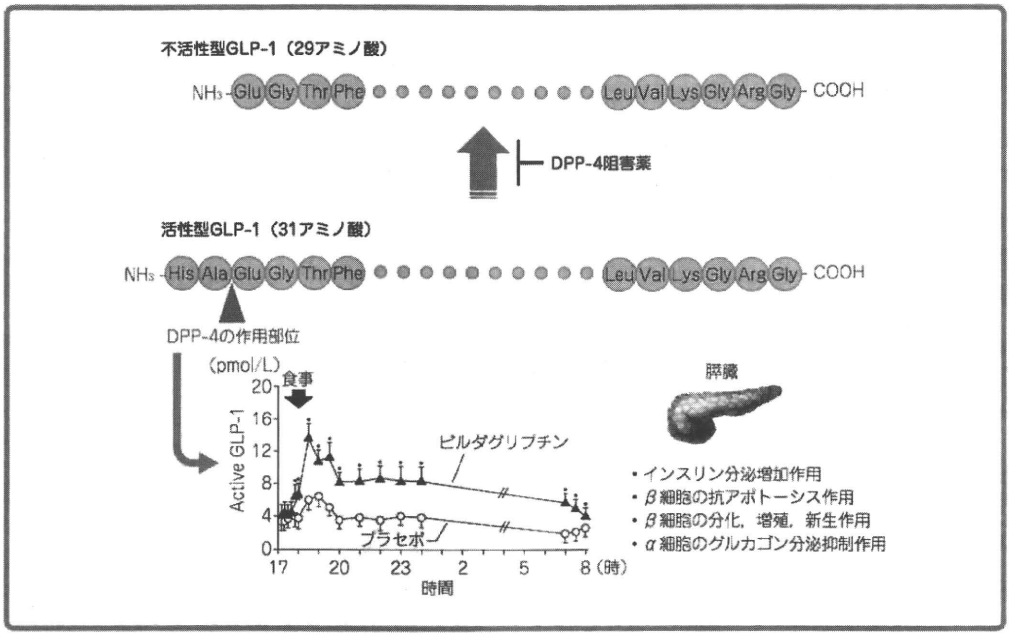

図2　DPP-4阻害薬

〔Balas B, et al : The dipeptidyl peptidase Ⅳ inhibitor vildagliptin suppresses endogenous glucose production and enhances islet function after single-dose administration in type 2 diabetic patients. J Clin Endocrinol Metab. 92 : 1249-1255, 2007より引用，改変〕

回あるいは2回で十分とされる。動物実験において，DPP-4ノックアウトマウスではGLP-1の血中レベルの増加，高脂肪食負荷による肥満，インスリン抵抗性の抑制を示した[3]。また，DPP-4活性を消失させたラットにおいてもインスリン分泌作用は増強することが報告されており，DPP-4を阻害することが糖尿病治療の戦略になりうることが確認されている[4]。DPP-4阻害薬の開発において問題となるのが，DPP-4と相同性の高い類似の活性をもつDPP-8，DPP-9である。これらの生理作用はまだ不明であるが，これらの阻害は重篤な毒性をもつことが示されており，DPP-4を選択的に阻害できることが重要となる。シタグリプチン，ビルダグリプチンに関してはDPP-4への選択性が高いため，問題ないとされる。

臨床的な応用（2型糖尿病患者における経口血糖降下薬の薬物治療戦略）

現在，欧米ではDPP-4阻害薬による治療がすでに開始されており，それらの報告からは，単剤療法でHbA1cを0.65～1.1%改善させ，空腹時血糖，食後血糖ともに有意な改善を認めている。また，HbA1c 9%以上のコントロール不良群ではより大きな改善を認めた[5]。わが国の臨床試験の結果でも同様な成績が報告されている。低血糖はプラセボ群と同等であり，体重に関しては両試験ともに増加は認めなかった。欧米で行われた併用療法の検討では，シタグリプチン（100mg/日）をメトホルミン（1,500mg/日）に追加し，24週後のHbA1cを0.65%低下させ，同様にピオグリタゾン（30mg/日），スルホニル尿素（SU）薬（グリメピリド4mg/日 以上）によって加療中の患者へのそれぞれの追加投与では，それぞれHbA1c 0.7%，0.74%の低下を認めた[6)-8)]。DPP-4阻害薬は他の経口血糖降下薬への追加投与によりいずれも血糖改善作用を示し，上乗せ効果が期待できる。また，SU薬の併用による低血糖の副作用増加は認めるも，他の有害事象に関して，プラセボ群とほぼ同等であり，臨床試験が行われた観察期間1～2年における安全性は問題ないと思われる。

では，この新たなDPP-4阻害薬が今までの治療において，どのような治療的な価値が見出せるかということを解説したい。2型糖尿病患者の治療には，「インスリン

分泌障害」と「インスリン抵抗性」の2つが主な治療ターゲットとして考えられてきた。インスリン分泌障害に対する治療としては，インスリン分泌増強作用が強ければ強いほど低血糖の頻度が増加し，また，ADOPT試験[9]で示されたように初期の治療として有効であったSU薬も体重増加につれ，血糖コントロールが不良となることが問題となっている。そのため，インスリン分泌障害改善薬のなかで，低血糖，体重増加を来さないDPP-4阻害薬は長期使用においても有効性が持続できる可能性をもつ。また，多剤併用においても，血糖改善効果を認めており，治療抵抗性の患者においてもそのまま上乗せすることで治療効果が期待できる。

