin Exp Nephrol (2009) 13:621–630
DOI 10.1007/s10157-009-0199-x

ORIGINAL ARTICLE

Prevalence of chronic kidney disease in the Japanese general population

Enyu Imai · Masaru Horio · Tsuyoshi Watanabe · Kunitoshi Iseki · Kunihiro Yamagata · Shigeko Hara · Nobuyuki Ura · Yutaka Kiyohara · Toshiki Moriyama · Yasuhiro Ando · Shoichi Fujimoto · Tsuneo Konta · Hitoshi Yokoyama · Hirofumi Makino · Akira Hishida · Seiichi Matsuo

Received: 28 January 2009 / Accepted: 28 April 2009 / Published online: 11 June 2009

Abstract
Background We previously estimated the prevalence of chronic kidney disease (CKD) stages 3–5 at 19.1 million based on data from the Japanese annual health check program for 2000–2004 using the Modification of Diet in Renal Disease (MDRD) equation multiplied by the coefficient 0.881 for the Japanese population. However, this equation underestimates the GFR, particularly for glomerular filtration rates (GFRs) of over 60 ml/min/1.73 m^2. We did not classify the participants as CKD stages 1 and 2 because we did not obtain proteinuria data for all of the participants. We re-estimated the prevalence of CKD by measuring proteinuria using a dipstick test and by calculating the GFR using a new equation that estimates GFR based on data from the Japanese annual health check program in 2005.

This work was presented in part at the 50th Annual Meeting of the Japanese Society of Nephrology at Fukuoka in 2008.

E. Imai (✉)
Department of Nephrology,
Osaka University Graduate School of Medicine,
Suita, Osaka 565-0871, Japan
e-mail: ADS12069@nifty.com

M. Horio
Department of Functional Diagnostic Science,
Osaka University Graduate School of Medicine,
Osaka, Japan

T. Watanabe
Third Department of Medicine,
Fukushima Medical University, Fukushima, Japan

K. Iseki
Dialysis Unit, University Hospital of The Ryukyus,
Nishihara, Okinawa, Japan

K. Yamagata
Department of Nephrology, Institute of Clinical Medicine,
Graduate School of Comprehensive Human Sciences,
University of Tsukuba, Ibaraki, Japan

S. Hara
Health Medical Center, Toranomon Hospital,
Tokyo, Japan

N. Ura
Department of General Medicine,
Teine Keijinkai Hospital, Sapporo, Hokkaido, Japan

Y. Kiyohara
Department of Environmental Medicine, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

T. Moriyama
Healthcare Center, Osaka University, Osaka, Japan

Y. Ando
Department of Nephrology, Jichi Medical School,
Tochigi, Japan

S. Fujimoto
First Department of Medicine, Miyazaki University,
Miyazaki, Japan

T. Konta
First Department of Medicine, Yamagata University,
Yamagata, Japan

H. Yokoyama
Division of Nephrology, Kanazwa Medical University,
Ishikawa, Japan

H. Makino
Department of Nephrology, Diabetes and Rheumatology,
Okayama University Graduate School of Medicine,
Dentistry and Pharmaceutical Sciences, Okayama, Japan

A. Hishida
First Department of Medicine, Hamamatsu University School of Medicine, Shizuoka, Japan

Methods Data were obtained for 574,024 (male 240,594, female 333,430) participants over 20 years old taken from the general adult population, who were from 11 different prefectures in Japan (Hokkaido, Yamagata, Fukushima, Tochigi, Ibaraki, Tokyo, Kanazawa, Osaka, Fukuoka, Miyazaki and Okinawa) and took part in the annual health check program in 2005. The glomerular filtration rate (GFR) of each participant was computed from the serum creatinine value using a new equation: GFR (ml/min/1.73 m^2) = 194 × $Age^{-0.287}$ × $S\text{-}Cr^{-1.094}$ (if female × 0.739). The CKD population nationwide was calculated using census data from 2005. We also recalculated the prevalence of CKD in Japan assuming that the age composition of the population was same as that in the USA.

Results The prevalence of CKD stages 1, 2, 3, and 4 + 5 were 0.6, 1.7, 10.4 and 0.2% in the study population, which resulted in predictions of 0.6, 1.7, 10.7 and 0.2 million patients, respectively, nationwide. The prevalence of low GFR was significantly higher in the hypertensive and proteinuric populations than it was in the populations without proteinuria or hypertension. The prevalence rate of CKD in Japan was similar to that in the USA when the Japanese general population was age adjusted to the US 2005 population estimate.

Conclusion About 13% of the Japanese adult population—approximately 13.3 million people—were predicted to have CKD in 2005.

Keywords Chronic kidney disease · Japanese · eGFR · Serum creatinine

Introduction

The number of chronic dialysis patients has been increasing over the last three decades in Japan, and it reached to 275,119 in 2007 [1]. The number of new dialysis patients has continuously increased, and 36,909 patients developed end-stage kidney disease (ESKD) in 2007 [1]. The latent chronic kidney disease (CKD) population therefore appears to be enormous in Japan. In addition, a growing body of evidence suggests that individuals with CKD are at high risk of cardiovascular disease (CVD) [2–4]. Thus, in order to gain a deeper knowledge of the target CKD population for better public policy making and government administration of medical affairs, it is necessary to estimate the prevalence of CKD in Japan with a nationwide epidemiological study.

In our previous study, we estimated the prevalence of CKD stages 3–5 at 19.1 million [5] based on data from the Japanese annual health check program in 2000–2004 using the MDRD equation multiplied by a coefficient of 0.881 for the Japanese population. However, this underestimates GFR, particularly for GFRs of over 60 ml/min/1.73 m^2 [6]. Therefore, the prevalence of CKD may be overestimated when using this equation. The creatinine was measured by an enzymatic method as well as by the uncompensated Jaffe method during that time period, and we corrected the creatinine to the uncompensated Jaffe method. In addition, we did not classify the participants as CKD stage 1 or 2 because we did not correct the data on proteinuria for all of the participants.

The Japanese Society of Nephrology recently established an equation for estimating GFR from serum creatinine and age for the Japanese general population [7]. The new equation provides reasonably accurate estimated GFR (eGFR) values for clinical practice and epidemiological study.

In this study, we used the new Japanese equation for estimating GFR, and the data were sampled from over half a million members of the general population who participated in an annual health check-up program in 2005 conducted in 11 prefectures of Japan; serum creatinine levels were calibrated against a central laboratory.

Methods

Study population

In this study, serum creatinine values were obtained from 574,024 members of the adult population (male 240,594, female 333,430) who participated in a large-scale annual health check-up program that was conducted in 11 prefectures of Japan (Hokkaido, Yamagata, Fukushima, Tochigi, Ibaraki, Tokyo, Kanazawa, Osaka, Fukuoka, Miyazaki and Okinawa) in 2005. All of the participants remained anonymous and the study was conducted according to Japanese privacy protection laws and ethical guidelines for epidemiological study published by the Ministry of Education, Science and Culture and the Ministry of Health, Labor and Welfare in 2005.

Calibration of serum creatinine values

Serum samples were assayed by an enzymatic method in all participating laboratories. To calibrate the samples, ten laboratories measured the calibration panel of 40 samples that was kindly provided by Dr. Frederic van Lante, Cleveland Clinic (Cleveland, Ohio). The creatinine values obtained in each laboratory were compared with the IDMS-traceable value at Cleveland Clinic (Cleveland, Ohio).

