予防のための施策となり，CKD 患者の予後が改善されることが期待される．

おわりに

CKD 診療ガイドが 2007 年に刊行されて以降，CKD において新たにわかったエビデンスが「CKD 診療ガイド 2012」に集約されている．今後さらに医療連携においても FROM-J で得られる知見を含めた新たなエビデンスが加わり，より臨床の場で実用的な診療ガイドになり，CKD 患者の重症化予防に寄与することが期待される．

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ガイドラインに基づいた実地医家のためのわかりやすいオーバービュー

CKD(慢性腎臓病)

—原発性と二次性CKDを実地医家の立場から総括する—

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CKDの原疾患の意義

CKDとはGFRで表される腎機能の低下があるか，もしくは蛋白尿をはじめとする腎臓の障害を示唆する所見が慢性的に持続する病態のすべてを包含する．CKDとしてスクリーニングされた集団は，さらに原疾患，GFRの値および蛋白尿(アルブミン尿)の程度によって将来の死亡，末期腎不全，心血管死亡発症のリスクが区分される．このCKDの重症度分類における尿検査はわが国の保険適応の関係で，糖尿病は尿アルブミンを，それ以外(高血圧，腎炎，多発性嚢胞腎，腎移植，不明，その他)は尿蛋白定量により評価することになり，原疾患による対応の違いがある．

末期腎不全の原疾患の割合は，日本透析医学会が毎年公表している「わが国の慢性透析療法の現況」[1]に掲載されている．**図1**は2012年までの透析導入患者の主要原疾患の割合推移を示している．1998年より糖尿病性腎症が最も多い割合となり，2012年は44.1%を占めている．第2位の慢性糸球体腎炎は年々割合が減少傾向にあり，2012年には19.4%とはじめて20%を下回っている．第3位は腎硬化症の12.3%であり，透析導入患者の高齢化を反映して漸増している．そして第4位は原疾患不明で11.2%を占める．この原疾患不明の割合も年々増加しており，透析導入までに腎症の精密検査を受け，正確な原疾患を探ることの重要性を改めて示す必要があると考えられる．

CKDの診療計画としてCKDの原疾患の診断と治療方針の決定が必要とされている．CKDの理念は腎臓病の早期診断，早期治療介入であり，CKDの原疾患の診断はCKDの最も有効な治療方法を決定するためにも不可欠である．本稿ではCKDの原疾患について原発性と二次性(全身性疾患に続発する場合)に分けて述べる．

CKDの原疾患の診断手順

CKDの原疾患を診断するための項目について解説する．

1. 問　診

過去の検尿異常の有無の確認は重要である．日本では学校検尿および職域健診，自治体による健診で尿検査が広く行われており，CKD患者ではこれまでの健診における検尿の履歴を確認する必要がある．他院での通院歴がある場合は尿検査の有無とその結果を確認する．また出産経験のある女性は母子手帳に妊娠中の尿検査が記されているため，妊娠高血圧症の発症の有無と併せてCKD診断の有用な情報になる．過去に検尿異常と，高血圧症や糖尿病などほかのCKDの誘因となるような病態が併存する場合は，検尿異常とそのほかの病態のいずれが先に発症したかも問診のポイントである．また，家族内の腎疾患の存在の聴取も遺伝性腎疾患などのCKD診断に有用である．常用薬など服用状況の確認も，薬剤性腎障害の合併の有無の評価に有用である．

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■ わが国の透析導入患者の主要原疾患は，第1位が糖尿病性腎症，第2位が慢性糸球体腎炎，第3位は腎硬化症であり，第1位と第3位は透析導入患者の高齢化を反映している．
■ 第4位は原疾患不明で11.2%を占めており，腎症の治療と進行防止のためには，正確な原疾患を探ることが重要である．
■ 健診の受診歴とその結果はCKDの原疾患を探索するうえで重要である．
■ 糖尿病では尿中アルブミンと尿中クレアチニン濃度の比，糖尿病非合併例では蛋白定量と尿中クレアチニン濃度の比を算出する．

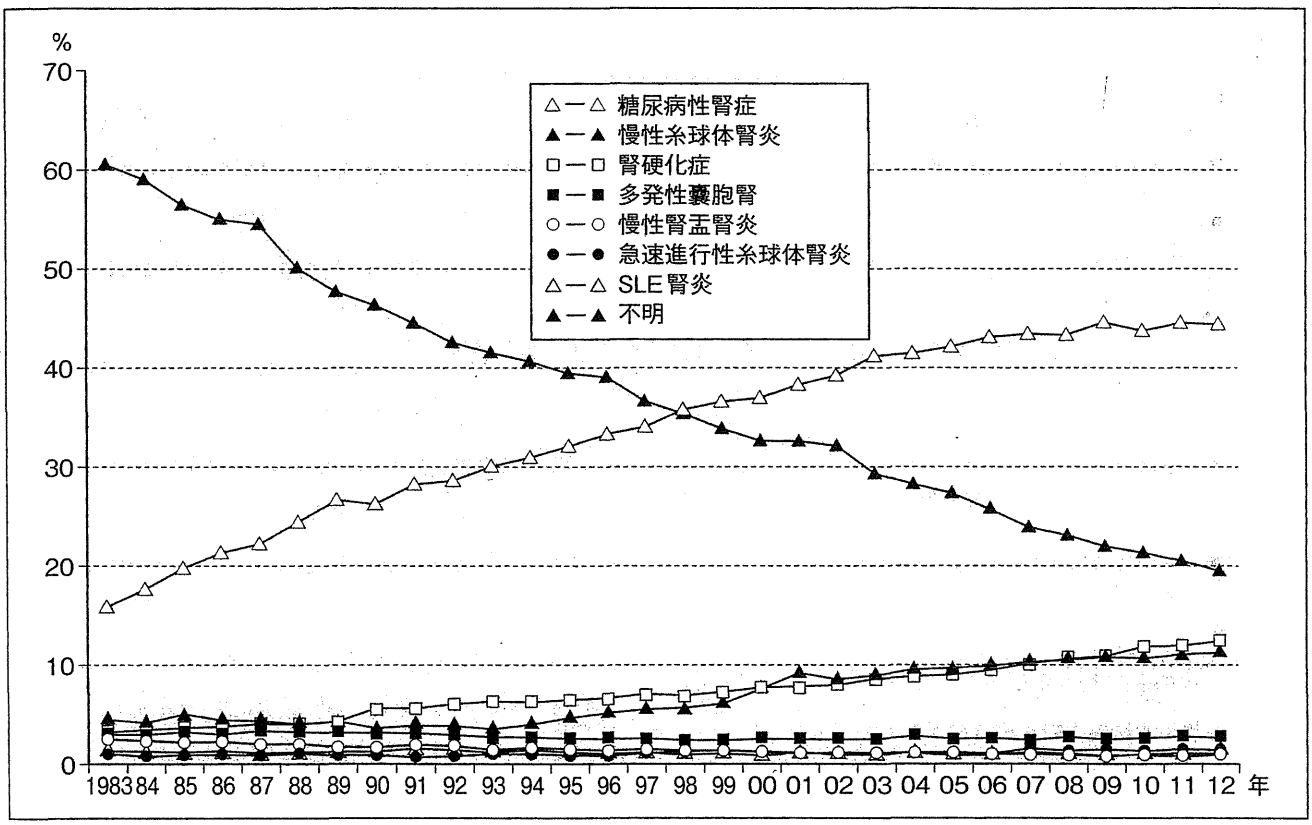

図1　年別透析導入患者の主要原疾患の割合推移
（文献1）より引用）

2. アルブミン尿・蛋白尿

尿中アルブミン・尿中蛋白の増加は糸球体に病変の主体があることが多い．試験紙法で陽性の場合は糖尿病患者では尿中アルブミン，糖尿病非合併例では蛋白定量と尿中クレアチニン濃度の比を算出し，それぞれmg/gCrあるいはg/gCrで表す．尿蛋白0.5 g/gCr以上，尿中アルブミン300 mg/gCr以上を顕性蛋白尿と定義する．尿蛋白0.5 g/gCr以上，あるいは尿蛋白0.5 g/gCr未満であっても血尿を伴う場合は糸球体腎炎の可能性があるため，腎生検を含めた精査を考慮する．

3. 血　尿

血尿は，尿中赤血球が顕微鏡下で5個/HPF以上，フローサイトメトリーで20個/μl以上とおおよそ定義される[3]．すなわち尿沈渣所見が血尿の診断には不可欠であり，尿潜血反応はあくまでスクリーニングの手段として用いられる．尿中赤血球の形態は血尿の由来を考える情報として有用であり，糸球体性血尿では多彩な

■ 血尿の診断には尿沈渣所見が不可欠である.