さらに，動物実験で証明されているような膵β細胞の保護作用がヒトでも同様に確立されたならば，それこそ，2型糖尿病発症前から，膵β細胞の保護を目的にDPP-4阻害薬が薬物治療のなかで第一選択となりうる可能性はある。2型糖尿病発症の時点で，もうすでに膵β細胞は約半数までに減少しており，また，糖尿病の進展にもβ細胞の減少が強く関わることはよく知られていることである。しかし，ヒトのβ細胞への保護効果を示すエビデンスがまだ確立されていないため，あくまでも可能性を示唆するにとどめる。

表1　DPP-4の基質となりうる生理活性物質

グルカゴンスーパーファミリー
- GLP-1
- GLP-2
- GIP
- VIP (vasoactive intestinal polypeptide)
- GHRH (growth hormone-releasing hormone)
- NPY (neuropeptide Y)
- PYY (peptide YY)
- PACAP27 (pituitary adenylate cyclase-activating polypeptide)
- PACAP38

ケモカイン
- MIG (interferon-γ-induced monokine)
- IP-10 (interferon-inducible protein-10)
- MCP (monocyte-chemoattractant protein)
- RANTES (regulated on activation normal T-cell expressed and secreted)
- MDC (macrophage-derived chemokine)
- Exotaxin
- GROb (growth-related protein)
- GCP-2 (granulocyte chemotactic protein-2)

その他
- Substance P
- SDF-1α (stromal cell-derived factor-1α)
- Vasostatin-1
- GRP (gastrin-releasing peptide)
- IGF-1 (insulin-like growth factor-1)
- PHM (peptide histidine methionine)
- β-Cacomorphin-2
- Endomorphin-2

〔Kirby M, et al : Inhibitor selectivity in the clinical application of dipeptidyl peptidase-4 inhibition. Clin Sci (Lond), 118 : 31-41, 2009より引用，改変〕

DPP-4阻害薬の投与の注意点——副作用など

薬剤の投与時間に関しては，食後，食間に関係なく吸収されるため，食事による制限はない。また，内服に関しても半減期が長いため，1日1～2回で十分効果は期待できる。

代謝に関してシタグリプチンは75%が未変化体で腎臓より排泄されるため，腎機能の低下している人，高齢者では血中濃度が高値になる可能性がある。そのため，クレアチニンクリアランス<50mL/minの人には用量を半量にするなどの対処が必要となる。一方，ビルダグリプチンは約70%が肝臓で代謝されるため，高齢，腎機能低下症例への減量は原則的には必要ないとされる。

一般的な副作用として，GLP-1受容体作動薬にみられるような悪心，嘔吐などの消化器症状はほとんどない。これはGLP-1，GIPの濃度が，GLP-1受容体作動薬による薬理学的な血中濃度に比べてかなり少なく，正常の2～3倍程度の増加にとどまるためと推測される。

体重に関しては増加しないとの報告が多い。DPP-4阻害薬ではGIP，GLP-1ともに血中濃度を増加させるため，GIPの膵外作用である体重増加作用とGLP-1の体重減少作用が拮抗されるためかもしれない。

DPP-4の生理学的な作用からもわかるように，DPP-4阻害薬は特異的にGIP，GLP-1などのインクレチンのみの分解を阻害するわけではなく，他にも数多くのペプチドの代謝に影響する（表1[10]）。例えば，シタグリプチンではジゴキシン投与中の患者においてジゴキシンの血中濃度を増加させたとの報告があり，薬物血中濃度測定

の注意書きが添えられている。また，サブスタンスPの不活化を抑制するため，ACE阻害薬内服中の患者では，よりサブスタンスPの濃度増加を来す可能性があり，血管性浮腫の増加が懸念される。リンパ球などの細胞膜表面に存在するものは，もともと免疫のシグナルに関わっており，DPP-4阻害による免疫系の低下の可能性が当初から考慮されていたが，現在の臨床試験においては重篤な免疫抑制効果は示されていない。また，他にも表1のような神経ペプチドやホルモンなどの分解にも影響を与えるため，今後，長期使用による影響がみられる可能性はあり，注意深く経過を観察する必要がある。

おわりに

インクレチンはインスリン分泌障害において，今までの治療でみられた低血糖，体重増加といった副作用の発現が少ない新たな治療法として注目されている。また，動物実験のレベルであるが，膵β細胞への保護効果，増殖作用が期待され，2型糖尿病の発症自体も予防できる可能性は今後の糖尿病治療を変貌させうる可能性を秘めている。日本でのDPP-4阻害薬の使用が可能となった現在，また，今後，使用可能となるGLP-1受容体作動薬は，糖尿病患者，糖尿病治療に携わっている医療従事者，社会的な問題となっている糖尿病患者の増加などに，多大な恩恵をもたらすことを期待する。また，長期使用に関する副作用に関しては慎重に観察する必要があるということはいうまでもない。

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II. 糖尿病性腎症

糖尿病性腎症の病理

Pathology of diabetic nephropathy

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Key words：糖尿病性糸球体硬化症，びまん性病変，結節性病変，滲出性病変，糸球体基底膜の肥厚