S. Matsuo
Department of Nephrology,
Nagoya University Graduate School of Medicine,
Nagoya, Japan

The serum creatinine values measured at each local laboratory (X) were corrected to the IDMS-traceable value obtained at Cleveland Clinic by the following formulae:

Miyazaki: $Y = 1.0617\ X - 0.1128$
Yamagata: $Y = 1.0543\ X - 0.0482$
Tochigi: $Y = 0.9558\ X + 0.0851$
Okinawa: $Y = 1.0176\ X - 0.0644$
Tokyo: $Y = 1.0595\ X - 0.0760$
Ibaraki: $Y = 1.0356\ X + 0.0074$
Hokkaido: $Y = 1.0418\ X + 0.0600$
Fukushima: $Y = 1.0429\ X - 0.0625$

Data from Ishikawa, and Osaka were not corrected because their data were accurate enough to be used without correction. Data from Fukuoka were not corrected on procedural grounds.

Estimation of GFR using the new Japanese equation for estimated GFR from serum creatinine

The GFR of each participant was calculated from their serum creatinine value (SCr) and their age using the new Japanese equation as follows [7]:

$$\text{GFR (ml/min/1.73 m}^2) = 194 \times \text{Age}^{-0.287} \times \text{S-Cr}^{-1.094} \text{ (if female} \times 0.739)$$

Evaluation of renal function and estimation of CKD prevalence

Renal function was evaluated in each participant using the estimated GFR. The prevalence of CKD was calculated for CKD stages 1, 2, 3, and 4 + 5, defined as GFR ≥90, 89–60, 30–59, and <30 ml/min/1.73 m^2, respectively. The age-specific prevalence of CKD stages 3–5 (ages 20–29, 30–39, 40–49, 50–59, 60–69, 70–79, and above 80 years) were calculated for each sex for the study population. The prevalence of CKD was also estimated for the general adult population using data on the Japanese adult population (103.2 million) obtained from a census in 2005 [8].

Comparison of the prevalence of CKD in Japan with that in the USA

The Japanese demographic statistics used were the population estimates from the census in 2005 [8].

The prevalence of CKD in the general population was reported on the basis of the National Health and Nutrition Examination Survey (NHANES 1999–2004, $n = 13233$) in the USA [9]. The demographic statistics for the USA that were used were the population estimates from a census from 2005 conducted by the Population Projections Branch, US Census Bureau (11 May 2004) [10].

Prevalence of CKD among hypertensive, proteinuric and diabetic populations

Proteinuria was defined as a urinary protein excretion of 1+ or more by dipstick test. Hypertension was defined as a blood pressure of 140/90 mmHg or more. The diabetic population was defined as having HbA1c ≥6.0%. The age-specific prevalence of CKD in the hypertensive proteinuric and diabetic populations were compared with those in the populations without hypertension, without proteinuria, and with HbA1c <6.0%, respectively.

Distribution of GFR in diabetic and nondiabetic populations

The distribution of estimated GFR in diabetic patients with HbA1c >6.0% was compared with that in patients with HbA1c <6.0%.

Statistics

Prevalence of proteinuria, hypertension and diabetes are expressed as percentages (%) with respect to the age-specific study population. The prevalences in males and females were compared by chi-square test. A P value of less than 0.05 was considered statistically significant. Age-specific prevalences of CKD stages are expressed as percentages (%) with respect to the age-specific study population with a 95% confidence interval (CI). The prevalences of CKD for subjects with complications such as hypertension, proteinuria and high HbA1c were compared with the prevalences in subjects without these complications by chi-square test.

Results

Prevalence of proteinuria, hypertension and diabetes in the Japanese general population

The prevalence of dipstick proteinuria (1+ or more) is shown in Fig. 1A. The prevalence of proteinuria in males increased from about 1.7 to 8.7% depending on age, while that in females remained approximately 2% (1.6–2.3%) until age reached the 70. Prevalence of hypertension, as defined by a blood pressure of 140/90 mmHg or more, increased from 5.1 to 41.5% as age increased from the 20s to the 80s in male subjects, while the prevalence also increased from 0.7 to 45.0% in females, although to a lesser extent until the 60s (Fig. 1B). Prevalence of diabetes, as defined by HbA1c >6.0%, increased from 0.2 to 12.9% as age increased from the 20s to 70s in males, while that in females also increased with age, although to a lesser extent (Fig. 1C).

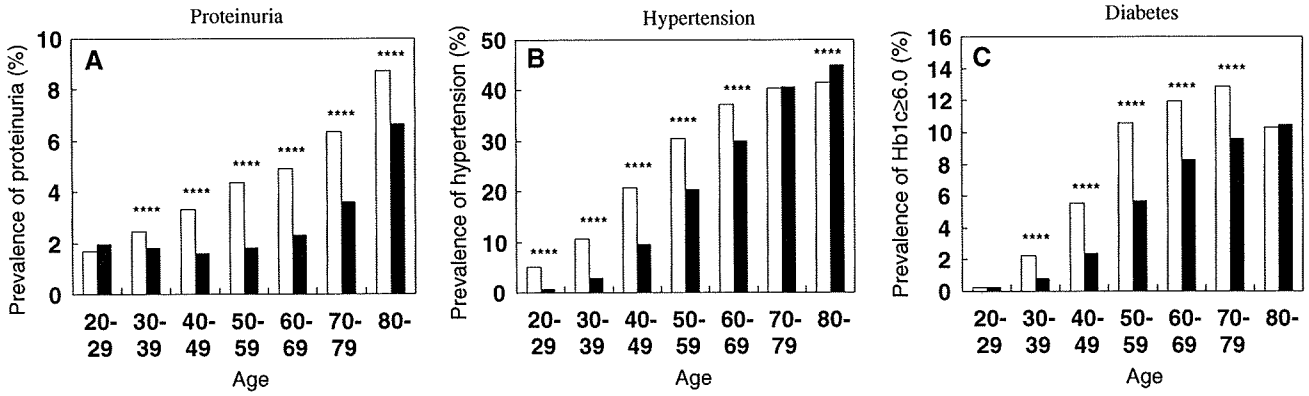

Fig. 1 Prevalence of proteinuria, hypertension, and diabetes in the study population. Proteinuria was defined as 1+ or more by dipstick test (**a**). Hypertension was defined as a systolic blood pressure of ≥40 mmHg, or a diastolic pressure of ≥90 mmHg (**b**). Diabetes was defined as HbA1c ≥6.0% (**c**). *White columns* male, *black columns* female. ****$p < 0.0001$ versus female