■ 腎臓の萎縮，腎皮質のエコー輝度の上昇や腎表面の凹凸不整は長期にわたる腎実質の障害を示唆する.

■ 尿蛋白の出現が糖尿病の発症に先行する場合や，急激な尿蛋白の増加，急激なGFRの低下は，糖尿病性腎症以外の可能性があるため腎生検の適応がある.

表1　CKDにおける腎生検の適応

尿蛋白のみが陽性の場合
尿蛋白0.5 g/日以上，もしくは0.5 g/gCr以上
尿蛋白・尿潜血ともに陽性の場合
尿蛋白0.5 g/日以下，もしくは0.5 g/gCr以下でも考慮
ネフローゼ症候群の場合
積極的に施行を考慮する
尿潜血のみ陽性の場合
尿沈渣に変形赤血球や病的円柱を認める場合などで考慮

(文献4)より引用)

表2　腎生検の禁忌

片腎*(機能的片腎も含む)
管理困難な出血傾向
嚢胞腎(大きな単嚢胞，多発性嚢胞腎)
水腎症
管理困難な全身性合併症(重症高血圧，敗血症)
腎実質内感染症(腎盂腎炎，腎周囲膿瘍，膿腎症)
腎動脈瘤
末期腎(高度の萎縮腎)
体動などで安静の保持が困難*

*開放腎生検や腹腔鏡下腎生検は必ずしも禁忌ではない

(文献4)より引用)

形や大きさの尿中赤血球が認められ，尿路性の血尿との鑑別に用いられる．また腎炎では血尿の有無が腎炎の診断に有用であり，特に高齢者などでCRP陽性など炎症所見を伴う血尿が新たに出現した場合は急速進行性糸球体腎炎の可能性も念頭におく.

4.　画像所見

腎臓の画像検査として，腎超音波検査は簡便かつ放射能被曝や造影剤の使用もないため，すべてのCKDや，尿路閉塞性疾患や嚢胞性腎疾患など腎形態変化の存在が疑われる場合には施行すべき検査である．腎臓の萎縮は長期にわたる腎障害の存在を示唆し，腎皮質のエコー輝度の上昇や腎表面の凹凸不整は腎実質の障害を示唆する．腎機能が低下しているにもかかわらず腎萎縮がみられない場合は，急速な腎機能低下の場合か，慢性な経過であれば腎アミロイドーシスや糖尿病性腎症などを疑う．また腎臓サイズの左右差を認める場合は，腎低形成あるいは腎血流の異常などを疑う.

5.　腎生検

腎生検は，腎疾患の確定診断のほか，腎病変の進展の評価，治療方針の決定，腎予後の推定，そして治療効果の判定などを目的に行われる．腎生検は侵襲的な処置であり，その適応は慎重に吟味する．**表1**にCKDにおける腎生検の適応，**表2**に腎生検の禁忌を示す[4].

尿蛋白陽性で長年の糖尿病歴や糖尿病性網膜症を有しており，糖尿病性腎症が強く疑われる場合は腎生検の意義は乏しい．ただし糖尿病性網膜症を認めない場合や，沈渣で多数の変形赤血球や顆粒円柱など活動性糸球体疾患を示唆する所見を認める，尿蛋白の出現が糖尿病の発症に先行する場合や急激な尿蛋白の増加や急激なGFRの低下がみられる場合などには，糖尿病性腎症以外の腎疾患の可能性があるため腎生検の適応がある.

年代別にみたCKDの原疾患

表3，4，5にそれぞれ，成人に多い腎疾患，小児でみられる腎疾患，高齢者に多い腎疾患を示す．小児では遺伝性・先天性腎疾患が見つかる例が多く，成人や高齢者になると糖尿病性腎

■ 小児では遺伝性・先天性腎疾患が見つかる例が多い.

■ 成人や高齢者になると糖尿病性腎症や血管性疾患による腎障害など二次性の腎疾患の割合が多くなる.

表3　成人に多い腎疾患

	一次性	二次性	遺伝性・先天性
糸球体疾患	IgA 腎症 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 半月体形成性腎炎 膜性増殖性糸球体腎炎	糖尿病性腎症 ループス腎炎 顕微鏡的多発血管炎 (ANCA 関連血管炎) 肝炎ウイルス関連腎症	良性家族性血尿 Alport 症候群 Fabry 病
血管性疾患		高血圧性腎症(腎硬化症) 腎動脈狭窄症(線維筋性形成異常, 大動脈炎症候群, 動脈硬化症) コレステロール塞栓症 腎静脈血栓症 虚血性腎症	
尿細管間質疾患	慢性間質性腎炎	痛風腎 薬剤性腎障害	多発性嚢胞腎 ネフロン癆

表4　小児でみられる腎疾患

	一次性	二次性	遺伝性・先天性
糸球体疾患	微小変化型ネフローゼ症候群 IgA 腎症 巣状分節性糸球体硬化症 急性糸球体腎炎 膜性増殖性糸球体腎炎	紫斑病性腎炎 ループス腎炎	良性家族性血尿 Alport 症候群 (そのほかの)遺伝性腎炎 先天性ネフローゼ症候群
尿細管・間質ならびに尿路系疾患		Fanconi 症候群(一次性も)	先天性水腎症 膀胱尿管逆流 低形成・異形成腎 多発性嚢胞腎 Dent 病 ネフロン癆

症や血管性疾患による腎障害など二次性の腎疾患の割合が多くなる. さらに高齢者では腎尿路の悪性腫瘍も腎疾患の鑑別にいれる必要が高くなる.

次の項では, 原発性 CKD, 二次性 CKD の主な疾患と, 遺伝性 CKD の中から頻度の高い疾患の概略を述べる.

原発性 CKD

1. IgA 腎症

IgA 腎症は血尿および蛋白尿を呈する糸球体疾患であり, 確定診断は腎生検による病理診断

■ 高齢者では腎尿路の悪性腫瘍も考慮する必要がある．

■ IgA 腎症は 20 年以内に約 40% が末期腎不全に至る予後不良の疾患である．

表 5　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	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 肝炎ウイルス関連腎炎	
血管性疾患		高血圧性腎症(腎硬化症) 腎動脈狭窄症(動脈硬化症) コレステロール塞栓症 虚血性腎症	
尿細管間質疾患・ほか	慢性間質性腎炎	骨髄腫腎 痛風腎 薬剤性腎障害	前立腺肥大症 (腎後性腎不全) 尿路結石 腎尿路悪性腫瘍

である．成人の原発性糸球体腎炎の多数を占め，20 年以内に約 40% が末期腎不全に至る予後不良の疾患である．特に高度蛋白尿，血清 Cr 高値，収縮期高血圧，障害度の高い腎生検所見は維持透析導入の独立したリスクファクターである．組織学的重症度分類および臨床的重症度分類により，透析導入リスクが層別化される．

治療には，ステロイド療法，RA 系阻害薬，抗血小板薬が用いられる．中等量以上の経口ステロイド療法は，組織障害が中等度の IgA 腎症の蛋白尿を減少させ腎機能障害進行を抑制する．腎機能障害が進行した IgA 腎症に対するステロイド療法について報告はあるが十分なエビデンスはない．ステロイドパルス療法は海外では前向き研究で腎機能障害を有意に抑制したが，わが国では有効性は十分に検証されていない．扁摘＋ステロイドパルス療法が IgA 腎症に有効との報告もあるが，エビデンスは十分でなく，治療プロトコールも標準化されていない．今後の大規模かつ長期間のコホート研究の成果が待たれる．

2.　特発性膜性腎症

膜性腎症には特発性膜性腎症のほか，悪性腫瘍，薬剤，感染症などに伴う二次性膜性腎症がある．二次性膜性腎症では原疾患の治療をまず行い，経過をみる．ここでは特発性膜性腎症について述べる．