はじめに

糖尿病性腎症は一般的に神経障害，網膜症に続いて，糖尿病発症後5-10年で緩徐に進行し，初期にはアルブミン尿主体で血尿は少なく，臨床的に診断が行われている．腎生検を行う症例は，①急速にタンパク尿が増加，②糖尿病発症早期からタンパク尿が出現，③持続性タンパク尿が存在するが網膜症などの他の合併症がない，④尿所見で高度の血尿などの活動性糸球体疾患を疑う所見がある，⑤腎肥大がないなど，臨床的に糖尿病性腎症の診断が困難な症例，他疾患との鑑別が必要な症例など[1,2]であり，糖尿病性腎症の特徴的な組織学的変化によって判断する．

本稿では，糖尿病性腎症にみられる病理学的な所見，頻度，腎機能との関連性について記載する．

1. 糖尿病性腎症の病理学的な特徴

a. 光学顕微鏡所見[3]

1）糸球体病変

糖尿病性腎症の特異的，かつ重要な病変として糖尿病性糸球体硬化症がある．その病変はびまん性病変，結節性病変，滲出性病変に大別される．ごく初期では糸球体肥大のみみられるが，進行するに伴い，これらの変化が認められるようになる．

a）びまん性病変（diffuse lesion）（図1-a）

びまん性病変は正常アルブミン尿期より認められ，糖尿病の経過とともに次第に進行していく最も普遍的な変化である．メサンギウム基質の増加によるメサンギウム領域の拡大と毛細血管壁の肥厚をみる．進行によって次第に管腔は狭小化し最終的に糸球体硬化へ至る．成分はIV型コラーゲンなどの細胞外基質であり，染色パターンはエオジン好性，PAS（periodic acid-Schiff）染色陽性である．糖尿病性腎症の腎組織で最も多く，罹患歴10年以上の1型糖尿病患者の約90％に存在するといわれる[4]．

b）結節性病変（nodular lesion）（図1-b）

Kimmelstiel-Wilson結節と呼ばれ，糖尿病性腎症に特徴的であり，診断的価値が高い．典型的なものでは，円形で糸球体毛細血管係蹄の中心部に形成され，結節の中心はほぼ均一，周囲にメサンギウム細胞の核が偏在することもある．発症機序に関しては諸説あり，断定されてはいない．成分はIII型，IV型，V型，VI型コラーゲンを含んだメサンギウム基質であり，染色パターンはびまん性病変と同様でエオジン好性，PAS染色陽性である．PAM（periodic acid-methenamine silver）染色では層状にみられる．ほとんどびまん性病変を伴っている．結節性病変をもつ糖尿病患者は27-46％の範囲でみられ

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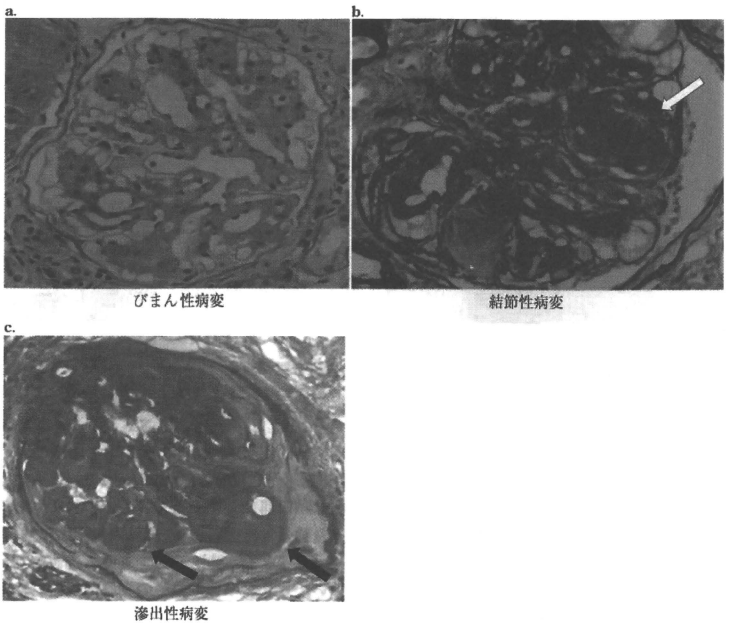


図1 糖尿病性腎症の糸球体病変

a. びまん性病変(PAS染色):メサンギウム細胞基質の増加.
b. 結節性病変(PAM染色):係蹄の中心部に位置し周辺に拡大.層状にみられる(矢印).
c. 滲出性病変(PAS染色):fibrin cap(矢印).

たとの報告がある[5].

c) 滲出性病変(exudative lesion)(図1-c)

滲出性病変は比較的少ないが特異的な所見で,比較的早期から認められる.滲出性病変には,末梢係蹄壁に半月状に突出して存在するfibrin capとボウマン嚢基底膜と上皮細胞の間に半球状に存在するcapsular dropがある.染色パターンは均一で,エオジン好性,PAS陽性,Masson-trichrome染色で赤色に染色される.

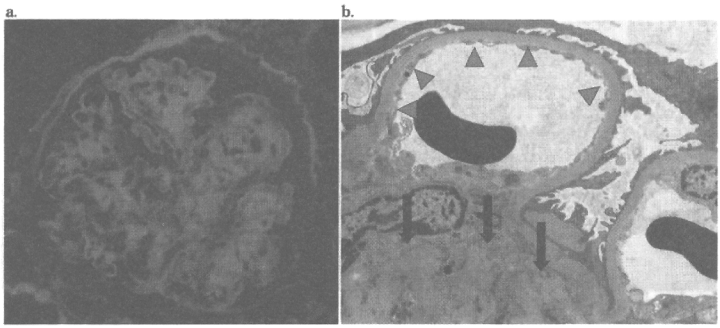
2) 尿細管・間質病変

尿細管では上皮細胞の膨化や尿細管基底膜の肥厚がみられ,進行し機能が廃絶した閉塞糸球体の下流尿細管では逆に萎縮がみられる.尿細管基底膜の肥厚は糸球体病変の進展と一致して進行する[6].血糖コントロール不良な症例では,まれではあるが皮髄境界の尿細管上皮細胞にグリコーゲンの蓄積を認め,Armanni-Ebstein病変と呼ばれる空胞化,膨化した尿細管がみられる.