Table 1 Age-specific prevalence of chronic kidney disease (CKD) stages in males

	Age						
	20–29	30–39	40–49	50–59	60–69	70–79	80 and over
GFR ≥90 ml/min/1.73 m^2							
N	5166	8684	7325	9056	7714	3374	539
Prevalence (%)	52.7	37.4	20.1	17.1	13.2	6.7	5.0
95% CI	51.7–53.7	36.8–38.1	19.7–20.5	17.4–18.1	12.9–13.4	6.5–6.9	4.6–5.4
GFR 60–89 ml/min/1.73 m^2							
N	4629	14295	27704	38167	41638	33190	5455
Prevalence (%)	47.2	61.6	75.9	74.8	71.0	65.6	50.4
95% CI	46.2–48.2	61.0–62.3	75.5–76.4	74.4–75.1	70.6–71.4	65.2–66.0	49.4–51.3
GFR 50–59 ml/min/1.73 m^2							
N	5	187	1290	3209	7030	9469	2864
Prevalence (%)	0.1	0.8	3.5	6.3	12.0	18.7	26.4
95% CI	0.0–0.1	0.7–0.9	3.4–3.7	6.1–6.5	11.7–12.3	18.4–19.1	25.6–27.3
GFR 40–49 ml/min/1.73 m^2							
N	4	17	107	439	1811	3476	1353
Prevalence (%)	0.0	0.1	0.3	0.9	3.1	6.9	12.5
95% CI	0.0–0.1	0.0–0.1	0.2–0.4	0.8–0.9	3.0–3.2	6.7–7.1	11.9–13.1
GFR 30–39 ml/min/1.73 m^2							
N	0	4	21	84	306	784	456
Prevalence (%)	0.0	0.0	0.1	0.2	0.5	1.5	4.2
95% CI	0.0–0.0	0.0–0.0	0.0–0.1	0.1–0.2	0.5–0.6	1.4–1.7	3.8–4.6
GFR <30 ml/min/1.73 m^2							
N	3	6	31	88	141	312	161
Prevalence (%)	0.0	0.0	0.1	0.2	0.2	0.6	1.5
95% CI	0.0–0.1	0.0–0.1	0.1–0.1	0.1–0.2	0.2–0.3	0.6–0.7	1.3–1.7

Prevalence of CKD in Japan

Age-specific percentages of specific GFR ranges (age <30, 30–39, 40–49, 50–59, 60–79 and ≥80 ml/min/1.73 m^2) in the study population indicated that the prevalence rate of low GFR increased with age (Tables 1, 2). The prevalences of CKD stage 3 and stages 4 + 5 in each age group are shown for each sex in Fig. 2. The prevalence of CKD stage 3 (GFR 40–59 ml/min/1.73 m^2), in particular, increased with age.

The prevalence rates of CKD stages 1, 2, 3, 4 + 5 in the Japanese population in 2005 were 0.6, 1.7, 10.4, and 0.2%, respectively (Table 3). The total predicted number of cases

Table 2 Age-specific prevalence of chronic kidney disease (CKD) stages in females

	Age						
	20–29	30–39	40–49	50–59	60–69	70–79	80 and over
GFR ≥90 ml/min/1.73 m^2							
N	7032	11161	17685	17819	7514	4633	681
Prevalence (%)	67.2	53.3	34.1	22.1	8.6	6.9	4.7
95% CI	66.3–68.1	52.7–54.0	33.7–34.5	21.8–22.4	8.4–8.8	6.7–7.1	4.4–5.0
GFR 60–89 ml/min/1.73 m^2							
N	3402	9575	32834	57354	67071	41410	7139
Prevalence (%)	32.5	45.8	63.3	71.1	76.6	61.4	49.2
95% CI	31.6–33.4	45.1–46.4	62.9–63.7	70.8–71.4	76.4–76.9	61.0–61.7	48.4–50.0
GFR 50–59 ml/min/1.73 m^2							
N	19	168	1206	4822	10601	15859	3385
Prevalence (%)	0.2	0.8	2.3	6.0	12.1	23.5	23.3
95% CI	0.0–0.3	0.7–0.9	2.2–2.5	5.8–6.1	11.9–12.3	23.2–23.8	22.6–24.0
GFR 40–49 ml/min/1.73 m^2							
N	2	13	98	521	1939	4333	2367
Prevalence (%)	0.0	0.1	0.2	0.6	2.2	6.4	16.3
95% CI	0.0–0.1	0.0–0.1	0.2–0.2	0.6–0.7	2.1–2.3	6.2–6.6	15.7–16.9
GFR 30–39 ml/min/1.73 m^2							
N	1	2	20	80	263	927	710
Prevalence (%)	0.0	0.0	0.0	0.1	0.3	1.4	4.9
95% CI	0.0–0.0	0.0–0.0	0.0–0.1	0.1–0.2	0.5–0.6	1.4–1.7	3.8–4.6
GFR <30 ml/min/1.73 m^2							
N	1	5	16	79	133	318	232
Prevalence (%)	0.0	0.0	0.0	0.1	0.2	0.5	1.6
95% CI	0.0–0.0	0.0–0.1	0.1–0.1	0.1–0.1	0.1–0.2	0.4–0.5	1.4–1.8

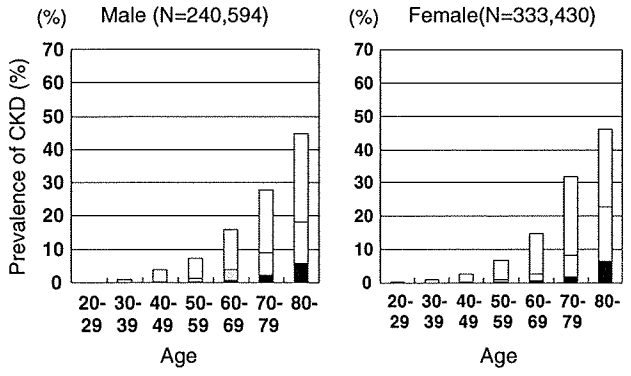

Fig. 2 Prevalence rates for CKD stages 3 to 5 for each age group in males and females in the study population. The prevalence of CKD (%) (as defined by <60 ml/min/1.73 m^2) for each age group was calculated separately for males and females in the study population. *White column* GFR 50–59 ml/min/1.73 m^2, *striped column* GFR 40–49 ml/min/1.73 m^2, *black column* GFR 40 or less ml/min/1.73 m^2

of CKD stages 1, 2, 3, 4 + 5 in the Japanese adult population in 2005 were 0.61, 1.71, 10.74, and 0.23 million, respectively (Table 3).

Prevalence of CKD stages 3–5 in proteinuric and hypertensive populations

The prevalence of CKD stages 3–5 was examined in proteinuric and hypertensive populations (Fig. 3A, B). The prevalence of CKD stages 3–5 was significantly higher in subjects with proteinuria ($P < 0.0001$) in all age groups, and in subjects with hypertension ($p < 0.01$ to $p < 0.0001$) in all age groups except for 80 years or older and in females in their 20s.

Prevalence of CKD stages 3–5 in the diabetic population

The prevalence of CKD stages 3–5 was examined in subjects with HbA1c ≥6.0 (Fig. 3C). The prevalence of CKD (defined as GFR <60 ml/min/1.73 m^2) was significantly lower in the diabetic population in some age groups (Fig. 3C), while its prevalence in subjects with reduced renal function (GFR <40 ml/min/1.73 m^2) was significantly higher in diabetic individuals in their 50s and 60s (Fig. 3D).