特発性膜性腎症は，40 歳以上のネフローゼ症候群の原因として最も頻度の高い疾患である．臨床経過が長く，自然寛解もしばしばみられることから，治療の有効性に関する評価がむずかしい．20 年腎生存率は 60.5% であり，長期予後は決して良好とはいえない．腎不全に至るリスクは男性，高齢者(60 歳以上)，血清 Cr レベル高値(≧1.5 mg/dl)，尿細管間質病変(20% 以上)である．またネフローゼ症候群の不完全寛解Ⅱ型と無効例は完全寛解と不完全寛

■ **膜性腎症には特発性膜性腎症のほか，悪性腫瘍，薬剤，感染症などに伴う二次性膜性腎症がある．**

■ **巣状分節性糸球体硬化症の20年腎生存率は33.5%と膜性腎症よりも不良である．**

■ **糖尿病性腎症は，顕性腎症期以降ではGFRの低下が顕著で，半数以上が10年以内に末期腎不全に至る．**

解Ⅰ型に比べ有意に予後不良であった．

初期治療にはステロイドが用いられ，4週以上治療しても完全寛解あるいは不完全寛解Ⅰ型に至らない場合はステロイド抵抗性として，シクロスポリン，ミゾリビンまたはシクロホスファミドの併用を考慮する．

3. 一次性巣状分節性糸球体硬化症

巣状分節性糸球体硬化症はすべての年代のネフローゼ症候群で認められ，蛋白尿と血尿を呈する．20年腎生存率は33.5%と膜性腎症よりも不良である．腎不全に至るリスクは血清Crレベル高値(≧1.5 mg/dl)，尿細管間質病変(20%以上)であり，膜性腎症と同様，初期治療に対する反応性が予後規定因子となる．

初期治療のステロイドは膜性腎症よりも高用量を用い，プレドニゾロン1 mg/kg/日(最大60 mg/日)か，重症例ではステロイドパルス療法も考慮される．4週以上治療しても完全寛解あるいは不完全寛解Ⅰ型に至らない場合はステロイド抵抗性として，ステロイドパルス療法やシクロスポリン，ミゾリビンまたはシクロホスファミドの併用を考慮する．また補助療法として，高コレステロール血症を伴う難治性ネフローゼ症候群に対してはLDLアフェレーシスを考慮する．

二次性CKD

1. 糖尿病性腎症

糖尿病はCKDと心血管病の病態を促進し，糖尿病性腎症はわが国における維持透析導入の原疾患の第1位である．さらに透析導入後の糖尿病患者の5年生存率が50%であるなど生命予後も不良である．

糖尿病性腎症は，顕性腎症期以降ではGFRの低下が顕著で，半数以上が10年以内に末期腎不全に至る．2型糖尿病では1型糖尿病に比べて，腎症発症前に高血圧を合併していることが多い．

長年の糖尿病歴や糖尿病性網膜症を有しており，尿蛋白が高度である場合は糖尿病性腎症の可能性が高い．しかし網膜症の存在がない場合や糖尿病性腎症の自然経過から大きく外れるときは糖尿病性腎症以外の疾患を疑う．

治療の基本は，厳格な血糖コントロール，血圧管理が重要であり，それを支えるための食事療法，運動療法，薬物療法，禁煙指導などの多角的な強化療法により早期糖尿病性腎症の進行や心血管イベント発生が抑制されることが証明されている．

2. 腎硬化症：尿所見の軽微なCKDを含む

腎硬化症は従来，悪性高血圧に伴う予後不良な悪性腎硬化症と，本態性高血圧に伴う軽微な尿所見で腎不全にはほとんど進行しないと考えられていた良性腎硬化症の二つに分類されてきた．しかしながら，従来予後良好とされていた(良性)腎硬化症がわが国の透析導入の原疾患の第3位となっており，人口の高齢化とともに罹患数も増えている．腎硬化症は高血圧症の長期間の持続により生じた小葉間動脈から輸入細動脈の硬化により，腎血流の低下から腎間質の線

■ 腎硬化症は人口の高齢化とともに罹患数も増えている.

■ 日本人のCKD患者で最も多いのは，ステージG3aおよびbで尿蛋白が－から±である「尿異常の乏しいCKD」である(表6).

■ 「尿異常の乏しいCKD」には腎硬化症のほか，可逆的で治療により進行抑制が可能な疾患も存在する可能性があることを念頭におく.

表6　日本におけるCKD患者数

GFRステージ	GFR (ml/分/1.73 m²)	尿蛋白 −〜±		尿蛋白 1＋以上	
G1	≧90	2,803万人		61万人	(0.6%)
G2	60〜89	6,187万人		171万人	(1.7%)
G3a	45〜59	886万人	(8.6%)	58万人	(0.6%)
G3b	30〜44	106万人	(1.0%)	24万人	(0.2%)
G4	15〜29	10万人	(0.1%)	9万人	(0.1%)
G5	＜15	1万人	(0.01%)	4万人	(0.03%)

のところが，CKDに相当する

(文献2)より改変引用)

表7　尿所見の乏しいCKDの原疾患

先天性・奇形
　腎の発生異常
　先天性代謝障害
腎血流の異常(糸球体前の血行障害)
　慢性心不全
　両側腎動脈狭窄
　腎梗塞後
　高血圧性腎症・腎硬化症
　加齢による腎障害(虚血性腎症)
間質性腎障害(糸球体以後の腎実質障害)
　加齢による腎障害
　慢性間質性腎炎
　薬剤性腎障害の一部(鎮痛薬性腎症，シクロスポリン腎症)
　寛解後の慢性糸球体腎炎
　急性腎不全後
閉塞性尿路疾患
　両側水腎症
　尿路結石
　尿道狭窄
　神経因性膀胱
　前立腺肥大

(文献3)より引用)

維化，糸球体の硬化が進行し腎実質の硬化に至る疾患とされる．高齢者の腎障害における虚血性腎症も多くの場合，臨床的には腎硬化症と鑑別は不可能である.

さらに日本人におけるCKD患者で最も多いのは，ステージG3aおよびbで尿蛋白が－から±である「尿異常の乏しいCKD」である(**表6**)[2]. この集団は臨床現場で医師が最も多く診療にあたる患者層である．**表7**[3]に尿所見の乏しいCKD患者の原疾患を示す．現時点において，高齢者における腎障害で尿所見も軽微な場合には，腎硬化症と判断される場合も多いが，腎硬化症(虚血性腎症)以外にも可逆的で治療により進行抑制が可能な疾患も存在する可能性があることを念頭におき，そのCKDの原疾患が何であるかを常に考え，慎重に対処することが求められる.

蛋白尿などの尿所見は軽微であるが，顕性蛋白尿を伴う場合は糸球体高血圧により腎機能障害の進行が促進される．腎硬化症への降圧療法は，海外ではエビデンスがあるものの日本ではまだない．一方腎硬化症では高血圧症を多く伴うこと，心血管病の合併が多いことから，降圧

■ 治療困難な高血圧やRA系阻害薬による急激な腎機能障害の進行を認める場合は腎動脈狭窄の存在を疑う必要がある.

■ ループス腎炎の治療はステロイドの副作用を考慮し，効果的な免疫抑制療法と組み合わせて治療を行うことが望ましい.

は腎機能障害および心血管病の進行抑制には重要である．また尿蛋白陰性者が尿蛋白陽性となる最も大きなリスク因子の一つが，GFR 60 m*l*/分/1.73 m^2 未満であることであり[4]，腎硬化症の患者は，その経過中に蛋白尿の出現，増悪をしばしばみかけることがあり，十分な注意が必要である．

3. 動脈硬化性腎動脈狭窄症

高齢者CKD患者の5～22%に動脈硬化性腎動脈狭窄が合併しており，治療困難な高血圧やRA系阻害薬による急激な腎機能障害の進行を認める場合は腎動脈狭窄の存在を疑う必要がある．動脈硬化性腎動脈狭窄は高頻度に脳梗塞，虚血性心疾患や閉塞性動脈硬化症を合併する．診断には腹部血管雑音の聴診のほか，腎サイズの左右差がある場合も存在を疑う必要がある．ドプラ超音波法やMRAなどが診断に用いられ，必要に応じて血管造影も行われるが造影剤を使用するため適応には十分注意する．

治療としては血圧管理，脂質異常症管理，糖尿病管理，抗血小板薬投与，禁煙指導など動脈硬化のリスクを軽減する治療を行う．両腎性腎動脈狭窄あるいは単腎性腎動脈狭窄ではRA系阻害薬は急速な腎機能障害を認めることがあり注意が必要である．血圧管理困難な症例では経皮的腎血管形成術による血行再建療法も行われる．