間質にはリンパ球,単球,マクロファージなどの炎症細胞浸潤や間質の線維化など,糖尿病性腎症以外の腎疾患で認められる非特異的な変化を呈する.

3) 血管病変

糖尿病では細動脈への硝子化が主体で,年齢,高血圧による変化に比べ,早期からみられ,程度も強い.輸入細動脈のみならず,輸出細動脈にもみられることが糖尿病に特徴的である.



糖尿病性腎症の蛍光抗体法　　糖尿病性腎症の電顕

図2　糖尿病性腎症の蛍光と電顕所見

a. 蛍光抗体法：IgGが糸球体係蹄壁，ボウマン嚢壁に線状に認められる．

b. 電顕所見：糸球体基底膜の肥厚（矢頭），メサンギウム基質の増加（矢印）が認められる．

b. 蛍光抗体法所見

蛍光抗体法では糸球体の係蹄壁に沿って断続的にIgGが線状に染色される（**図2-a**）．しかし，この所見は診断的な価値は少なく，IgA腎症などの免疫学的な機序による腎症との鑑別を目的として行われたときに，糖尿病性腎症でみられる程度である．その他，アルブミン，IgM，C3，fibrinogenなども同様に係蹄壁に線状に染色されることがあるが，まれである．

c. 電子顕微鏡所見

1）糸球体病変（図2-b）

糖尿病性腎症における糸球体病変の基本的な電顕所見は，糸球体基底膜（glomerular basement membrane：GBM）の肥厚とメサンギウム基質の増加である．

GBMの肥厚は緻密層の肥厚であり，IV型コラーゲンによる六角形の立体的編み目構造の径の拡大（size barrier）も尿中アルブミン排泄の原因であることを示した[7]．GBMの肥厚は特に結節性病変を伴う部位で著明であるが，部分的には菲薄化，蛇行，断裂などがみられ，糸球体内に均一にみられるものではない．

メサンギウム基質はコラーゲン線維，calcific deposit，細胞膜や細胞内小器官の断片が認められる．ときには本来メサンギウムとGBMが接着していた部分（anchor point）にも解離が生じ，隣同士の毛細血管腔が一つになり，嚢胞状に拡張した血管腔（糸球体内微小血管瘤）を形成することもある．メサンギウム基質の増加に伴い，メサンギウム細胞の細胞内小器官は減少，萎縮，変性していく．

結節性病変では無構造な物質が層状に，滲出性病変は均一にみられる．

また，上皮細胞について，タンパク尿の増加とともに広範囲に足突起幅の増加を認める．内皮細胞の多くは腫大し，内皮下腔の拡大，内皮細胞の剥離が認められる．

2）尿細管・間質病変

光顕所見でも述べたように尿細管基底膜の肥厚など，尿細管上皮細胞の空胞変性などを認める．

2. 病理学的所見と頻度

病理学的な所見の頻度については病型によって報告が異なる．1型糖尿病は若年発症の症例が多く，高血糖以外の高血圧，脂質異常症，肥満などの他の因子の影響を比較的受けにくく，組織学的な変化についてある程度一定の所見をみる．しかし，2型糖尿病の場合は，種々の因子の影響を受け，過剰な間質の線維化，著明な

表1 1型糖尿病患者における糖尿病性腎症の病理所見と頻度

常にみられる	しばしばみられる	時々みられる
・糸球体基底膜の肥厚 ・尿細管基底膜の肥厚 ・メサンギウムの拡大 （びまん性糸球体硬化症） ・間質の拡大 （細胞外基質の増加） ・糸球体基底膜・尿細管基底膜・ボウマン嚢へのIgG，アルブミンの沈着	・Kimmelstiel-Wilson結節 ・部分的な尿細管萎縮 ・輸入・輸出細動脈の硝子化	・滲出性病変 （fibrin cap，capsular drop） ・動脈硬化 ・糸球体微小動脈瘤

（Brenner BM, et al: Brenner & Rector's The Kidney, 8th ed, p1266, Saunders, 2008より引用）

メサンギウム領域の拡大のない糸球体硬化など非典型的な所見をみることがあり，ばらつきが多い傾向がある[8,9]．そのため，1型糖尿病患者を対象とした腎組織の変化について，所見と頻度について**表1**に記載した[10-12]．病理学的な診断には他疾患との鑑別とこれら特異的な糖尿病性腎症の所見を組み合わせて判断する必要がある．

3. 病理組織学的所見と腎機能との関連

糖尿病性腎症の病理組織学的特徴と実際の腎機能との関連性について，1型糖尿病ではメサンギウム基質の増加，拡大，糸球体基底膜の肥厚と尿タンパク量，GFRの低下とは相関することが報告されている[13]．2型糖尿病では，病理組織学的な所見が不均一であり，腎機能との関連性についても一様な結果を得られていない．

おわりに

他疾患の鑑別目的による腎生検，症例数の制限などの問題があるが，病理組織と糖尿病性腎症の関係を確立するには，今後ともエビデンスの集積が必要であり，また，多施設での結果を比較，検討していくうえで，画一的な手法，評価方法を確立し検討していく必要があるかと思われる．

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INTERNAL MEDICINE

ORIGINAL ARTICLE

Relation between the Estimated Glomerular Filtration Rate and Pulse Wave Velocity in Japanese

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Abstract

Objective We investigated the link between renal function as evaluated by estimated glomerular filtration rate (eGFR) and pulse wave velocity (PWV) in Japanese without medications.