Table 3 Prevalence rates of CKD stages in Japanese adults (20 years or older), and estimated number of CKD cases per CKD stage based on the 2005 census

GFR (ml/min/1.73 m^2)	Total	Proteinuria (+)	Proteinuria (−)
Prevalence rate (%)			
GFR ≥90	27.8	0.6	27.2
60–89	61.6	1.7	60.0
30–59	10.4	0.8	9.6
<30	0.2	0.1	0.1
Stage 3			
50–59	7.6	0.4	7.2
40–49	2.3	0.3	2.0
30–39	0.6	0.1	0.4
Estimated number of Japanese adults in 2005			
GFR ≥90	28639274	605313	28033961
60–89	63576938	1708870	61868068
30–59	10743236	8238881	9919355
<30	236569	125190	111379
Stage 3			
50–59	7809261	425146	7384116
40–49	2363987	267158	2096828
30–39	569988	131577	438411

Prevalence of hyperfiltration in the diabetic population

The prevalence of subjects with GFR ≥120 ml/min/1.73 m^2 was significantly higher in the diabetic population ($p < 0.05$ to $p < 0.0001$) at ages 30–79 (Fig. 4). The distribution of GFR in the diabetic population was shifted to higher values than for the population with HbA1c <6.0%. A representative figurefor ages 50–59 is shown in Fig. 5. The prevalence of hypertension with GFR ≥120 ml/min/1.73 m^2 was significantly higher in the diabetic population ($p < 0.0001$) compared with the nondiabetic population (Fig. 5).

Comparison of GFR in the general population between Japan and the USA

The distribution of GFR across the whole Japanese population, calculated on the basis of the census from 2005, is shown in Fig. 6. Japan is an aging society, and the age pyramid for the population is shifted towards the elderly. An aging population tends to have low GFR, and this aging affects the distribution of GFR in the country. We recalculated the distribution of GFR by age adjusting the Japanese population to the 2005 US population estimate. As shown in Fig. 6, the distribution of GFR in the Japanese population is shifted to higher values after the correction for aging affects.

Discussion

In this study, we examined the prevalence of CKD for participants in a nationwide annual health check program in 11 prefectures of Japan using a new equation for estimating GFR from serum creatinine in the Japanese population [7]. The prevalence rates of CKD stages 1, 2, 3, and 4 + 5 in the study population of 574,024 were 0.6, 1.7, 10.4 and 0.2%, which resulted in predictions of 0.6, 1.7, 10.7 and 0.2 million patients, respectively, nationwide based on the census from 2005. Proteinuria resulted in a preponderance of declining GFR. The prevalence of concurrent CKD was significantly higher in the hypertensive population than in the population without hypertension, particularly in males. The diabetic population showed a preponderance of hyperfiltration, defined as GFR ≥120 ml/min/1.73 m^2.

The prevalence of CKD stages 1–5 has been reported for several countries (Fig. 7). According to the reliable and unbiased NHANES III surveys conducted from 1988 to 1994, from 1999 to 2000 [11], and from 1999 to 2004 [9], the prevalence of CKD remained the same between the first two surveys but increased for the third screening. For CKD stages 3 and stage 4, the prevalences were 4.2 and 0.19% in the first survey and 3.7 and 0.13% in the second survey, respectively [11]. In the third survey, the prevalences of CKD stages 1, 2, 3, 4 were 1.78, 3.24, 7.69, 0.35%, respectively (Fig. 7) [9], suggesting that the prevalence rates of CKD stages 3 and 4 increased in the USA. In Nord-Trondelag, a county in Norway, the prevalences were 4.2% for CKD stage 3 and 0.2% for CKD stages 4 + 5 [12]. The reported prevalence of CKD varies among countries in Asia. In Taiwan, about half a million participants were examined, and the MDRD equation was applied without correction using an ethnic coefficient; here, the prevalence rate of CKD was 11.9%, and those for CKD stages 1, 2, 3, 4, and 5 were 1.0, 3.8, 6.8, 0.2, 0.1%, respectively [13]. In Beijing, China, the prevalence of CKD was obtained using the original Chinese equation for estimating GFR, and the prevalences of CKD stages 1, 2, 3, 4 and 5 were 5.5, 3.3, 1.3, 0.0010 and 0.0003%, respectively [14]. Overall, about 10–13% of the population exhibited CKD in these countries. The different prevalences of CKD stages 1 and 2 among the countries appears to be mainly due to how proteinuria is defined. The definition of albuminuria differed considerably between countries. China defined albuminuria as 17 mg/g Cr [14], while the USA defined it as 30 mg/g Cr [9]. Taiwan defined proteinuria as (±) on dipstick test [13], while Japan defined a dipstick of (1+) as proteinuria. This difference in definition must affect the the prevalences of CKD stages 1 and 2 considerably. In addition, the methods used for creatinine measurement varied considerably among countries. We advocate the use of the