4. ループス腎炎

全身性エリテマトーデス(SLE)による腎病変のうち，ループス腎炎は一般的には免疫複合体の沈着による糸球体腎炎を指す．SLE患者において活動性の腎炎所見(0.5 g/日以上の持続性尿蛋白で，血尿や細胞性円柱を伴う場合)がみられる場合は禁忌がなければ腎生検が推奨される．従来WHO分類による病理組織分類がなされていたが，2003年にISN/RPS分類が発表され，病変の定義がより明確になった．ISN/RPS分類ではⅠ型からⅥ型まで分類される．2012年にアメリカリウマチ学会，KDIGO，EULAR/ERA-EDTAによる三つの国際的なガイドラインが提言された．

治療は，Ⅰ，Ⅱ型には尿蛋白が高度な場合はステロイドあるいはカルシニューリンインヒビターなどの免疫抑制薬を投与する．Ⅲ，Ⅳ型には中等度以上のステロイドあるいはステロイドパルスにシクロホスファミド，海外ではミコフェノール酸モフェチルなどの免疫抑制薬を併用する．Ⅴ型ではステロイドに免疫抑制薬を併用する．ステロイドは長期服用となりさまざまな副作用が生じる危険性があり，効果的な免疫抑制療法と組み合わせて治療を行うことが望ましい．

5. 顕微鏡的多発血管炎

顕微鏡的多発血管炎は，病理学的にはPauci-immune型の肉芽腫を伴わない壊死性半月体血管炎であり，中型の血管もしばしば障害される．腎組織ではPauci-immune型の壊死性半月体形成性腎炎を認める．

欧米の報告では，MPO-ANCA陽性が60%，PR3-ANCA陽性が30%程度とされているが，

■ 顕微鏡的多発血管炎の腎障害は70～80%に認め，そのうちの60%が急速進行性糸球体腎炎を呈し，早期発見が必要な疾患である．

■ 常染色体優性多発性嚢胞腎は，ほとんどが30～40歳代まで無症状で経過するが，70歳までに約半数が末期腎不全に至る．

表8　MPO-ANCA型急速進行性糸球体腎炎の臨床所見スコア化による重症度分類

スコア	血清クレアチニン (mg/dl)*	年齢 (歳)	肺病変の有無	血清CRP (mg/dl)*
0	[ ]<3	<60	無	<2.6
1	3≦[ ]<6	60～69		2.6～10
2	6≦[ ]	≧70	有	>10
3	透析療法			

*初期治療時の測定値

臨床重症度	総スコア
Grade Ⅰ	0～2
Grade Ⅱ	3～5
Grade Ⅲ	6～7
Grade Ⅳ	8～9

（文献5）より引用）

わが国ではMPO-ANCA陽性が90%，PR3-ANCA陽性が3%程度とMPO-ANCA陽性が圧倒的に多い．

腎障害は70～80%に認め，そのうちの60%が急速進行性糸球体腎炎を呈する．さらに間質性肺炎や末梢神経障害の合併症を認めることもある．

MPO-ANCA型急速進行性糸球体腎炎の臨床所見をスコア化した重症度分類を**表8**に示す[5]．この分類に基づき，ステロイドあるいはシクロホスファミドを含む治療方針が決定される．

遺伝性CKD

1．常染色体優性多発性嚢胞腎

多発性嚢胞腎の中でも常染色体優性多発性嚢胞腎は，最も頻度の高い遺伝性腎疾患である．加齢とともに嚢胞が増加・増大し，進行性に腎機能が低下し，70歳までに約半数が末期腎不全に至る．多くは家族歴があり，ほとんどが30～40歳代まで無症状で経過する．

画像検査では両側の腎臓に多発する嚢胞を認める．ときに肉眼的血尿，腰痛，腹痛，腹部膨満の症状を認めることがある．

進行を抑える治療として，高血圧合併例には降圧管理が進行抑制に有効である．また水分摂取はバソプレシンの分泌を抑えて嚢胞の進展を抑制する可能性が期待され，十分に行うことが望ましく，脱水は避ける．肝嚢胞や脳動脈瘤の合併症の評価も併せて行う．

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ORIGINAL ARTICLE

Medication-prescribing patterns of primary care physicians in chronic kidney disease

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Abstract
Background We investigated the medication-prescribing patterns of primary care physicians in chronic kidney disease (CKD).
Subjects and methods This cross-sectional study included 3,310 medical doctors who graduated from Jichi Medical University. The study instrument was a self-administered questionnaire to investigate their age group, specialty, workplace, existence of a dialysis center at workplace, and their prescription frequencies (high, moderate, low, very low) of the following agents—calcium (Ca) inhibitors, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor antagonist (ARBs), statins, anti-platelet agents, erythropoietin (Epo), AST-120, vitamin D, and sodium hydrogen carbonate ($NaHCO_3$).
Results From a total of 933 responses, 547 (61.0 %) medical doctors prescribed medication for CKD. The prescription frequencies of Ca inhibitors, ACEIs, and ARBs were high (>90 %, high + moderate), those of statins, anti-platelet agents, Epo, and AST-120 were moderate (90–50 %, high + moderate), and those of vitamin D and $NaHCO_3$ were low (<50 %, high + moderate). The primary care physician's specialty was significantly associated with their prescription frequency of Ca inhibitors ($p < 0.01$). Their workplace was significantly associated with their prescription frequency of ACEIs ($p < 0.01$), ARBs ($p < 0.01$), Epo ($p < 0.01$) and vitamin D ($p < 0.01$). The existence of a dialysis center at their workplace was significantly associated with their prescription frequency of Epo ($p < 0.01$), vitamin D ($p < 0.01$) and $NaHCO_3$ ($p < 0.01$). Their age was not associated with their prescription frequency of any agents.
Conclusion Antihypertensives were highly prescribed, and vitamin D and $NaHCO_3$ were less prescribed by primary care physicians for CKD. There were certain associations between the prescribing patterns of primary care physicians for CKD and their specialty, workplace and the existence of a dialysis center at their workplace.

Keywords Primary care physician · Chronic kidney disease · Prescription pattern

Introduction

The prevalence of chronic kidney disease (CKD) has been increasing globally [1]. Since CKD is a great risk for progression to end-stage renal failure, which has a poor prognosis and high medical costs, it has become a worldwide public health problem [1, 2]. In addition, CKD is related to many other diseases [3, 4]. Recently, diabetes and hypertension have been reported as the two leading causes of CKD [5]. Idiopathic glomerulonephritis, ureteral obstruction, autoimmune disease, and genetic renal disease are also causes of CKD [5]. Alternatively, CKD has been reported to be an independent risk factor for cardiovascular disease [6]. These lines of evidence suggest the importance of appropriate pharmacological medication in CKD not only by nephrologists but also by primary care physicians, who first counsel patients about their health problems and

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closely manage various patients, not limited by cause, organ, and classifications of disease, to improve the prognosis of CKD. Several studies have reported the prescription patterns in CKD [7, 8]; however, those of primary care physicians remain to be revealed. In the present study, we investigated the medication-prescribing patterns of primary care physicians in CKD.

Subjects and methods

This study was conducted in accordance with the Declaration of Helsinki and was approved by a member of the ethics committee of Jichi Medical University.

Subjects

This cross-sectional study included 3,310 medical doctors who graduated from Jichi Medical University from 1978–2012. The majority of graduates of this medical university work as primary care physicians.

Study instrument

The study instrument was a self-administered questionnaire with an enclosed return envelope that was mailed in August 2012. This was designed to obtain detailed information about the characteristics of primary care physicians, including their age group, specialty, workplace, personal exercise habits, and their management of CKD (exercise counseling practice, medical prescription patterns). The results of their own exercise habits and exercise counseling for CKD will be analyzed and reported elsewhere. This study focused on the medication-prescribing patterns of primary care physicians in CKD. The questions used in this study were as follows—age (years) (1) 24–30 (24 years is the youngest age to obtain a medical license in Japan), (2) 30–40, (3) 40–50, (4) 50–60, (5) ≥60; specialty (1) internal medicine, (2) surgery, (3) general medicine (the branch of medicine that deals with the diagnosis and treatment of adult patients with a variety of complex medical conditions), (4) pediatrics, (5) other; workplace (1) university hospital, (2) polyclinic hospital, (3) hospital, (4) clinic, (5) other (including health facilities for recuperation); dialysis center at their workplace (1) present, (2) absent; management of CKD patients (1) yes, (2) no; prescription drugs for CKD patients (1) yes, (2) no. The next questions were for those who answered 'yes' for the question regarding prescription drugs for CKD patients. The frequency of prescription (1) high, (2) moderate, (3) low, (4) very low for prescribing the following agents—calcium (Ca) inhibitors, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor antagonists (ARBs), statins, anti-platelet agents, erythropoietin (Epo), AST-120, vitamin D, and sodium hydrogen carbonate ($NaHCO_3$).