Methods A total of 1,244 Japanese subjects, aged 20-79 years, were recruited in a cross-sectional clinical investigation study. They received no medications. eGFR was calculated using serum creatinine (Cr), age and sex. Peripheral arterial stiffness was evaluated by brachial-ankle PWV (baPWV).

Results eGFR and baPWV were significantly correlated with age. eGFR was negatively correlated with baPWV (men: r=-0.308, p<0.0001, women: r=-0.293, p<0.0001). Twenty-six men (5.6%) and 35 women (4.5%) were diagnosed as reduced eGFR (eGFR <60 mL/min/1.73 m^2). We compared clinical parameters between subjects with reduced eGFR (Group R) and without such reduction (Group N). baPWV in Group R was significantly higher than that in Group N even after adjusting for age. In women, systolic blood pressure in Group R was also significantly higher than that in Group N.

Conclusion eGFR was closely associated with peripheral arterial stiffness in Japanese.

Key words: estimated glomerular filtration rate (eGFR), brachial-ankle pulse wave velocity (baPWV), peripheral arterial stiffness, creatinine

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Introduction

Chronic kidney disease (CKD) (1) has become a public health challenge in Japan (2). For example, 18.7% of adults have CKD, which is defined as kidney damage or a glomerular filtration rate (GFR) <60 mL/min/1.73 m^2 for at least three months regardless of cause, and 4.1% have moderate or severe CKD (2). We have also previously reported in a cross-sectional study that estimated glomerular filtration rate (eGFR) (3) in men with abdominal obesity and in women with hypertension was significantly lower than that without such components (unpublished data). CKD is associated with an increased risk of cardiovascular disease (CVD) outcomes after adjustment for traditional risk factors (4, 5).

Arterial stiffness represents one of the major hemodynamic factors determining pulse pressure even at an early stage of disease and its changes have been shown to be an independent predictor of hard endpoints in patients with a high cardiovascular risk. Pulse pressure and heart rate constitute other outcomes that may be useful as additional factors in risk assessment (6). Pulse wave velocity (PWV) is measured from the initial upstroke of pressure wave and constitutes an established index of arterial stiffness. It is directly related to arterial compliance, arterial distensibility and other factors describing arterial stiffness (7). PWV is not only a good tool for assessing vascular damage, but also an independent predictor of all-cause and cardiovascular mortality (8). Therefore, evaluation of the relationship between eGFR and PWV may provide quite useful data for preventing future diseases in the general population.

In this study, we evaluated the link between eGFR and brachial-ankle PWV (baPWV) and compared clinical pa-

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Table 1. Clinical Profiles of Subjects

	Men(n=464)				Women(n=780)			
	Mean ± SD		Minimum	Maximum	Mean ± SD		Minimum	Maximum
Age	44.7 ± 12.7		20	79	45.0 ± 12.6		20	79
Height (cm)	169.7 ± 6.1		143.7	187.5	157.1 ± 5.4		141.4	175.1
Body weight (kg)	69.8 ± 11.3		39.1	164.8	55.0 ± 8.5		36.8	113.9
Body mass index (kg/m^2)	24.2 ± 3.5		13.6	52.9	22.3 ± 3.3		15.2	44.9
Abdominal circumference (cm)	84.3 ± 9.6		62.0	150.0	75.8 ± 9.8		55.1	120.0
Hip circumference (cm)	94.2 ± 6.5		77.4	153.5	91.8 ± 6.1		75.5	127.5
Heart rate (beat/min)	65.2 ± 10.7		39.0	110.0	65.0 ± 9.8		35.0	104.0
Systolic blood pressure (mmHg)	126.2 ± 13.6		94.0	191.0	116.5 ± 16.4		87.0	193.0
Diastolic blood pressure (mmHg)	75.9 ± 10.1		52.0	112.0	68.5 ± 10.9		43.0	111.0
baPWV (right)	1338.0 ± 207.5		693.0	2375.0	1223.8 ± 227.4		838.0	2449.0
baPWV (left)	1341.7 ± 211.5		677.0	2476.0	1244.3 ± 224.6		840.0	2369.0
baPWV (mean)	1339.9 ± 206.8		685.0	2425.5	1234.1 ± 224.2		841.5	2409.0
ABI (right)	1.14 ± 0.08		0.88	1.43	1.11 ± 0.09		0.75	1.69
ABI (left)	1.12 ± 0.09		0.87	1.72	1.09 ± 0.08		0.73	1.46
ABI (mean)	1.13 ± 0.08		0.88	1.38	1.10 ± 0.75		0.75	1.36
Creatinine (mg/dL)	0.85 ± 0.12		0.51	1.20	0.62 ± 0.09		0.29	0.98
eGFR (mL/min/1.73m^2)	81.2 ± 14.5		50.2	138.6	84.3 ± 16.9		45.7	173.2

baPWV: brachial-ankle pulse wave velocity
ABI: ankle brachial index
eGFR : estimated glomerular filtration rate

rameters between subjects with reduced eGFR and without such reduction in Japanese without medications.