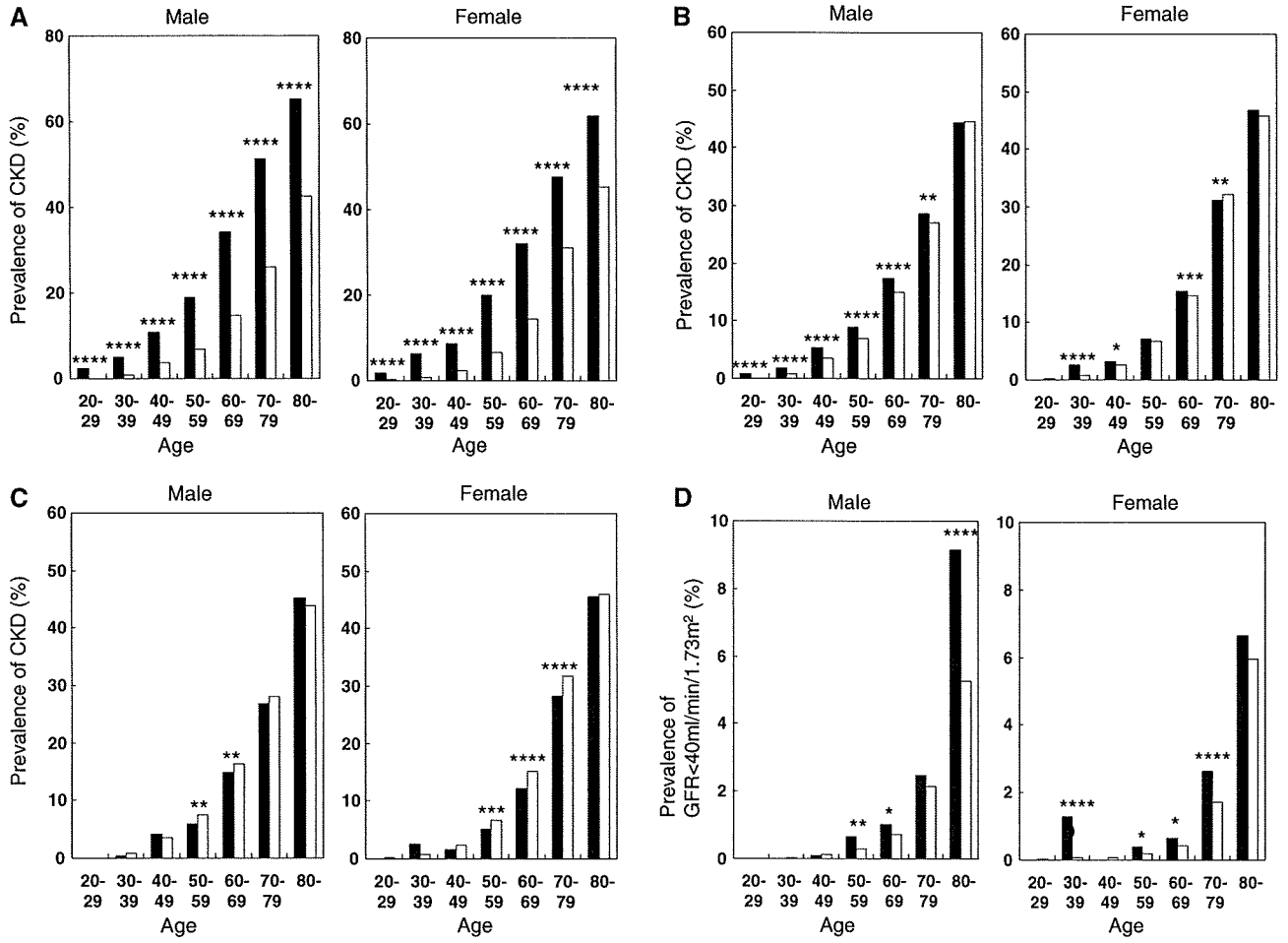

Fig. 3 Prevalence of CKD in proteinuria, hypertensive and diabetic populations. The prevalence of CKD (defined by GFR <60 ml/min/1.73 m^2) in the proteinuric population, shown by the *black column*, was compared with that in the population without proteinuria, shown by the *white column*, for each generation (**a**). Proteinuria was defined as 1+ or more by dipstick test. Prevalence of CKD (defined as GFR <60 ml/min/1.73 m^2) in the hypertensive population, shown by the *black column*, was compared with that in the population without hypertension, shown by the *white column*, for each generation (**b**). Hypertension was defined as a blood pressure of 140/90 mmHg or over. Prevalences of GFR <60 ml/min/1.73 m^2 and of GFR <40 ml/min/1.73 m^2 in the diabetic population (*black columns*) are compared with that in the nondiabetic population (*white columns*) (**c**, **d**). Diabetes was defined as HbA1c ≥6.0%. $*p < 0.05$, $**p < 0.01$, $***p < 0.001$, $****p < 0.0001$ versus individuals without cormobidity of proteinuria (**a**), hypertension (**b**), or diabetes (**c**, **d**)

following in order to compare the prevalence of CKD among different countries. First, the definition and method of measuring proteinuria must be unified across countries. Albuminuria or albuminuria-to creatinine ratio, which is scientifically more reliable than the dipstick test, should be used for proteinuria. Repeated measurements are recommended. Second, the serum creatinine that is used to estimate GFR should be measured by isotope diluted mass spectrometry (IDMS)-traceable creatinine assay. Third, the equation used to estimate GFR for each ethnic group must be established. Another alternative is to establish an IDMS-traceable MDRD equation [15] with an ethnic coefficient. The measurement of proteinuria by dipstick test and serum creatinine is accurate enough for daily practice and screening, but international comparisons of the prevalence of CKD should be done by a unified standard method involving the measurement of albuminuria and serum creatinine with an IDMS-traceable creatinine assay.

Our aging society results in a decline in the average GFR in this country. More than 20% of the Japanese population is over 60 years old, and the elderly population (over 75 years old) is much higher than in other countries. Because of this increased average age, the prevalence of CKD is higher in Japan. In fact, the distribution of the age-adjusted eGFR was shown to be similar for Japan and the USA (Fig. 6).

The prevalence of proteinuria increased as GFR decreased (Table 3) in this study. However, the prevalences of proteinuria in CKD stages 3 and 4 + 5 were 7.7 and 52.9%, respectively. In data from a mass health

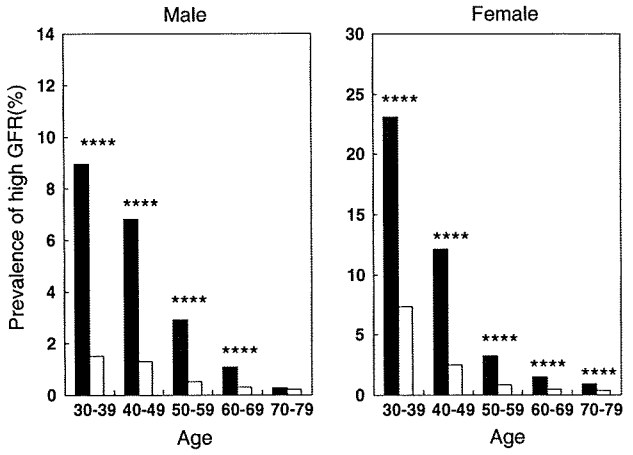

Fig. 4 Prevalence of GFR ≥120 ml/min/1.73 m^2 in the diabetic population. Individuals with diabetes as defined by HbA1c ≥6.0% are represented by the *black column*. Individuals with HbA1c <6.0% are represented by the *white column*. ****$p < 0.0001$ versus individuals with HbA1c <6.0%

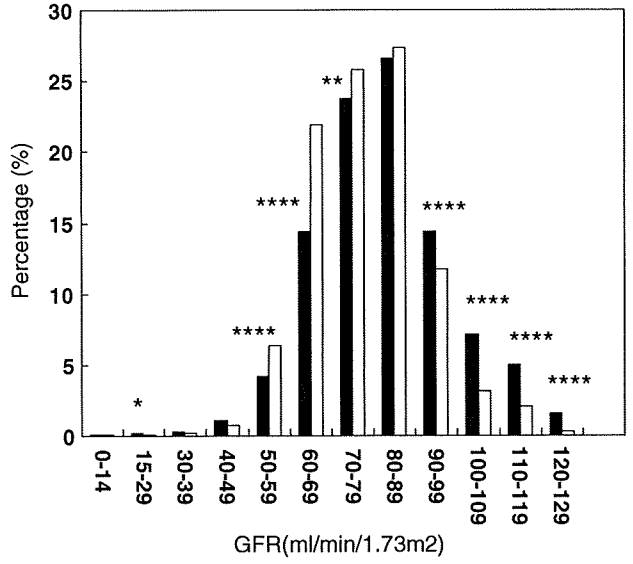

Fig. 5 Distribution of estimated GFR in populations with HbA1c ≥6.0% and HbA1c <6.0%. Distributions of estimated GFR are shown separately for diabetic individuals (defined as HbA1c ≥6.0%) and for individuals with HbA1c <6.0%. The population with diabetes is represented by the *black column*, and individuals with HbA1c <6.0% are represented by the *white column*. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, ****$p < 0.0001$ versus individuals with HbA1c <6.0%

screening in Okinawa, proteinuria (defined as a dipstick urinalysis result of 1+ or more) was a strong predictor of ESKD [16]. The rate of decline of GFR in individuals with proteinuria was more than twofold faster than that in individuals without proteinuria [17]. This may suggest that most of CKD stage 3 and half of Japanese stage 4 + 5 CKD patients without proteinuria may progress slowly to ESKD and may not even reach ESRD during their

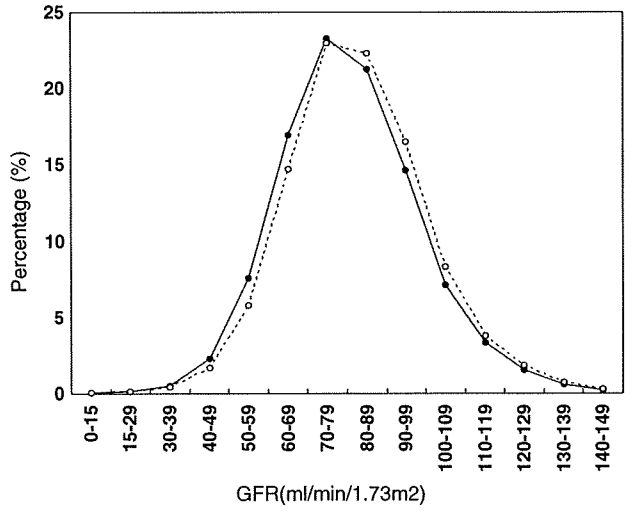

Fig. 6 Distribution of GFR in the Japanese general population. The distribution of estimated GFR for Japanese is shown by the *solid line*. We then recalculated the distribution of the GFR by age adjusting the Japanese population to the US population, as shown by the *dotted line*