Statistical analysis

The associations between primary care physicians' age group, specialty, workplace, existence of a dialysis center at their workplace, and their prescription frequency of each agent were analyzed by multinominal logistic regression analysis to determine the independent variables. Values of $p < 0.01$ were considered to be significant.

Results

The survey was mailed to 3,310 medical doctors, with a total of 933 (28.2 %) responses; 37 were excluded from this study due to their inadequacy. Among the remaining 896, 581 (64.8 %) medical doctors were managing CKD, and 547 (61.0 %) were prescribing medical drugs for CKD patients (Table 1). In the present study, these 547 medical doctors were defined as CKD primary care physicians and their answers to the self-administered questionnaire were analyzed. A breakdown of CKD primary care physicians' age group, specialty, workplace, and existence of a dialysis center at their workplace was as follows—age: 24–30 years 51 (9.3 %), 30–40 years 175 (32.0 %), 40–50 years 169 (30.9 %), 50–60 years 144 (26.3), and ≥60 years 8 (1.5 %); specialty: internal medicine 339 (62.0 %), surgery 35 (6.4 %), general medicine 142 (26.0 %), pediatrics 12 (2.2 %), and other 19 (3.5 %); workplace: university hospital 43 (7.9 %), polyclinic hospital 78 (14.3 %), hospital 179 (32.7 %), clinic 234 (42.8 %), and other 13 (2.4 %); existence of a dialysis center at their workplace: yes 203 (37.1 %), no 344 (62.9 %).

Prescription practices of CKD primary care physicians

The prescription frequencies of each drug by CKD primary care physicians were as follows (high–moderate–low–very low) (Table 2)—Ca inhibitors 266 (51.0 %)–214 (41.0 %)–35 (6.5 %)–7 (1.3 %); ACEIs 227 (43.7 %)–192

Table 1 Proportion of CKD primary care physicians

Managing CKD patients	Number (%)	Prescription for CKD patients	Number (%)
Yes	581 (64.8)	Yes	547 (61.0)
		No	34 (3.8)
No	315 (35.1)		
Total	896 (100)		

CKD chronic kidney disease

Table 2 Prescription frequencies of medical drugs for CKD

	Prescription frequencies (%)				
	High	Moderate	Low	Very low	Total
Ca inhibitors	266 (51.0)	214 (41.0)	35 (6.7)	7 (1.3)	522 (100)
ACEIs	227 (43.7)	192 (37.0)	71 (13.7)	29 (5.6)	519 (100)
ARBs	395 (73.7)	129 (24.1)	10 (1.9)	2 (0.4)	536 (100)
Statins	168 (32.2)	243 (46.6)	83 (15.9)	28 (5.4)	522 (100)
Anti-platelet agents	86 (16.6)	209 (40.3)	151 (29.2)	72 (13.9)	518 (100)
Epo	101 (19.3)	201 (38.4)	111 (21.2)	111 (21.2)	524 (100)
AST-120	147 (27.7)	243 (45.8)	66 (12.5)	74 (14.0)	530 (100)
Vitamin D	60 (11.6)	175 (33.9)	172 (33.3)	109 (21.1)	516 (100)
$NaHCO_3$	26 (5.1)	79 (15.5)	186 (36.4)	220 (43.1)	511 (100)

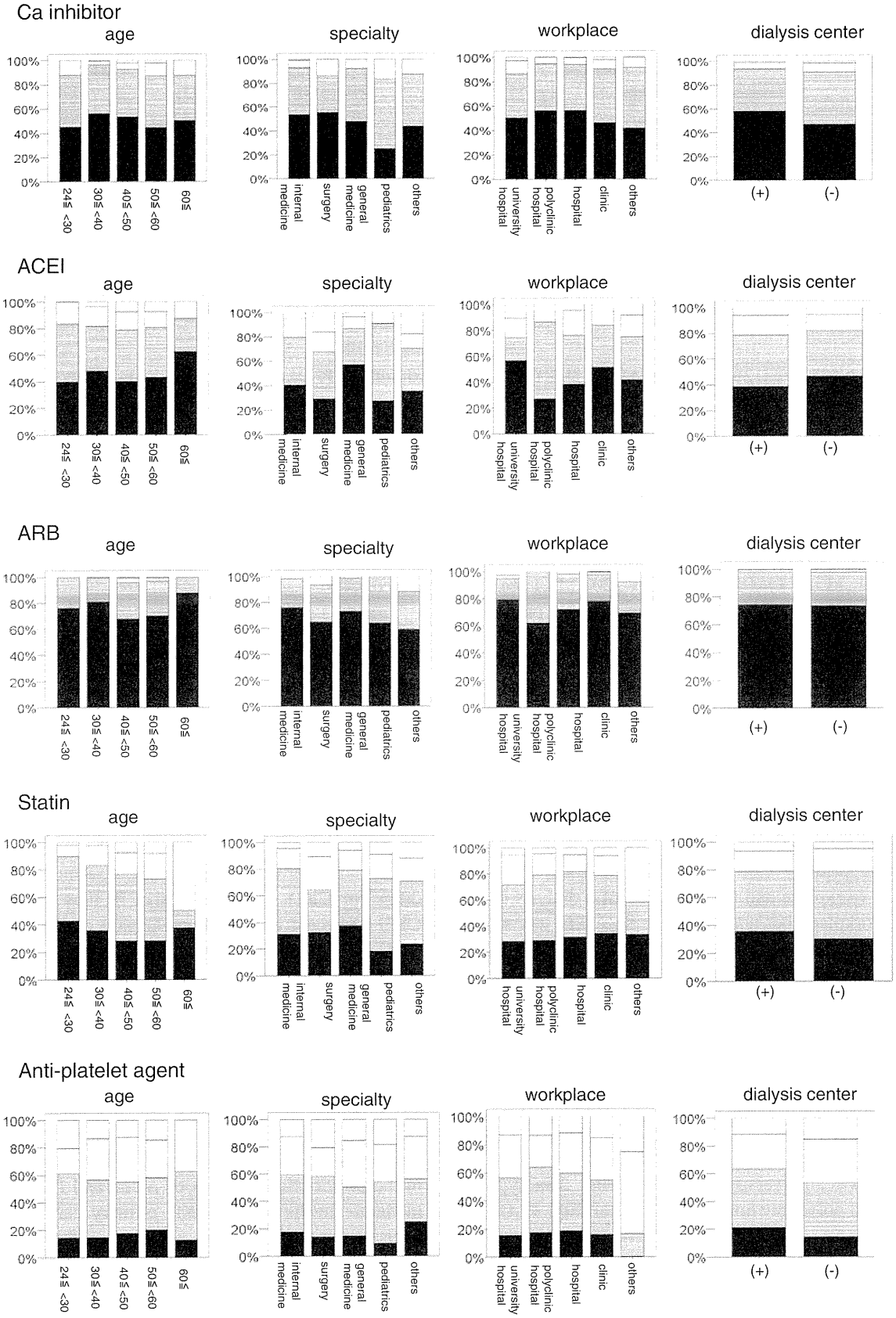
CKD chronic kidney disease, *ACEI* angiotensin-converting enzyme inhibitors, *ARB* angiotensin II receptor antagonists, *Epo* erythropoietin, *$NaHCO_3$* sodium hydrogen carbonate