Subjects and Methods

Subjects

We used data of 1,244 Japanese, aged 20-79 years in a cross-sectional study (Table 1). All subjects met the following criteria: 1) they had undergone an annual health checkup from April 2006 to May 2008 at Okayama Southern Institute of Health; 2) they had received creatinine, baPWV and anthropometric measurements as part of their annual health checkup; 3) received no medications for diabetes, hypertension, and/or dyslipidemia and 4) they provided informed consent. Ethical approval for the study was obtained from the Ethical Committee of Okayama Health Foundation.

Anthropometric measurements

The anthropometric parameters were evaluated by using the following respective parameters such as height, body weight, body mass index (BMI), abdominal circumference, hip circumference. BMI was calculated by weight/[height]^2 (kg/m^2). The abdominal circumference was measured at the umbilical level and the hip was measured at the widest circumference over the trochanter in standing subjects after normal expiration (9).

Blood sampling and assays

We measured overnight fasting serum levels of creatinine (Cr) (enzymatic method). eGFR was calculated using the following equation: eGFR (mL/min/1.73 m^2) =194×Cr$^{-1.094}$× Age$^{-0.287}$×0.739 (if women) (3). Reduced eGFR was defined as an eGFR <60 mL/min/1.73 m^2.

PWV measurements

The baPWV and ankle brachial index (ABI) were measured using a form PWV/ABI (Colin, Co., Ltd., Komaki, Japan) after resting at least 15 minutes as described previously (10). This instrument records PWV, blood pressure, electrocardiogram and heart sounds simultaneously. The subjects were examined in the spine position after at least 5 minutes rest, with electrocardiogram electrodes placed on both wrists, a microphone for detecting heart sounds placed on the left edge of the sternum, and cuffs wrapped on both the brachia and ankles. The cuffs were connected to a plethymographic sensor that determines volume pulse form and an oscillometric pressure sensor that measures blood pressure. Volume waveforms for the brachium and ankle were stored, and the sampling time was 10s with automatic gain analysis and quality adjustment.

Statistical analysis

Data are expressed as means ± standard deviation (SD) values. A comparison of parameters between the 2 groups was made using an unpaired t test, covariance analysis and stepwise multiple regression analysis. Simple correlation analysis was performed as well to test for the significance of the linear relationship among continuous variables; $p<0.05$ was considered to indicate statistical significance.

Results

Clinical profiles are summarized in Table 1. eGFR was 81.2±14.5 mL/min/1.73 m^2 in men and 84.3±16.9 mL/min/1.73 m^2 in women. Mean baPWV was 1339.9±206.8 cm/min in men and 1234.1±224.2 cm/min in women.

We evaluated the age-related changes in baPWV (Fig. 1) and eGFR (Fig. 2). baPWV was positively correlated with age (men: $r=0.519$, $p<0.0001$, women: $r=0.651$, $p<0.0001$)

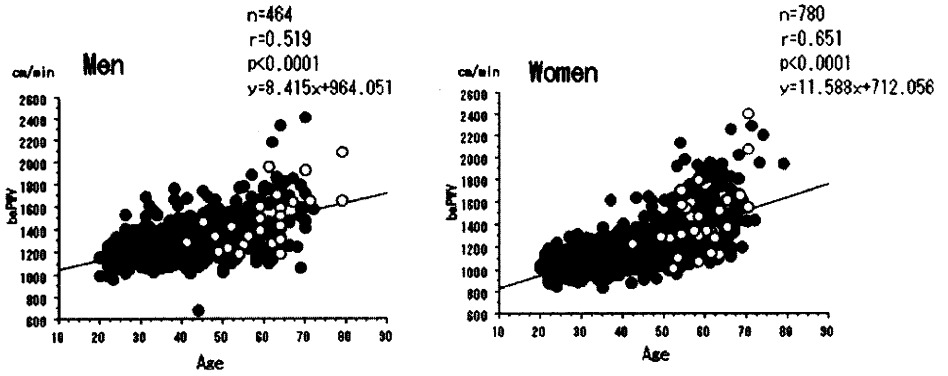

Figure 1. **Simple correlation analysis between baPWV and age. baPWV: brachial-ankle pulse wave velocity. ● : eGFR (estimated glomerular filtration rate) ≧ 60mL/min/1.73m², ○ : eGFR < 60mL/min/1.73m²**

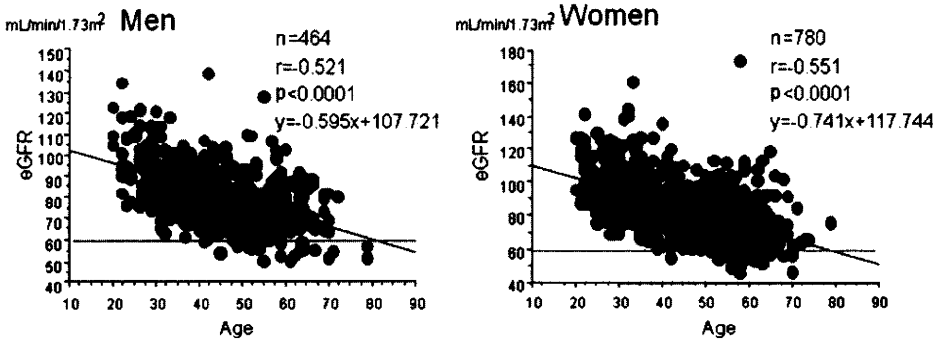

Figure 2. **Simple correlation analysis between eGFR and age. Red line is the level of 60 mL/min/1.73m² in eGFR. eGFR: estimated glomerular filtration rate**