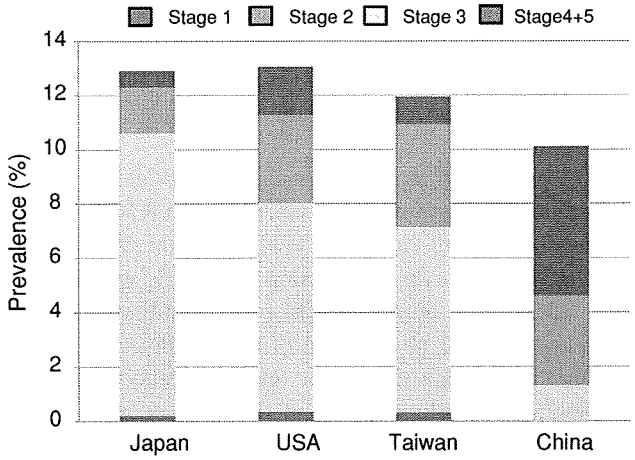

Fig. 7 Prevalences of CKD stages 1, 2, 3, and 4 + 5 in Japan, USA, Taiwan and China. The prevalence of each stage of CKD was obtained from previous publications. In Japan, the prevalence of CKD was estimated from accumulated data on 570,244 individuals aged 20 and over in the annual health check program in 2005. Proteinuria was evaluated by dipstick test, where 1+ and over was defined as proteinuria. In the USA, the prevalence of each stage of CKD was studied using data on nationally representative samples from 13,233 adults aged 20 and over taken from 1999 to 2004 [9]. The presence of albuminuria was estimated from the albumin-to-creatinine ratio, and microalbuminuria was defined as 30 mg/g creatinine. In Taiwan, the prevalence of each stage of CKD was estimated based on data from a private firm on 462,293 individuals aged 20 and over, obtained from 1994 to 2007 [13]. Proteinuria was evaluated by dipstick test, and (± or 1+) was defined as minimal proteinuria and (2+ and over) as overt proteinuria. In China, representative samples from 13,925 individuals aged 18 and older were analyzed [14]. Albuminuria was measured, and microalbuminuria was determined as ranging from 17 to 250 mg/g creatinine for males and from 25 to 355 mg/g creatinine for females

lifetimes. Further study is required to obtain risk stratifications for the stage 3 and 4 populations.

In the diabetic population, the prevalences of high GFR (GFR $\geq$120 ml/min/1.73 m^2) and low GFR (<40 ml/min/1.73 m^2) were higher than those in the population with HbA1c <6.0%, suggesting that diabetes shifts the distribution of GFR to the high and low ranges. We speculated that hyperfiltration plays a major role in this shift, and may contribute to the rapid decline in GFR in diabetic individuals. Hyperfiltration may aid the development of microalbuminuria in type 1 diabetic patients. Amin and colleagues reported a strong relationship between the risk for the development of microalbuminuria in individuals who had diabetes for five and ten years and the development of glomerular hyperfiltration in individuals who had diabetes for five years, independent of glycemic control [18].

The prevalence of CKD comorbid with other concurrent conditions in the Japanese population was similar to the corresponding prevalences in the US and Chinese populations. The prevalence of CKD was higher among hypertensive and diabetic individuals in the white US population, as previously reported [19]. The prevalence of CKD was reported to increase in hypertensive and diabetic populations in Chinese [20]. This study also supports the notion that prevalence of CKD comorbidity is higher in hypertensive and diabetic populations than in the normal population.

We previously reported that the rate of decline of GFR was more than twofold faster when the eGFR was less than 50 ml/min/1.73 m^2 in adults [17]. From the viewpoint of risk stratification for progression to ESKD, we estimated that 3.1% of the adult population (3.17 million) had GFR <50 ml/min/1.73 m^2 in 2005 (Table 3). Presence of proteinuria is a strong risk factor for ESKD and CVD. From Table 3, 2.74 million (2.7%) of the adult population have proteinuria and GFR >50 ml/min/1.73 m^2. Taken together, the CKD population with risk of progression to ESKD is predicted to be 5.91 million, 5.8% of the adult population in 2005.

The limitations of the present study are as follows. First, the study cohort was a proportion of the general population that participated in an annual health check program; it was not representative of the whole Japanese population. Second, the serum creatinine was not measured at a single laboratory, so the values of serum creatinine may have drifted. Third, we only measured proteinuria once. Therefore, the presence of proteinuria was confirmed, not persistent proteinuria.

In conclusion, about 13% of Japanese adult population, approximately 13.3 million people, were predicted to have CKD in 2005. From the viewpoint of risk stratification to progression to ESKD, about 5.8% of the adult population—approximately 6 million people—who have proteinuria or GFR <50 ml/min/1.73 m^2 are estimated to have CKD in Japan.

References

1. Japanese Society of Dialysis Therapy. An overview of regular dialysis treatment in Japan as of Dec 31, 2007. 2008. http://docs.jsdt.or.jp/overview/. Accessed 1 Dec 2008.
2. Sarnak MJ, Levey AS, Schoolwerth AC, Coresh J, Culleton B, Hamm LL, et al. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. Circulation. 2003;108:2154–69.
3. Irie F, Iso H, Sairenchi T, Fukasawa N, Yamagishi K, Ikehara S, et al. The relationships of proteinuria, serum creatinine, glomerular filtration rate with cardiovascular disease mortality in Japanese general population. Kidney Int. 2006; 69:1264–71.
4. Ninomiya T, Kiyohara Y, Kubo M, Tanizaki Y, Doi Y, Okubo K, et al. Chronic kidney disease and cardiovascular disease in a general Japanese population: the Hisayama Study. Kidney Int. 2005;68:228–36.
5. Imai E, Horio M, Iseki K, Yamagata K, Watanabe T, Hara S, et al. Prevalence of chronic kidney disease (CKD) in the Japanese general population predicted by the MDRD equation modified by a Japanese coefficient. Clin Exp Nephrol. 2007; 11:156–63.
6. Imai E, Horio M, Nitta K, Yamagata K, Iseki K, Hara S, et al. Estimation of glomerular filtration rate by the MDRD study equation modified for Japanese patients with chronic kidney disease. Clin Exp Nephrol. 2007;11:41–50.
7. Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, Yamagata K, Tomino Y, Yokoyama H, Hishida A, on behalf of the collaborators developing the Japanese equation for estimated GFR. Revised equations for estimated GFR from serum creatinine in Japan. Am J Kidney Dis. 2009;53:982–92.
8. Bureau of the Census, Ministry of Internal Affairs and Communications. http://www.stat.go.jp/data/jinsui/index.htm. Accessed 10 Jan 2009.
9. Coresh J, Selvin E, Stevens LA, Manzi J, Kuseck JW, Eggers P, et al. Prevalence of chronic kidney disease in the United States. JAMA. 2007;298:2038–47.
10. Population Projections Branch, U.S. Census Bureau Year of Projection (2000–2050). http://www.census.gov/population/www/projections/usinterimproj/. Accessed 10 Jan 2009.
11. Coresh J, Byrd-Holt D, Astor BC, Briggs JP, Eggers PW, Lacher DA, et al. Chronic kidney disease awareness, prevalence, and trends among U.S. adults 1999 to 2000. J Am Soc Nephrol. 2005;16:180–8.
12. Hallan S, Coresh J, Astor B, Asberg A, Powe N, Romundstad S, et al. International comparison of the relationship of chronic kidney disease prevalence and ESRD risk. J Am Soc Nephrol. 2006;17:2275–84.
13. Wen CP, Cheng TYD, Tsai MK, Chang YC, Chan HT, Tsai SP, et al. All-cause mortality attribute to chronic kidney disease: a prospective cohort study based on 462293 adults in Taiwan. Lancet. 2008;371:2173–82.
14. Zhang LX, Zhang PH, Wang F, Zuo L, Zhou Y, Shi Y, et al. Prevalence and factors associated with CKD: a population study from Beijing. Am J Kidney Dis. 2008;51:373–84.