(37.0 %)–71 (13.7 %)–29 (5.6 %); ARBs 395 (73.7 %)–129 (24.1 %)–10 (1.9 %)–2 (0.4 %); statins 168 (32.2 %)–243 (46.6 %)–83 (15.9 %)–28 (5.4 %); anti-platelet agents 86 (16.6 %)–209 (40.3 %)–151 (29.2 %)–72 (13.9 %); Epo 147 (27.7 %)–243 (45.8 %)–66 (12.5 %)–74 (14.0 %); AST-120 101 (19.3 %)–201 (38.4 %)–111 (21.2 %)–111 (21.2 %); vitamin D 60 (11.6 %)–175 (33.9 %)–172 (33.3 %)–109 (21.1 %); and $NaHCO_3$ 26 (5.1 %)–79 (15.5 %)–186 (36.4 %)–220 (43.1 %). Ca inhibitors, ARBs, and ACEIs were highly prescribed (>90 %, high + moderate). Statins, anti-platelet agents, AST-120, and Epo were moderately prescribed (90–50 %, high + moderate), and vitamin D and $NaHCO_3$ were less prescribed (<50 %, high + moderate). The primary care physicians' prescription patterns for each drug categorized by their age group, specialty, workplace and existence of a dialysis center at their workplace are shown in Fig. 1. As shown in Table 3, multinominal logistic regression analysis showed certain associations between the prescribing patterns of primary care physicians for CKD and their specialty, workplace and the existence of a dialysis center at their workplace but not their age. Specialty was significantly associated with their prescription frequency of Ca inhibitors ($p < 0.01$) (Table 3). Ca inhibitors were less likely to be prescribed by CKD primary care physicians in pediatrics than by those in internal medicine, surgery and general medicine (Fig. 1). The workplace was significantly associated with their prescription frequency of ACEIs ($p < 0.01$), ARBs ($p < 0.01$), Epo ($p < 0.01$) and vitamin D ($p < 0.01$) (Table 3). ACEIs and ARBs were more likely to be prescribed by CKD primary care physicians whose workplace was a university hospital or clinic than by those working in a polyclinic hospital or hospital (Fig. 1). On the other hand, Epo and vitamin D were less likely to be prescribed by CKD primary care physicians whose workplace was a university hospital or clinic than by those working in a polyclinic hospital or hospital (Fig. 1). The existence of a dialysis center at their workplace was significantly associated with their prescription frequency of Epo ($p < 0.01$), vitamin D ($p < 0.01$) and $NaHCO_3$ ($p < 0.01$) (Table 3). They were more likely to be prescribed by CKD primary care physicians whose workplace had a dialysis center than by those without a dialysis center (Fig. 1).

Discussion

The results of the present study showed that antihypertensives were highly prescribed, statins, anti-platelet agents, AST-120, and Epo were moderately prescribed, and vitamin D and $NaHCO_3$ were less prescribed for CKD by primary care physicians. Furthermore, there were certain associations between prescribing patterns of primary care physicians for CKD and their specialty, workplace and the existence of a dialysis center at their workplace.

CKD patients usually require several medical drugs for CKD and other comorbidities [3, 4]. Among the medical drugs for CKD, antihypertensive therapy is important in CKD treatment because hypertension is often observed in CKD patients and is a major risk factor for the progression of CKD and cardiovascular disease [9, 10]. The National Kidney Foundation Kidney Disease Outcome Quality Initiative (K/DOQI) clinical practice guidelines recommend the use of ACEs or ARBs in CKD patients as first-line antihypertensives because they can be used safely in most CKD patients and have beneficial effects for hypertension, cardiovascular disease, and kidney disease itself [11]. In the present study, although there were several differences in the prescription patterns of ACEs and ARBs at high or moderate levels by the CKD primary care physicians in different workplaces, they were reported to be positively prescribed (>90 %, high + moderate prescription rate) by all CKD primary care physicians in the present study. These results suggest that guideline recommendation seem to be widely known among primary care physicians.


Ca inhibitor
age
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Statin
age
specialty
workplace
dialysis center
Anti-platelet agent
age
specialty
workplace
dialysis center
100%
80%
60%
40%
20%
0%
24≤ <30
30≤ <40
40≤ <50
50≤ <60
60≤
internal medicine
surgery
general medicine
pediatrics
others
university hospital
polyclinic hospital
hospital
clinic
others
(+)
(-)

◀ **Fig. 1** Associations between each drug prescribed by CKD primary care physicians for CKD patients and their age group, specialty, workplace and the existence of a dialysis center at their workplace. *ACEI* angiotensin-converting enzyme inhibitors, *ARB* angiotensin II receptor antagonists, *Epo* erythropoietin, *$NaHCO_3$* sodium hydrogen carbonate

Although the high prescription frequency of Ca inhibitors was likely to be lower by CKD primary care physicians in pediatrics than by those in internal medicine, surgery and general medicine, a positive prescription frequency (high + moderate prescription rate) at a similar high level

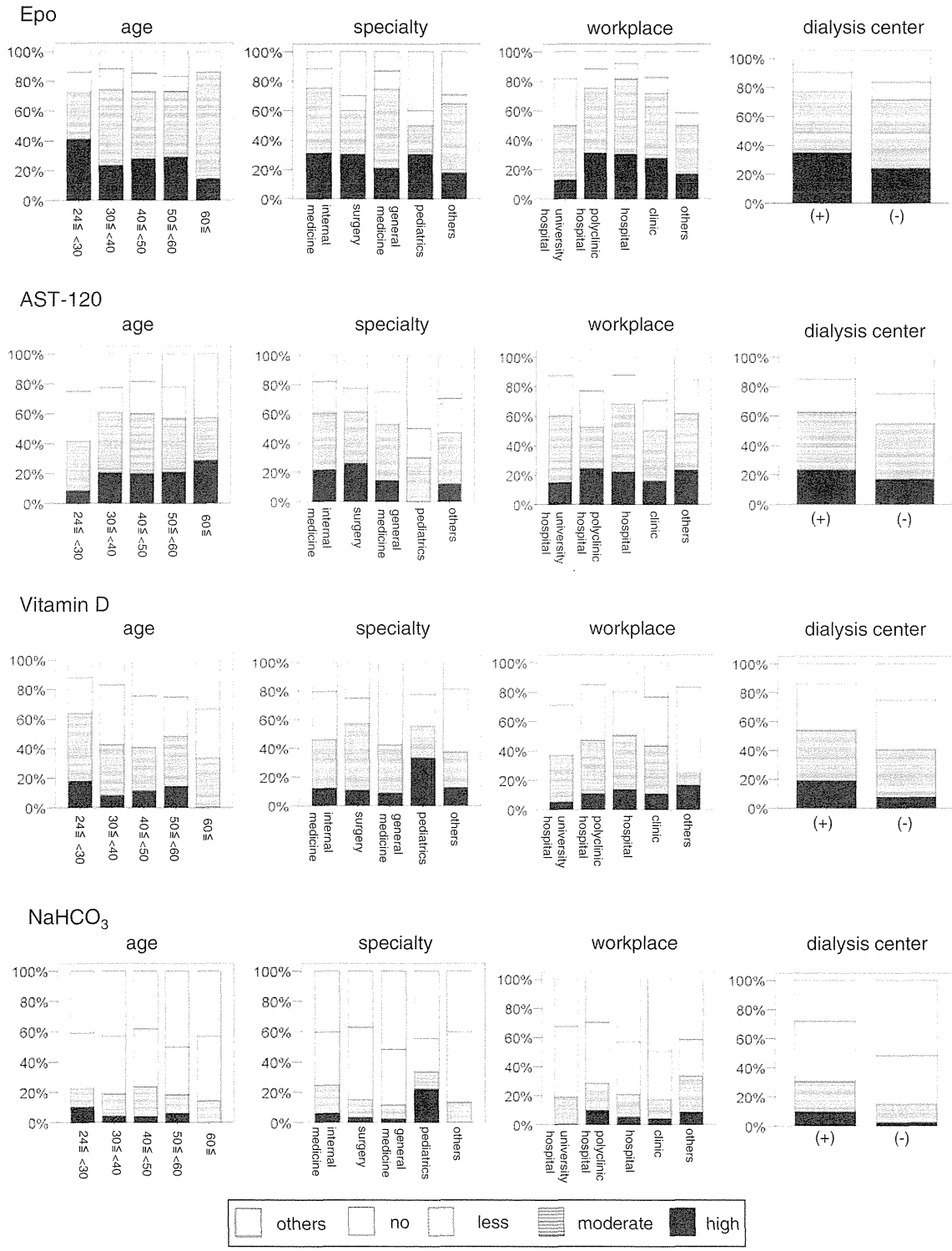

Fig. 1 continued

Table 3 Multinominal logistic regression analysis of the association between prescription frequencies of medical drugs for CKD with primary care physicians' age group, specialty, workplace and the existence of a dialysis center at their workplace

	Association of prescription frequency			
	Age	Speciality	Workplace	Dialysis center
Ca inhibitors	0.27	<0.01**	0.62	0.13
ACEIs	0.23	0.04	<0.01**	0.88
ARBs	0.11	0.06	<0.01**	0.12
Statins	0.07	0.77	0.17	0.02
Anti-platelets	0.53	0.80	0.36	0.10
Epo	0.23	0.58	<0.01**	<0.01**
AST-120	0.20	0.38	0.04	0.20
Vitamin D	0.23	0.58	<0.01**	<0.01**
$NaHCO_3$	0.80	0.10	0.31	<0.01**

was seen throughout. The small sample number of pediatricians in the present study ($n = 12$) may affect these results. Further large-scale studies are necessary to investigate prescription patterns of primary care physician in pediatricians for CKD.