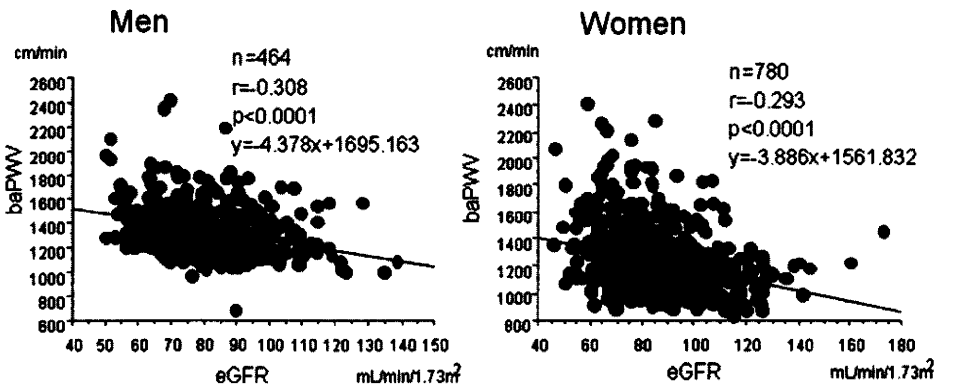

Figure 3. **Simple correlation analysis between baPWV and eGFR. baPWV: brachial-ankle pulse wave velocity, eGFR: estimated glomerular filtration rate**

and eGFR was negatively correlated with age (men: r= -0.521, p<0.0001, women: r=-0.551, p<0.0001). We also evaluated the relationship between baPWV and eGFR (Fig. 3). baPWV was weakly correlated with eGFR (men: r=-0.308, p<0.0001, women: r=-0.293, p<0.0001).

We further investigated the difference of clinical parameters between subjects who had different levels of eGFR [Group R: eGFR <60 mL/min/1.73 m², Group N: eGFR ≧ 60 mL/min/1.73 m²] (Table 2). baPWV was also positively correlated with age in subjects with CKD (men: r=0.649, p= 0.0003, women: r=0523, p=0.0013). The slope of regression line in subjects CKD was higher than that in all subjects in either sex. There were significant differences in diastolic blood pressure, baPWV and ABI between the two groups in both sexes. In women, abdominal circumference and systolic blood pressure in Group R were significantly higher than

Table 2. Comparison of Parameters between Group R and Group N

	Group R	Group N	p	p (After adjusting for age)
Men				
Number of subjects	26	438		
Age	59.8 ± 9.4	43.8 ± 12.4	<0.0001	
Body weight (kg)	70.0 ± 8.3	69.8 ± 11.5	0.9273	0.2260
Body mass index (kg/m^2)	24.5 ± 2.2	24.2 ± 3.6	0.6971	0.4238
Abdominal circumference (cm)	86.9 ± 7.5	84.1 ± 9.7	0.1522	0.2940
Hip circumference (cm)	93.7 ± 5.0	94.3 ± 6.5	0.6484	0.1134
Heart rate (beat/min)	64.0 ± 10.0	65.3 ± 10.8	0.5351	0.5255
Systolic blood pressure (mmHg)	128.2 ± 13.1	126.1 ± 13.7	0.4349	0.4346
Diastolic blood pressure (mmHg)	80.8 ± 8.1	75.6 ± 10.1	0.0114	0.1018
baPWV (right)	1468.5 ± 231.1	1330.2 ± 203.6	0.0009	0.0415
baPWV (left)	1500.8 ± 273.3	1332.2 ± 203.8	<0.0001	0.0141
baPWV (mean)	1484.6 ± 249.2	1331.3 ± 201.1	0.0002	0.0222
ABI (right)	1.20 ± 0.07	1.13 ± 0.08	0.0001	0.1458
ABI (left)	1.16 ± 0.07	1.12 ± 0.09	0.0174	0.4252
ABI (mean)	1.18 ± 0.06	1.13 ± 0.08	0.0006	0.2086
Women				
Number of subjects	35	745		
Age	58.9 ± 6.2	44.4 ± 12.4	<0.0001	
Body weight (kg)	55.9 ± 6.5	55.0 ± 8.6	0.5084	0.4327
Body mass index (kg/m^2)	22.8 ± 2.7	22.3 ± 3.4	0.3702	0.1200
Abdominal circumference (cm)	80.4 ± 9.2	75.6 ± 9.8	0.0045	0.3307
Hip circumference (cm)	91.8 ± 4.2	91.8 ± 6.2	0.9688	0.4599
Heart rate (beat/min)	63.6 ± 10.2	65.1 ± 9.8	0.3912	0.3018
Systolic blood pressure (mmHg)	124.3 ± 20.2	116.1 ± 16.1	0.0038	0.0178
Diastolic blood pressure (mmHg)	72.8 ± 11.8	68.3 ± 10.8	0.0162	0.3262
baPWV (right)	1418.3 ± 284.1	1214.7 ± 220.4	<0.0001	0.0126
baPWV (left)	1444.5 ± 277.3	1234.9 ± 217.5	<0.0001	0.0221
baPWV (mean)	1431.4 ± 278.9	1224.8 ± 217.1	<0.0001	0.0152
ABI (right)	1.16 ± 0.08	1.11 ± 0.09	0.0013	0.9763
ABI (left)	1.15 ± 0.09	1.09 ± 0.08	<0.0001	0.5987
ABI (mean)	1.15 ± 0.08	1.10 ± 0.07	<0.0001	0.7638

Group R: eGFR<60mL/min/1.73m^2
Group N: eGFR≧60mL/min/1.73m^2
baPWV: brachial-ankle pulse wave velocity
ABI: ankle brachial index
eGFR : estimated glomerular filtration rate

those in Group N. However, significant difference in age was also noted between the two groups. To avoid the influence of age on clinical parameters, we used age as a covariate and compared clinical parameters using covariance analysis. After adjusting for age, baPWV in Group R was significantly higher than that in Group N in both sexes. In women, systolic blood pressure in Group R was also significantly higher than that in Group N. The differences in other clinical parameters between the two groups did not show statistical significance after adjusting for age.

We also used stepwise multiple regression analysis to evaluate the effect of clinical parameters *i.e.* abdominal circumference, systolic blood pressure, diastolic blood pressure and eGFR on baPWV (mean), and found that systolic blood pressure, diastolic blood pressure and eGFR were significant (men: baPWV (mean) =511.906+4.150 (systolic blood pressure) +6.580 (diastolic blood pressure) -2.407 (eGFR), r^2= 0.388, p<0.0001, women: baPWV (mean) =264.104+7.562 (systolic blood pressure) +3.598 (diastolic blood pressure) -1.868 (eGFR), r^2=0.567, p<0.0001). Age is also thought to be a strong predictor of baPWV and we further analyzed stepwise multiple regression analysis by also using age and found that age, systolic blood pressure, diastolic blood pressure and eGFR were significant in women (baPWV (mean) = -58.089+7.593 (age) +6.090 (systolic blood pressure) +2.530 (diastolic blood pressure) +0.797 (eGFR), r^2=0.671, p<0.0001). However, in men, clinical impact of eGFR on baPWV was attenuated (baPWV (mean) =102.719+6.717 (age) +5.959 (systolic blood pressure) +2.438 (diastolic blood pressure), r^2=0.498, p<0.0001).

Discussion

It is well known that baPWV increases with age (11, 12), and eGFR also decreases with age (13). El Feghali et al have reported a significant correlation between PWV and age (r=0.59, p<0.001) by a cross-sectional multi-center study performed in 46 healthcare centers, from 14 countries (11). Ni et al also reported that PWV was positively related to age (r=0.531, p=0.001) in 3156 Chinese (12). According to the link between eGFR and age, by the large sample of Japanese cohort, the decline rate of eGFR was 0.36 mL/min/1.73 m^2/year (13). In this study, we also found that baPWV was positively correlated with age and eGFR was negatively correlated with age by cross-sectional analysis. The decline rate of eGFR in this study was 0.595 mL/min/1.73 m^2/year in men and 0.741 mL/min/1.73 m^2/year in women. This study was cross-sectional and the enrolled subjects in this study were younger than those in the previous report. Therefore, the rate of decline in eGFR in this study

might differ from the previous report.

Some studies have evaluated the link between baPWV and eGFR in Japanese (14-16). Kawamoto et al investigated 107 men, aged 68±9 years and 203 women, aged 67±7 years during their annual health examination in a single community, and eGFR [$eGFR=0.741\times175\times Cr^{-1.154}\times Age^{-0.203}\times 0.742$ (if female)] was significantly correlated with PWV ($r=-0.317$, $p<0.001$) (14). A reduced eGFR was significantly correlated with increased PWV in the heart-femoral in Japanese patients with type 2 diabetes ($r=-0.199$, $p<0.001$) (15). Ohya et al also showed that significant correlation between baPWV and creatinine clearance estimated by Cockcroft-Gault formula was noted in 3,387 subjects (mean age, 52 years) who attended a health checkup in Okinawa, Japan (16). In this study, we used newly developed equations for eGFR and the link between baPWV and eGFR in Japanese without medications. eGFR was negatively correlated with baPWV, and baPWV in Group R was significantly higher than that in Group N even after adjusting for age. Although Sengstock et al recently reported that the contribution of eGFR was not clinically meaningful when compared with traditional cardiovascular risk factors (17), eGFR especially in women, as well as systolic blood pressure, diastolic blood pressure and age, was good predictor for baPWV by stepwise multiple regression analysis. The present results are in agreement with the mild impairment of renal function might increase arterial stiffness even in Japanese without medications.

Potential limitations remain in our study. First, the cross-sectional study design and small sample size in subjects with reduced eGFR in our study make it difficult to infer association between baPWV and some parameters. Second, Insulin resistance is associated with high arterial stiffness and hemodynamic alterations in the common carotid artery (18). Insulin resistance causes diabetes, hypertension, metabolic syndrome and renal dysfunction through increased sympathetic stimulation, aldosterone activation, endothelial dysfunction as well as increased renal sodium absorption, advanced glycation end products, activation of the renin-angiotensin-aldosterone system and lipid peroxidation, resulting in vascular remodeling (19-22). Decreased renal function may increase PWV through insulin resistance. However, we could not prove the mechanism of the link between baPWV and eGFR. Third, Large 'central' artery stiffness predicts cardiovascular events in the general population and in end-stage renal disease (23, 24). However, we could not separately evaluate PWV of central and peripheral arteries. Therefore, our findings are applicable to clinical and public health practice settings. In conclusion, lower eGFR is associated with higher baPWV in Japanese. Further intervention studies are necessary to investigate the link between baPWV and eGFR.

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