15. Levey A, Coresh J, Greene T, Lesley A, Zhang Y, Hendriksen S, et al. Using strandardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med. 2006;145:247–54.
16. Iseki K, Ikemiya Y, Iseki C, Takishita S. Proteinuria and the risk of developing end-stage renal disease. Kidney Int. 2003;63:1468–74.
17. Imai E, Horio M, Yamagata K, Iseki K, Hara S, Ura N, et al. Slower decline of glomerular filtration rate in the Japanese general population: a longitudinal 10-year follow-up study. Hypertens Res. 2008;31:433–41.
18. Amin R, Turner C, van Aken S, Bahu TK, Watts A, Lindsell DR, et al. The relationship between microalbuminuria and glomerular filtration rate in young type 1 diabetic subjects: The Oxford Regional Prospective Study. Kidney Int. 2005;68:1740–9.
19. Klag M, Whelton P, Randall B. Blood pressure and end-stage renal disease in men. N Engl J Med. 1996;334:13–8.
20. Chen J, Wildman R, Gu D, Kusek J, Spruill M, Reynolds K, et al. Prevalence of decreased kidney function in Chinese adults aged 35 to 75 years. Kidney Int. 2005;68:2837–45.

Clin Exp Nephrol (2009) 13:460–466
DOI 10.1007/s10157-009-0179-1

ORIGINAL ARTICLE

Tonsillectomy and steroid pulse (TSP) therapy for patients with IgA nephropathy: a nationwide survey of TSP therapy in Japan and an analysis of the predictive factors for resistance to TSP therapy

Naoto Miura · Hirokazu Imai · Shogo Kikuchi · Shogo Hayashi · Masayuki Endoh · Tetsuya Kawamura · Yasuhiko Tomino · Kumiko Moriwaki · Hideyasu Kiyomoto · Kentaro Kohagura · Eiko Nakazawa · Eiji Kusano · Toshio Mochizuki · Shinsuke Nomura · Tamaki Sasaki · Naoki Kashihara · Jun Soma · Tadashi Tomo · Iwao Nakabayashi · Masaharu Yoshida · Tsuyoshi Watanabe

Received: 16 October 2007 / Accepted: 16 March 2009 / Published online: 19 May 2009

Abstract
Background Tonsillectomy and steroid pulse (TSP) therapy was proposed as a curative treatment for IgA nephropathy by Hotta et al. (Am J Kidney Dis 38:736–742, 2001) based on data that about 50% of patients achieved clinical remission (CR) of urinary abnormalities.

Materials and methods As a primary survey, we sent a questionnaire and letter to 848 hospitals in Japan, each of which employed a Fellow of the Japanese Society of Nephrology between October and December of 2006, in order to gather information about the prevalence and efficacy of TSP therapy for patients with IgA nephropathy. As a secondary survey, we collected data from both low- and

N. Miura · H. Imai (✉)
Division of Nephrology and Rheumatology,
Department of Internal Medicine, Aichi Medical University
School of Medicine, Nagakute, Aichi 480-1195, Japan
e-mail: imaihiro@aichi-med-u.ac.jp

S. Kikuchi
Department of Public Health,
Aichi Medical University School of Medicine,
Nagakute, Aichi, Japan

S. Hayashi
Medical Education Center,
Aichi Medical University School of Medicine,
Nagakute, Aichi, Japan

M. Endoh
Division of Nephrology and Metabolism,
Department of Internal Medicine,
Tokai University School of Medicine,
Isehara, Kanagawa, Japan

T. Kawamura
Department of Nephrology and Hypertension,
School of Medicine, Jikei University, Minato-ku, Tokyo, Japan

Y. Tomino
Division of Nephrology, Department of Internal Medicine,
Juntendo University School of Medicine, Bunkyo-ku,
Tokyo, Japan

K. Moriwaki · H. Kiyomoto
Department of Cardio Renal and Cerebrovascular Medicine,
Kagawa University Faculty of Medicine, Miki, Kagawa, Japan

K. Kohagura
Department of Cardiovascular Medicine,
Nephrology and Neurology, University of the Ryukyus School
of Medicine, Nishihara, Okinawa, Japan

E. Nakazawa · E. Kusano
Division of Nephrology, Department of Internal Medicine,
Jichi Medical University, Shimotsuke, Tochigi, Japan

T. Mochizuki
Department of Internal Medicine II, Hokkaido University
Graduate School of Medicine, Sapporo, Hokkaido, Japan

S. Nomura
Departments of Cardiology and Nephrology,
Mie University Graduate School of Medicine, Tsu, Mie, Japan

T. Sasaki · N. Kashihara
Division of Nephrology and Rheumatology,
Department of Internal Medicine, Kawasaki Medical School,
Kurashiki, Okayama, Japan

J. Soma
Department of Nephrology, Iwate Prefectural Central Hospital,
Morioka, Iwate, Japan

T. Tomo
Department of Internal Medicine II,
Oita University Faculty of Medicine, Yufu, Oita, Japan

high-CR-rate groups to determine which factors predicted resistance to TSP therapy.

Results A total of 2,746 patients received TSP therapy between 2000 and 2006. The CR rates, calculated by measuring urinary criteria 6 and 12 months after TSP therapy, were 32.0% (347/1,085) and 45.6% (452/991), respectively. Analysis of the 30 hospitals in which TSP therapy had been performed on at least ten patients revealed that the CR rates varied from below 10% to 100%. A secondary survey of ten hospitals revealed that, after correction of the CR rate from each hospital, patients could be categorized into three groups: those with a low CR rate (122 patients in four hospitals), a middle CR rate (78 patients in four hospitals), and a high CR rate (103 patients in two hospitals). The CR rate of all patients ($N = 303$) was 54.1%. A comparison of patient data between the low- and high-CR-rate groups showed a significant difference in age at onset (years; $P = 0.05$), amount of proteinuria (g/day; $P = 0.02$), total protein (g/dl; $P = 0.02$), pathological grade ($P = 0.009$), and prognostic score as described by Wakai et al. [Nephrol Dial Transplant 21:2800–2808, 2006, ($P = 0.04$)]. Univariate analysis revealed that there was a significant difference between non-CR and CR subgroups in duration from diagnosis until TSP therapy (6.9 ± 6.8 versus 5.3 ± 5.2 years; $P = 0.02$), amount of proteinuria (1.5 ± 1.6 versus 0.8 ± 0.8 g/day; $P < 0.0001$), serum creatinine (0.99 ± 0.40 versus 0.87 ± 0.34 mg/dl; $P = 0.006$), pathological grade ($P = 0.0006$), and Wakai et al.'s prognostic score (37.4 ± 17.8 versus 28.1 ± 15.1; $P < 0.0001$). A multivariate logistic analysis demonstrated that resistance to TSP therapy depends on age at onset, amount of proteinuria, hematuria grade, and pathological grade, and a score predicting resistance to TSP therapy could be derived by the formula: [(−0.0330) × (age) + (0.4772) × log (amount of proteinuria) − (0.0273) × (hematuria grade: 0, 1, 2, and 3) + (0.7604) × (pathological grade: 1, 2, 3, and 4) − 0.1894]. A receiver operating characteristic (ROC) curve showed that patients with a resistance score of greater than −0.02 easily resist TSP therapy (sensitivity 69%, specificity 75%, positive likelihood ratio 2.76).

Conclusion TSP therapy shows promise as a treatment that can bring about CR of urinary abnormalities, but unfortunately the average CR rate is about 50% at 1 year after treatment. Predictive factors for resistance to TSP therapy are age at onset, amount of proteinuria, hematuria grade, and pathological grade. The present study suggests that patients with either early-stage or mild to moderate IgA nephropathy easily achieve CR following TSP therapy, whereas patients with late-stage or severe disease are prone to TSP therapy resistance.

Keywords IgA nephropathy · Tonsillectomy · Steroid pulse therapy · Resistance to tonsillectomy and steroid pulse therapy

I. Nakabayashi · M. Yoshida
Renal Unit, Department of Internal Medicine,
Hachioji Medical Center, Tokyo Medical University,
Hachioji, Tokyo, Japan

T. Watanabe
Department of Internal Medicine III, School of Medicine,
Fukushima Medical University, Fukushima, Fukushima, Japan

Introduction

IgA nephropathy is the most common type of glomerulonephritis in the world, and is characterized by mesangial proliferation with predominantly IgA deposition. A study of patient prognosis showed that, 20 years after disease onset, about 30% of patients had undergone spontaneous remission with a normalized urinalysis and stable kidney function, about 30% had retained stable kidney function but persistent urinary abnormalities, and almost 40% had experienced a progressive course that necessitated dialysis. On the other hand, renal survival rate 20 years after diagnosis is about 60% [1, 2].

Steroid pulse therapy using intravenous administration of 1,000 mg/day prednisolone has been reported to be efficacious at preventing disease progression, with 98% of steroid pulse therapy patients remaining stable 10 years after diagnosis as compared with 65% of placebo-treated patients [3].

There are controversial results about the efficacy of tonsillectomy alone for IgA nephropathy patients. Rasche et al. [4] reported that the renal survival rate of a tonsillectomy group was almost 60% that of a control group at 10 years. On the other hand, Xie et al. [5] demonstrated that the renal survival rate of a tonsillectomy group 20 years after diagnosis was 89.6% compared with 63.7% in a control group, even though there was no significant difference between groups at 10 years.

A retrospective study by Hotta et al. [6] revealed that tonsillectomy and steroid pulse (TSP) therapy induced clinical remission (CR), or absence of urinary abnormalities, in 48% of patients after an observation period of 82.3 ± 38.2 months. Furthermore, the renal survival rate of patients who achieved CR was 100% at 10 years, compared with 77.4% of the group who did not achieve CR.

Following the publication of the above results in 2001, TSP therapy began to be widely used in Japan before a consensus had been reached. The purpose of this study is to determine the prevalence of TSP therapy for patients with IgA nephropathy in Japan, and to identify the factors that predict resistance to TSP therapy 1 year after treatment.

Methods

Primary survey about prevalence of TSP therapy

We sent a questionnaire about TSP therapy for IgA nephropathy patients to 848 Fellows of the Japanese Society of Nephrology. The recipients of the survey worked in hospitals, excluding outpatient and dialysis clinics, between October 27 and December 28, 2006. The questionnaire included the items listed below.

Q1 Have you ever treated IgA nephropathy patients with tonsillectomy and steroid pulse (TSP) therapy? Please continue if you answered "yes."

Q2 When did you start TSP therapy for IgA nephropathy patients?

Before 2000, how many cases did you have?
In 2000, how many cases did you have?
In 2001, how many cases did you have?
In 2002, how many cases did you have?
In 2003, how many cases did you have?
In 2004, how many cases did you have?
In 2005, how many cases did you have?
In 2006, how many cases did you have?

Q3 How many of the patients who received TSP therapy achieved CR within 6 months of starting treatment?

Q4 How many of the patients who received TSP therapy achieved CR within 12 months of starting treatment?

If you answered "no" in Q1

Q4 Are you currently planning to begin TSP therapy for patients with IgA nephropathy?

CR criteria were determined by urinary analysis.

Remission of proteinuria was defined as negative (−) or trace (±) protein on urine dipstick, while remission of occult hematuria was specified as absence of blood on dipstick and urinalysis. CR was defined as complete resolution of both proteinuria and hematuria.

Secondary survey of hospitals in which more than ten patients with IgA nephropathy received TSP therapy

We collected clinical and laboratory data from ten hospitals whose CR rate was over 70% or below 30%, in order to clarify the predictive factors for resistance to TSP therapy. This data included patient age, sex, duration from diagnosis to TSP therapy, grade of proteinuria on dipstick, amount of proteinuria, hematuria grade on dipstick, systolic blood pressure, diastolic blood pressure, serum creatinine, serum total protein, pathological activity score, and prognostic score as outlined by Wakai et al. [7]. We also collected information about the individuals who performed the tonsillectomies and about the steroid amount and pulse timing used in TSP therapy.

Statistical analysis

1. Numerical data are expressed as mean ± standard deviation (SD) and categorical data are reported as proportions. The baseline characteristics of the two patient groups, including age, amount of proteinuria, systolic and diastolic blood pressures, serum creatinine, total protein, and prognostic score [7], were compared using Student's t test, while Fisher's test was used to assess sex, and Mann–Whitney's U test was used to assess urinary occult blood reaction and pathological grade. All P values were two-sided, with $P < 0.05$ indicating statistical significance.
2. A stepwise logistic regression model was performed using each of the predictor variables. All analyses were performed with SAS® software version 9.1 (SAS Institute, Inc., Cary, NC, USA). A receiver operating characteristic (ROC) curve analysis was used to determine the cutoff point on the items which showed significant difference.

Results

Prevalence of TSP therapy in Japan

Of the 848 fellows queried, 317 replied on behalf of the hospitals at which they worked. Despite the response rate of 37.4%, we believe that the present data provides a solid foundation for conclusions about TSP therapy use nationwide because responding hospitals provided the primary source of kidney disease care in their local communities.

1. The number of hospitals performing TSP therapy

Of the 317 responding hospitals, 128 (40.4%) performed TSP therapy for patients with IgA nephropathy.

2. The number of patients receiving TSP therapy in Japan

In 2000 and 2001, an annual total of 140 and 160 patients received TSP therapy, respectively, which included 100 patients per year at Sendai Shakaihoken Hospital. After 2002, the total number of patients treated annually with this modality increased gradually to 220 in 2002, 340 in 2003, 520 in 2004, 690 in 2005, and 620 in 2006. The total number of patients who received TSP therapy between 2000 and 2006 reached 2,746 (Fig. 1).