More than 30 % of patients already have anemia (hemoglobin (Hb) levels <12 g/dL) by stage 3 CKD, and many patients develop anemia before being diagnosed with CKD [12]. Anemia increases the risk for cardiovascular disease and all-cause mortality in CKD patients [13]. These lines of evidence suggest that the treatment and management of anemia in CKD patients are important to improve the prognosis of CKD. Although there were differences in the prescription frequency of Epo among the workplace and the existence of a dialysis center at the workplace in the present study, the CKD primary care physicians appeared to manage anemia well in CKD patients considering the high prescription frequency of Epo (>70 %: high + moderate prescription rate). In addition, the fact that the prescription frequency was positively associated with the existence of a dialysis center at their workplace also suggested that the number of advanced-stage CKD patients who required Epo was high and they were treated well at medical establishments with a dialysis center.

Statins (>70 %: high + moderate prescription rate) were reported to be highly prescribed in CKD in this study by primary care physicians irrespective of their age group, specialty, workplace, and the existence of a dialysis center at their workplace. The effectiveness of lipid lowering on the reduction of cardiovascular endpoints or the progression of renal disease is under investigation and requires further evaluation [14, 15]. Evidence about the use of statins in CKD should be established to guide CKD primary care physicians in the near future.

AST-120, an adsorbent of uremic toxins, has been reported to delay the progression of renal failure [16] and is widely used in Japan. In the present study, AST-120 was reported to be moderately (73.5 %, high + moderate prescription rate) prescribed in CKD patients by primary care physicians irrespective of their age group, specialty, workplace and the existence of a dialysis center at their workplace. These results suggest that AST-120 is widely used and prescribed in advanced-stage CKD patients.

The overall reported prescription frequencies of vitamin D (45.5 %, high + moderate prescription rate) and $NaHCO_3$ (20.6 %, high + moderate prescription rate) by CKD primary care physicians were low in the present study. Vitamin D was less likely to be prescribed by CKD primary care physicians whose workplace was a university hospital or a clinic than by those working in a polyclinic hospital or hospital. It was prescribed more by CKD primary care physicians with a dialysis center at their workplace. $NaHCO_3$ was also prescribed more by CKD primary care physicians with a dialysis center at their workplace. These results may suggest that vitamin D and $NaHCO_3$ were prescribed more in advanced-stage CKD patients including maintenance dialysis patients. Another possibility for the overall low prescription frequencies of vitamin D and $NaHCO_3$ may be due to the fact that primary care physicians in the present study referred to a nephrologist about management of CKD patients before using these drugs; this trend may increase in primary care physicians who work at a university hospital or clinic compared with those working at a polyclinic hospital or hospital. Recent studies showed that metabolic acidosis presents early in CKD and could be associated with decreasing renal function [17]. Vitamin D therapy can slow the progression of secondary hyperparathyroidism, which begins at an early stage of CKD [18, 19]. These lines of evidence suggested that periodic estimation of the necessity of pharmacological treatment by vitamin D and $NaHCO_3$ is required in CKD patients, even when they are at an early stage. Although we did not evaluate that estimation of metabolic acidosis, electric abnormality, and hyperparathyroidism by CKD primary care physicians in CKD in the present study, the levels of such estimation and treatment may be insufficient considering the reported low prescription frequencies of vitamin D and $NaHCO_3$. Further studies are necessary to investigate the details of the low prescription frequency of vitamin D and $NaHCO_3$ by primary care physicians.

There are several limitations to this study. First, since the study instrument was a mailed self-administered questionnaire, there may be self-selection bias, and it may also contribute to the low response rate (28.2 %) to questionnaire. Second, the primary care physicians in this study may not be a representative population of all primary care

physicians because all medical doctors in this study graduated from one medical university; however, the majority of graduates of this medical university work as primary care physicians. Third, the questionnaire did not include definition and classification of CKD; therefore, recognition of CKD by primary physicians in the present study may vary, and may influence their answers. Fourth, the sample number of CKD primary care physicians in pediatrics and surgery was small. This small sample number may affect the analysis results in the present study. Fifth, it should be noted that the results of this study were from a self-administered questionnaire and were not objectively evaluated in terms of prescription frequencies of drugs. Finally, primary care physicians' reports of their own answers may not always be accurate [20]. Further studies will be needed to investigate the prescription pattern of primary care physicians in each CKD stage compared with the actual prescribed dose.

In conclusion, antihypertensives were highly prescribed, and vitamin D and $NaHCO_3$ were less prescribed for CKD by primary care physicians. There were certain associations between the prescribing patterns of primary care physicians for CKD and their specialty, workplace and the existence of a dialysis center at their workplace. Further dissemination and implementation of clinical practice guidelines for CKD [1, 11, 21] for primary care physicians, as well as the partnership between primary care physicians and nephrologists in terms of clinical practice for CKD, are important for improving the management of CKD.

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Conflict of interest The authors declare no conflicts of interest.

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Original Article

Association between Cystatin C and Arteriosclerosis in the Absence of Chronic Kidney Disease

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Aim: Chronic kidney disease (CKD) is a known risk factor for cardiovascular disease (CVD). Cystatin C was recently reported to be an endogenous surrogate of kidney function, and a high level of cystatin C is reported to be a strong predictor of CVD; however, the association between cystatin C and arteriosclerosis in a non-CKD population is unclear. This study aimed to clarify the association between cystatin C and arteriosclerosis in a non-CKD population.
Methods: Of the 637 Japanese adults (264 men, 373 women) enrolled, we analyzed 446 participants with an estimated glomerular filtration rate (eGFR) >60 mL/min and no proteinuria (177 men, 269 women) without a history of CVD. Kidney function was evaluated according to serum cystatin C levels and eGFR. Arteriosclerosis was evaluated on the basis of the cardio-ankle vascular index (CAVI) and carotid intima-media thickness (CIMT).
Results: The mean age of our subjects was 67.0 ± 10.0 years. No variables showed any significant differences according to gender. The results of multiple linear regression analysis showed a significant correlation between serum cystatin C and CAVI only in women, but not CIMT.
Conclusion: We observed a significant correlation between cystatin C and CAVI, which is a marker of early-stage arteriosclerosis, in women in a non-CKD population with no proteinuria and eGFR >60 mL/min.

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Key words: Cystatin C, Cardiovascular disease, Cardio-ankle vascular index (CAVI), Carotid intima-media thickness (CIMT)

Introduction

Recently, chronic kidney disease (CKD) has become an important public health problem worldwide. In the United States, it is estimated that there are 25 million people with CKD[1]. In Japan, about 13% of the Japanese adult population (approximately 13.3 million people) was predicted to have CKD in 2005[2]. CKD has been recognized as a risk factor not only for end-stage renal disease but also for the development of cardiovascular disease (CVD)[3,4] and is a known predictor of cardiovascular mortality[5,6]. In fact, an independent and graded association has been observed in a community-based population between renal dysfunction and the risk of death, cardiovascular events, and hospitalization[7]. Therefore, it is necessary and important to detect CKD in its early stages to reduce cardiovascular disease events.

The glomerular filtration rate (GFR) is an important indicator of kidney function for detecting, evalu-

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ating, and managing CKD. The accurate and internationally accepted method of measuring GFR is by measuring inulin clearance; however, this is a complex procedure and is normally not used in clinical practice in Japan. Instead, creatinine clearance is often used as a surrogate marker of GFR. However, several factors other than GFR, such as muscle mass and dietary intake, affect the serum creatinine level. Recently, cystatin C has been proposed as an endogenous surrogate marker for GFR, because it can easily pass through the glomerular filtration barrier because of its size[8]. Cystatin C is a non-glycosylated 13-kDa basic protein that is a cysteine protease inhibitor; it is also a member of the human cysteine superfamily, functioning as a housekeeping gene protein that is stably produced by most nucleated cells[9]. Furthermore, cystatin C is filtered by the glomeruli and reabsorbed and catabolized by tubular epithelial cells, with only small amounts being excreted in the urine[10]. Further, in comparison to traditional markers of renal dysfunction, an advantage of cystatin C is that very small reductions in GFR cause a significant increase in cystatin C serum[11]; cystatin C is therefore gaining attention as a marker of early-stage renal impairment.

It is very important to establish effective and accurate screening methods for arteriosclerosis to prevent CVD. Several non-invasive parameters, such as the ankle brachial index (ABI), carotid intima-media thickness (CIMT), and pulse wave velocity (PWV), have been useful for evaluating arteriosclerotic lesions in the clinical setting. CIMT is an established measure of subclinical arteriosclerosis that holds prognostic significance for cardiovascular events in the general population[12-15]. Among the several methods available for the evaluation of arterial stiffness, PWV is easy, fairly reproducible, and correlates well with arterial stiffness determined by an invasive method[16]. However, since PWV is influenced by blood pressure, severe fluctuations in blood pressure values at the time of measurement of PWV can cause clinical difficulties. Therefore, a novel arterial stiffness parameter that reflects the stiffness of the aorta, the cardio-ankle vascular index (CAVI)[17, 18], has been recently developed; this index is independent of blood pressure[17].

To date, a large number of studies have demonstrated that CKD patients are at a high risk of arteriosclerosis-related CVD[7]. However, based on studies that have assessed the association between kidney function and arteriosclerosis in the non-CKD adult population, this relationship is considered controversial[19-26]. Currently, CKD is defined by either GFR <60 mL/minute per 1.73 m^2 of body-surface area or the presence of kidney damage, regardless of the cause, for 3 or more months[5]. Thus, in the present study, the "non-CKD population" included people with eGFR >60 mL/min and without proteinuria, and without an apparent past or present history of cerebral infarction or hemorrhage or ischemic heart disease. Thereafter, we measured cystatin C as an indicator of kidney function, and CIMT and CAVI as indicators of arteriosclerosis, and we investigated the association between cystatin C and arteriosclerosis in a Japanese non-CKD population.

Materials and Methods

Subjects

Ethics approval was obtained from the Special Committee of Nagasaki University (project registration number 08043068) before commencement of the study. The study population was chosen by using a medical screening program for individuals aged over 40 years living in Goto city (total population in 2007, 44,874), Nagasaki Prefecture, Japan. After obtaining informed consent, we enrolled 637 Japanese adults (264 men, 373 women) in the study. We excluded 164 participants based on eGFR <60 mL/min and proteinuria; patients with a urine albumin-to-creatinine ratio of 300 mg/gCr or higher were judged to be positive for proteinuria. In addition, we excluded 27 other participants because they had an apparent past or present history of cerebral infarction or hemorrhage or ischemic heart disease. Finally, 446 participants (177 men and 269 women) were included for further analysis. With regard to underlying diseases in the study participants, we adhered to the following definitions (based on values observed during physical examination or self-reported at an interview): hypertension was defined as blood pressure $\geq 140/90$ mmHg[27]; dyslipidemia, as low-density lipoprotein-cholesterol (LDL-C) ≥ 140 mg/dL or high-density lipoprotein-cholesterol (HDL-C) <40 mg/dL[28]; and diabetes mellitus (DM), as hemoglobin A1c (HbA1c) $\geq 6.4\%$ (HbA1c notation converted from the original Japan Diabetes Society (JDS) values to the National Glycohemoglobin Standardization Program (NGSP) values[29].

Data Collection and Laboratory Measurements

Sociodemographic characteristics, past medical history, and details regarding lifestyle behaviors (smoking) were obtained by means of a questionnaire. Height, weight, and waist circumference (WC) were measured, and body mass index (BMI: kg/m^2) was calculated as an index of obesity. Systolic and diastolic blood pressure (SBP and DBP) were recorded at rest,

Table 1. Characteristics of the study participants

	Men (n=177)	Women (n=269)	p value	All participants (n=446)
Age (years)	66.5±11.0	67.4±9.2	n.s.	67.0±10.0
BMI (kg/m^2)	23.5±3.1	23.0±3.5	n.s.	23.2±3.4
WC (cm)	84.5±9.3	82.1±10.2	n.s.	83.1±9.9
SBP (mmHg)	144±18	144±21	n.s.	144±20
TG (mg/dL)	99±71	94±53	n.s.	96±61
HDL-C (mg/dL)	57±14	60±13	n.s.	59±14
LDL-C (mg/dL)	118±27	126±25	n.s.	122±26
UA (mg/dL)	6.1±1.3	4.7±1.0	n.s.	5.2±1.3
HbA1c (%)	5.6±0.7	5.6±0.5	n.s.	5.6±0.6
U-Alb/Cre (mg/g·Cre)	18.7±32.4	25.7±36.7	n.s.	22.9±35.2
Cre (mg/dL)	0.78±0.09	0.59±0.07	n.s.	0.67±0.12
eGFR (mL/min/1.73 m^2)	78.0±12.0	76.8±11.6	n.s.	77.3±11.8
CysC (mg/L)	0.78±0.13	0.73±0.11	n.s.	0.75±0.12
CIMT (mm)	0.72±0.12	0.69±0.11	n.s.	0.70±0.12
CAVI	8.4±1.5	8.1±1.4	n.s.	8.2±1.4

with the simultaneous measurement of CAVI. Blood samples were collected from each participant after overnight fasting. Serum and plasma were separated and stored at −20℃ and −80℃, respectively, until the assay. Serum concentrations of total cholesterol (TC), triglyceride (TG), and HDL-C were measured by standard laboratory procedures, and LDL-C values were calculated by the Friedewald equation. In addition to fasting blood sugar and HbA1c, serum creatinine (Cre) and uric acid (UA) were measured by standard laboratory procedures. Serum cystatin C was measured in plasma specimens by the latex immunoturbidimetric method using OLYMPUS AU600 (Ikagaku Co. Ltd., Kyoto, Japan).

We also analyzed random urine samples from each patient to measure urinary albumin and creatinine excretions.

eGFR was calculated by the following formula[30]:

$$eGFR = 194 \times \text{standardized Scr}^{-1.094} \times \text{Age}^{-0.287} \ (\times 0.739 \text{ [if female]})$$

Measurement of CAVI and CIMT

CAVI was recorded using a VaseraVS-1000 vascular screening system (Fukuda Denshi, Tokyo, Japan) with the participant resting in the supine position. The principles underlying CAVI have been described by Yambe *et al.*[18] ECG electrodes are placed on both wrists, a microphone for detecting heart sounds is placed on the sternum, and cuffs are wrapped around both the arms and ankles. After automatic measurements, the obtained data were analyzed using VSS-10 software (Fukuda Denshi), and the values for right and left CAVI were calculated. Averages of the right and left CAVI were used for analysis.

Measurement of CIMT by ultrasonography of the left and right carotid arteries was performed using a LOGIC Book XP with a 10-MHz linear array transducer (GE Medical Systems, Milwaukee, WI, USA).

Statistical Analysis

Results are expressed as the mean±standard deviation. Differences between women and men in laboratory values were evaluated using the t-test. Simple linear regression analysis was conducted to determine the correlation between cystatin C and the other variables measured. Variables that showed a significant association were subjected to multiple linear regression analysis. Probability values <0.05 were considered significant. All statistical analyses were performed using SPSS v. 11.0 software (SPSS Japan, Tokyo, Japan).

Results

The characteristics of the study participants are shown in **Table 1**. The mean age was 67.0±10.0 years. With regard to the presence of underlying diseases among the study participants, 30 (6.7%) had DM, 159 (35.7%) had dyslipidemia, and 291 (65.2%) suffered from hypertension. Further, 49 participants (11.0%) had a positive history of smoking.

No variables showed any significant differences according to gender. Simple linear regression analysis revealed that cystatin C was significantly correlated with CAVI in all the participants (men: r=0.24, $p<$ 0.01; women: r=0.247, $p<0.01$; total population: