評価方法はまだ不足しているが、⑤、⑥で示した方法は、今後、他の合併症発症率、あるいは、保存期 CKD 患者での合併症発症率を検討する上で応用できると考えられた。

以上の結果をふまえて、今後我々は本研究事業で下記の 3 つの研究を行う（図 3）。以下に説明する。

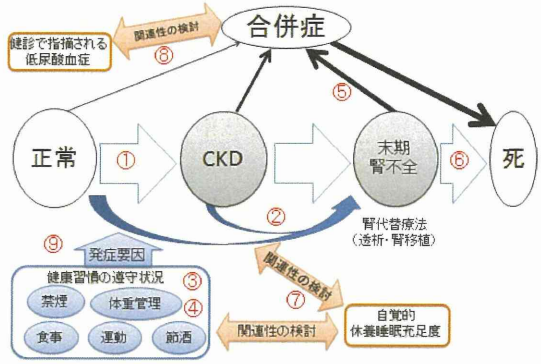

図 3．今後行う予定の研究

⑦自覚的休養睡眠充足度と生活習慣・CKD との関係

睡眠障害の改善は重要視されている。事実、21 世紀における第二次国民健康づくり運動（健康日本 21（第二次））の目標の一つに、睡眠による休養を十分とれていない者の割合の減少があげられている。しかし、具体的に何をどうすれば、睡眠による休養を十分とれていない者の割合を減らせるのかは明らかではない。睡眠と生活習慣病には相互に密接な関連があることから、睡眠障害の改善は生活習慣病対策にも重要である可能性が考えられる。そこで、特定健診の標準的な問診票で得られる自覚的睡眠休養充足度がどのような生活習慣と関連するかを明らかにする。これが明らかになれば、特定健診での保健指導時に、生活習慣のみならず睡眠障害にもあわせて介入することが可能になり、さらに睡眠障害の改善が健診受診者の生活習慣の行動変容へのモチベーションに繋がる可能性が考えられる。

⑧低尿酸血症の疫学

健診時に発見された低尿酸血症に対してどのような対応をすべきかについての明確な答えはない。尿酸は活性酸素のスカベンジャーであり、生体内の全抗酸化作用の 3 分の 2 を担うため、低尿酸血症患者で動脈硬化性疾患が多い、あるいは生命予後が不良である可能性があるが、それを支持する疫学データはない。そもそも低尿酸血症は頻度が低く、疫学データが不足しているのが現状である。本研究事業で作成される全国コホート群のような大規模の調査で検討する必要がある。

⑨５つの健康習慣と CKD の詳細な検討

③で行った検討に加えて、より多数例で、より長期の観察期間で、詳細な検討を行う。

さらに保健指導等による 5 つの健康習慣の改善による CKD 新規発症への効果もあわせて検討を行う予定である。

これらの研究により、より包括的な CKD 評価が可能になり、ひいては地域の実情に即した効果的な CKD 地域医療連携システムの制度設計に繋がると考える。

E．結論

現時点で可能な、地域における CKD の包括的評価方法をまとめた。健診時の血清クレアチニン測定は、個人の腎機能評価のみならず、集団としての評価も可能にする。集団としての評価は、地域の実情に即した効果的な CKD 地域医療連携システムの制度設計を行う上で、極めて有用な情報になると考える。より包括的な評価を行うために、本研究事業でさらなる臨床疫学研究を開始した。

G. 研究発表

1. 論文発表

1) Wakasugi M, Kazama JJ, Narita I. Differences in the local and national prevalences of chronic kidney disease based on annual health check program data. *Clin Exp Nephrol.* 16: 749-754, 2012.

2) Wakasugi M, Kazama JJ, Narita I. Use of Japanese Society for Dialysis Therapy dialysis tables to compare the local and national incidence of dialysis. *Ther Apher Dial.* 16: 63-67, 2012

3) Wakasugi M, Kazama JJ, Yamamoto S, Kawamura K, Narita I. A combination of healthy lifestyle factors is associated with a decreased incidence of chronic kidney disease: a population-based cohort study. *Hypertens Res.* 2012 Nov 22. doi: 10.1038/hr.2012.186. [Epub ahead of print]

4) Wakasugi M, Narita I, Iseki K, Moriyama T, Yamagata K, Tsuruya K, Yoshida H, Fujimoto S, Asahi K, Kurahashi I, Ohashi Y, Watanabe T. Weight gain after 20 years of age is associated with prevalence of chronic kidney disease. *Clin Exp Nephrol.* 16: 259-68, 2012.

5) Wakasugi M, Kazama JJ, Taniguchi M, Wada A, Iseki K, Tsubakihara Y, Narita I. Increased Risk of Hip Fracture among Japanese Hemodialysis Patients. *J Bone Miner Metab* 2013 Jan 6. [Epub ahead of print]

6) Wakasugi M, Kawamura K, Yamamoto S, Kazama JJ, Narita I. High mortality rate of infectious diseases in dialysis patients: a comparison with the general population in Japan. *Ther Apher Dial.* 16: 226-231, 2012.

7) Wakasugi M, Kazama JJ, Yamamoto S, Kawamura K, Narita I. Cause-Specific Excess Mortality Among Dialysis Patients: Comparison With the General Population in Japan. *Ther Apher Dial.* 2012 Dec 11. doi: 10.1111/j.1744-9987.2012.01144.x [Epub ahead of print]

2. 学会発表

1) 若杉三奈子、成田一衛、井関 邦敏、守山 敏樹、山縣 邦弘、鶴屋 和彦、吉田 英昭、藤元 昭一、旭 浩一、渡辺 毅. 成人以降の体重増加は慢性腎臓病と関連する. 第109回日本内科学会講演会, 京都, 2012年4月

2) 若杉三奈子、風間順一郎、和田篤志、谷口正智、井関邦敏、椿原美治、成田一衛. わが国における血液透析患者の大腿骨頸部骨折発症率は一般住民の約5倍である. 第109回日本内科学会講演会, 京都, 2012年4月

3) 若杉三奈子、風間順一郎、成田一衛. 地域における慢性腎臓病の包括的評価方法. 第55回日本腎臓学会学術総会, 横浜, 2012年6月3日、

4) 若杉三奈子、川村和子、風間順一郎、成田一衛. わが国の透析患者における感染症死亡率～一般住民との比較～第57回日

本透析医学会学術集会・総会ワークショップ，札幌，2012年6月

5) 若杉三奈子、風間順一郎、山本卓、川村和子、成田一衛．5つの健康習慣（禁煙、体重管理、飲酒、運動、食事）は慢性腎臓病の発症率を減少させる．第35回日本高血圧学会総会，名古屋，2012年9月

6) 若杉三奈子、風間順一郎、谷口正智、和田篤志、井関邦敏、椿原美治、成田一衛．一般住民の大腿骨頸部骨折発症率で認められる地域差は、血液透析患者でも認められる．第14回日本骨粗鬆症学会　骨ドック・健診分科会，新潟，2012年9月

7) Wakasugi M, Kazama JJ, Nagai M, Yokota S, Omori K, Narita I. Interobserver reliability of diagonal ear lobe crease in hemodialysis patients. 30th Annual Meeting of the International Society of Blood Purification, Yokohama, September 8, 2012

H. 知的財産権の出願・登録状況

1．特許取得　　なし。

2．実用新案登録　なし。

3．その他　　なし。

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分担研究報告書

「自治体の特定健診データからみたCKDの実態調査
～血清クレアチニンを測定しない場合のCKD見逃し率の推定等～」

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研究要旨
特定健診はCKDを早期発見できる絶好の機会であるが血清クレアチニンが必須項目となっていないため、CKDを見逃す可能生が指摘されている。本研究では血清クレアチニンを自主的に測定している20の自治体の578,965人の特定健診のデータを用いて検証した。対象住民におけるCKDの頻度は、18.6％であった。eGFR＜60 ml/min/1.73m^{2}の81,572人のうち尿蛋白陰性者は72,956人(89.4%)であった。eGFR＜60 ml/min/1.73m^{2}および／または尿蛋白1+以上で定義されたCKD 102,061人の住民のうち、尿蛋白陰性者は71.5％であった。すなわち、特定健診では血清クレアチニンを測定しなければ、CKDの70～90%を見逃す可能性があった。特定健診では、血清クレアチニンの測定を必須化することが必要である。

A. 研究目的

特定健診はCKDを早期発見できる絶好の機会であるが血清クレアチニンが必須項目となっていない。そのため、CKDを見逃す可能生が指摘されている。本研究では血清クレアチニンを自主的に測定している自治体の特定健診のデータを用いて、もし、血清クレアチニンが測定されなかったらどの程度CKDを見逃す可能生があるかを検証することを目的とした。

B. 研究方法

対象者:表１に示す２０府県の２００８年の健診受診者のうち血清クレアチニンが自主的に測定されていた578,965人のデータを対象とした。男性42%、年齢６１±１０（平均±SD）歳であった。

解析
SPSS version 17.0 (IBM, Chicago, IL)を用いた。

表１．解析に用いた住民

		度数	パーセント	有効パーセント	累積パーセント
有効	茨城県	15708	2.7	2.7	2.7
	沖縄県	137996	23.8	23.8	26.5
	宮崎県	46234	8.0	8.0	34.5
	宮城県	15772	2.7	2.7	37.3
	熊本県	10913	1.9	1.9	39.1
	高知県	29	.0	.0	39.1
	佐賀県	2834	.5	.5	39.6
	埼玉県	3433	.6	.6	40.2
	新潟県	35579	6.1	6.1	46.4
	神奈川県	50054	8.6	8.6	55.0
	石川県	6005	1.0	1.0	56.1
	大阪府	18707	3.2	3.2	59.3
	長崎県	6708	1.2	1.2	60.4
	長野県	11718	2.0	2.0	62.5
	東京都	26161	4.5	4.5	67.0
	徳島県	4328	.7	.7	67.7
	栃木県	5838	1.0	1.0	68.7
	福岡県	145426	25.1	25.1	93.9
	福島県	9221	1.6	1.6	95.5
	北海道	26301	4.5	4.5	100.0
	合計	578965	100.0	100.0	

（倫理面への配慮）

匿名化された健診データを用いる後ろ向き解析であるため、倫理的な問題は生じない。個人情報は取り扱わない。

C．研究結果

１．CKD の頻度

eGFR<60 ml/min/1.73m^2 の頻度は 14.6%、尿蛋白１＋以上の頻度は 5.2%で、どちらかまたは両者を有する CKD の頻度は 18.6%であった。

２．eGFR による CKD のステージの頻度

G1 4.1%, G2 15.4%, G3a 71.2%, G3b 7.7%, G4 1.1%, G5 0.5% で、ステージ別の頻度には男女で大きな差異は見られなかった。

３．血清クレアチニンを測定しない場合の CKD の見逃し率（表２，表３，表４、表５）

血清クレアチニンと尿蛋白を測定した住民 560,758 人のうち eGFR < 60 ml/min/1.73m^2 の CKD は 81,572 人であった。そのうち尿蛋白陰性者は 72,956 人(89.4%)であった。すなわち、血清クレアチニンを測定しなければ、eGFR < 60 ml/min/1.73m^2 の住民の 89.4%が CKD と認識されないという結果であった。また、尿蛋白陰性群での CKD の頻度は 13.7% であった。

表２．eGFR(1: eGR < 60 ml/min/1.73m^2) と尿蛋白(0: 陰性)のクロス表

			UP01		
			0	1	合計
GFR01	0	度数	458697	20489	479186
		GFR01 の %	95.7%	4.3%	100.0%
		UP01 の %	86.3%	70.4%	85.5%
	1	度数	72956	8616	81572
		GFR01 の %	89.4%	10.6%	100.0%
		UP01 の %	13.7%	29.6%	14.5%
合計		度数	531653	29105	560758
		GFR01 の %	94.8%	5.2%	100.0%
		UP01 の %	100.0%	100.0%	100.0%

eGFR < 60 ml/min/1.73m^2 and/or 尿蛋白 1+ 以上で定義された CKD 102,061 人の住民のうち、尿蛋白を有するのはわずか 28.5 % であった。すなわち、尿蛋白のみの測定では CKD の 71.5 % を見逃す可能性があることが示された。eGFR によるステージ別の見逃し率は、G3a 91.8%, G3b 76.9%, G4 41.6%, G5 42.6% で、特に G3 で見逃し率が高いことが分かった（CKD の定義から G1 と G2 における CKD では尿蛋白は 100% 陽性である）。

表３．CKD（1: eGR < 60 ml/min/1.73m^2 and/or 尿蛋白 1+以上）と尿蛋白(0:陰性)のクロス表

			UP01		
			0	1	合計
GFRgrade	G1	度数	0	4355	4355
		%	.0%	100.0%	100.0%
	G2	度数	0	16134	16134
		%	.0%	100.0%	100.0%
	G3a	度数	66276	5917	72193
		%	91.8%	8.2%	100.0%
	G3b	度数	6041	1812	7853
		%	76.9%	23.1%	100.0%
	G4	度数	450	632	1082
		%	41.6%	58.4%	100.0%
	G5	度数	189	255	444
		%	42.6%	57.4%	100.0%
合計		度数	72956	29105	102061
		%	71.5%	28.5%	100.0%

年齢別にみると、年齢が上がるにつれて、CKDが増加するとともに、尿蛋白陰性のCKDの割合も増加することも示された。すなわち、CKDのうち、尿蛋白陰性の割合は40歳台では54.1％、50歳台では65.5%、60歳台では73.4％、70歳以上では74.2%であった。

表４．全体での年代別CKDの割合

			CKD01		
			0	1	合計
年齢10歳刻み	40歳未満	度数	11145	2114	13259
		%	84.1%	15.9%	100.0%
	40歳代	度数	53395	6608	60003
		%	89.0%	11.0%	100.0%
	50歳代	度数	85605	13922	99527
		%	86.0%	14.0%	100.0%
	60歳代	度数	198978	45513	244491
		%	81.4%	18.6%	100.0%
	70歳以上	度数	109578	36786	146364
		%	74.9%	25.1%	100.0%
合計		度数	458701	104943	563644
		%	81.4%	18.6%	100.0%

表５．CKD群での年代別尿蛋白の有無

			UP01		
			0	1	合計
年齢10歳刻み	40歳未満	度数	1110	549	1659
		%	66.9%	33.1%	100.0%
	40歳代	度数	3089	2624	5713
		%	54.1%	45.9%	100.0%
	50歳代	度数	8423	4438	12861
		%	65.5%	34.5%	100.0%
	60歳代	度数	33118	12032	45150
		%	73.4%	26.6%	100.0%
	70歳以上	度数	27216	9462	36678
		%	74.2%	25.8%	100.0%
合計		度数	72956	29105	102061
		%	71.5%	28.5%	100.0%

４．リスク因子の有無による解析

（１）高血圧

高血圧の有無とCKDの有無が同時に判断出来た住民492,118人のうち、高血圧患者は229,751人、46.7％であった。高血圧患者でのCKDは55,086人、24％と、この住民群におけるCKD 95,063人、19.3％に比して高頻度であった。CKDのうち尿蛋白陰性はこの住民群では71.5％であったが、高血圧患者では66.8％であった。尿蛋白の陽性率はこの住民全体では5.2％であったが、高血圧を有する住民では7.8％と高かった。

（２）糖尿病

糖尿病の有無とCKDの有無が同時に判断出来た住民319,661人のうち糖尿病患者は54,790人、17.1%であった。糖尿病患者でのCKDは14,377人、26.2％、この住民におけるCKD 61,116人、19.1％に比して高頻度であった。CKDのうち尿蛋白陰性はこの住民では71.5％、糖尿病患者では49.9％であった。尿蛋白の陽性率は全住民では5.2％であったが、糖尿病を有する住民では13.0％と高かった。

（３）脂質異常症

脂質異常症の有無とCKDの有無が同時に判断出来た住民513,556人のうち脂質異常症患者294,266人、57.3％であった。脂質異常症でのCKDは58,953人、20.0％で、この住民でのCKD 93,083人、18.1％に比して高頻度であった。この住民群におけるCKDのうち71.5％は尿蛋白陰性であったが、脂質異常症患者では70.2％であった。CKDのうち尿蛋白陰性はこの住民では71.5％、脂質異常症では70.2％であった。尿蛋白の陽性率は全住民では5.2％であったが、脂質異常症を有する住民では6.0％とやや高かった。

（４）肥満

BMIが増えるとCKDの頻度が上昇することが示された（表５）。

表５．BMI と CKD のクロス表

		CKD01		
		0	1	合計
18.5未満　やせ	度数	27238	4573	31811
	%	85.6%	14.4%	100.0%
18.5～25.0 普通	度数	312684	65581	378265
	%	82.7%	17.3%	100.0%
25.0～35.0 軽度肥満	度数	102971	29543	132514
	%	77.7%	22.3%	100.0%
35.0～40.0 中等度肥満	度数	12622	4151	16773
	%	75.3%	24.7%	100.0%
35.0～40.0 高度肥満	度数	1437	513	1950
	%	73.7%	26.3%	100.0%
40.0以上　超肥満	度数	258	113	371
	%	69.5%	30.5%	100.0%
合計	度数	457210	104474	561684
	%	81.4%	18.6%	100.0%

また、今回の横断データの解析では、高齢になるにしたがい尿蛋白陰性の CKD が増加していることも示された。いわゆる腎硬化症の頻度が増加していることを反映している可能性がある。腎硬化症は末期腎不全で透析導入になる原因疾患として増加しつつあることを考えると、高齢化社会を迎えて重要な知見と思われる。また、高血圧、糖尿病、脂質異常症、肥満では CKD の頻度が高くなることも示された。

D. 考察

今回の約 58 万人の特定健診データからは、血清クレアチニンを測定しない場合の CKD の見逃しが、CKD 全体の 71.5％にもなることが示されたことは意義が大きい。特に、eGFR ＜ 60 ml/min/1.73m^2 の CKD に限ると実に 89.4%が見逃されることになる。

特定健診は CKD のスクリーニングとして計画されているわけではないが、CKD を早期に発見して対策をたてることのできる絶好のチャンスである。CKD は末期腎不全のみならず心血管疾患の高危険群であるから、特定健診を活かして CKD 対策を立てることは国民の健康を維持するためには喫緊の課題である。そのためには尿蛋白のみでは全く不十分であり、血清クレアチニンを測定することが必須であることが示された。

E. 結論

特定健診では血清クレアチニンを測定しなければ、CKD の 70～90％を見逃す可能性が示された。特定健診で血清クレアチニンの測定を必須化することが必要である。

G. 研究発表

１．論文発表　　なし。

２．学会発表　　なし。

H. 知的財産権の出願・登録状況

１．特許取得　　なし。

２．実用新案登録　なし。

３．その他　　なし。

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分担研究報告書

「特定健康診査による慢性腎臓病早期発見早期治療の財源影響に関する研究」

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研究要旨

特定健康診査による個人リスク評価に基づく、保健指導と連結した効果的な慢性腎臓病（CKD）地域連携システムの制度設計の、医療経済面の基礎研究として、特定健康診査による腎機能検査項目に着目して CKD 早期発見早期治療の財源影響に関する研究を行った。現行の尿蛋白のみを必須項目としている政策では医療費の削減が生じていることが明らかになった。

A. 研究目的

特定健康診査による個人リスク評価に基づく、保健指導と連結した効果的な慢性腎臓病（CKD）地域連携システムの制度設計の医療経済面の基礎研究として、特定健康診査による CKD 早期発見早期治療の医療財源への影響を明らかにすることを目的とした。特に、健康診査項目としての尿蛋白と血清クレアチニンの影響を明らかにすることを目的とした。本研究の結果は、腎臓病対策の観点からの特定健康診査における腎機能検査項目を検討するに際に有用な経済エビデンスのひとつとなる。

B. 研究方法

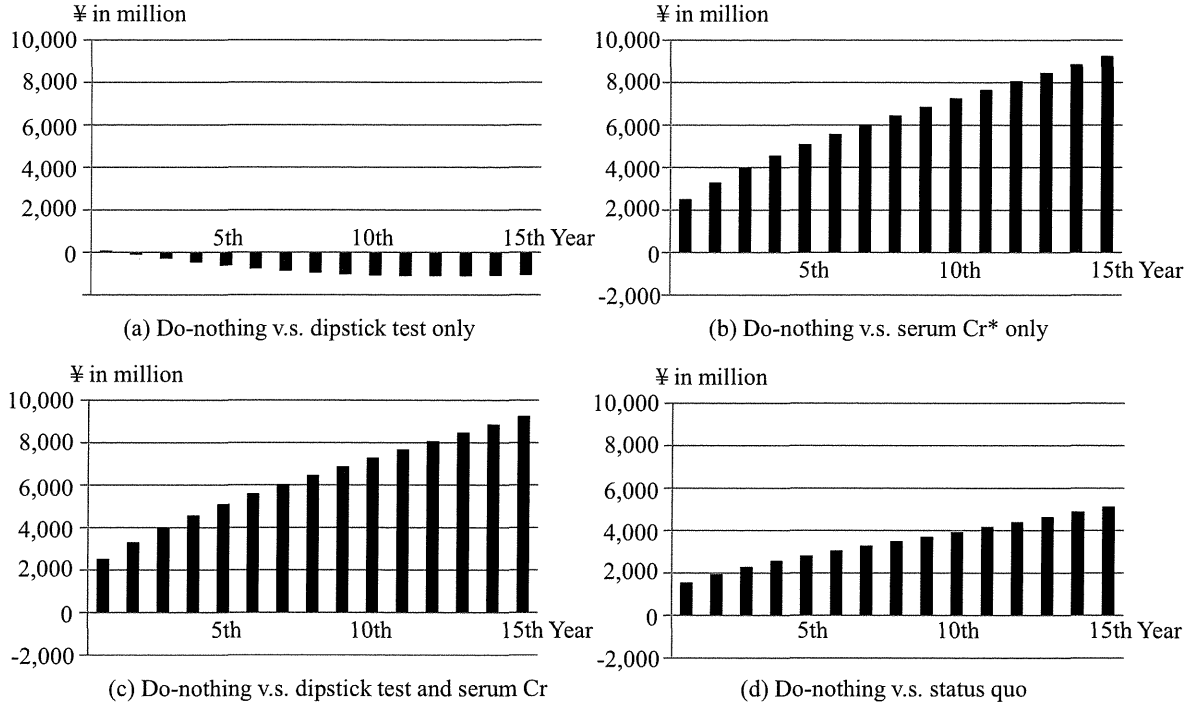
特定健康診査の腎機能検査項目に関する費用効果分析として発表している経済モデル（Kondo, Yamagata, et al. Clin Exp Nephrol. 2012;16(2):279-91.）を用いて、この経済モデルが 15 年間有効であると仮定して、国立社会保障・人口問題研究所の全国将来推計人口を当てはめて、財源影響分析を行った。分析対象とした財源の範囲は保険者が負担する特定健康診査での腎機能検査費と、慢性腎臓病とその続発症としての慢性腎不全及び心血管疾患にかかる診療報酬である。なお、使用した経済モデルによる費用効果分析の結果としては、尿蛋白のみが必須項目とされているものの約 60%の保険者が血清クレアチニンも健診項目に含めている現状から血清クレアチンも必須項目化する場合や、尿蛋白のみを必須項目とする現状維持の場合の、いずれも費用対効果に優れる政策であることが明らかにされている。

（倫理面への配慮）

経済モデル研究のため倫理面の問題はない。

C. 研究結果

Figure 1 が特定健康診査で腎機能検査を行わない（Do-nothing）場合と（a）尿蛋白のみを行う場合、(b) 血清クレアチニンのみを行う場合、(c) 尿蛋白と血清クレアチニンの両方を行う場合、(d) 現状である尿蛋白を全対象者で行い血清クレアチニンを 60%の対象者で行う場合、を比較した財源影響分析の結果である。(a) では、2 年目から財源影響が負となっており、いわゆる医療費の削減が生じることが明らかになった。9 年目以降では年間 10 億円程度の削減が生じる。しかし、(b)、(c)、(d) では財源影響は正となっており、10 年目にはそれぞれ、72 億円、72 億円、39 億円の医療費の増大が生じる。

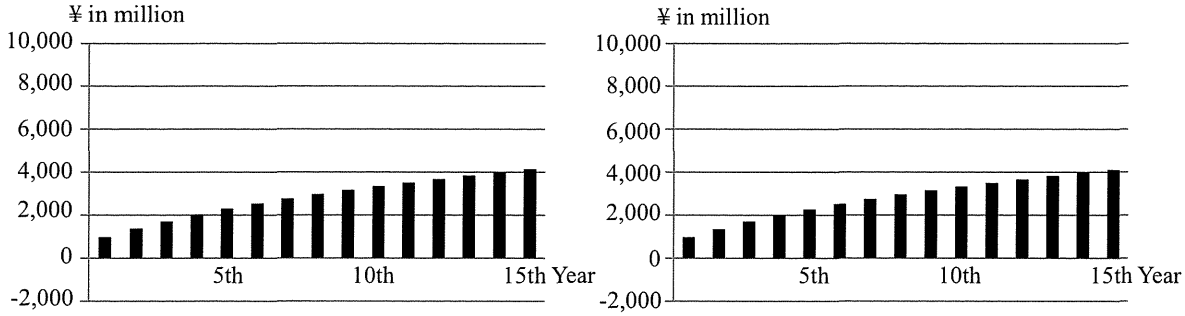


* Cr stands for creatinine

Figure 1 Budget impact model estimators

Figure 2 が特定健康診査で尿蛋白を全対象者で行い血清クレアチニンを 60%の対象者で行う現状の場合と、(a) 加えて血清クレアチニンを必須項目化する場合、(b) 血清クレアチニンのみ必須項目化して尿蛋白を必須項目から除外し全保険者が尿蛋白を行わない場合、を比較した財源影響分析の結果である。(b) で全保険者が尿蛋白を行わないことを仮定したのは特定健康診査での糖尿病検査で尿糖が必須項目から除外され採血による HbA1c のみが必須項目化される場合を考えてのことである。

(a) と (b) ともに財源影響は正となっており、10 年目にはそれぞれ、33 億円、33 億円の医療費の増大が生じる。



(a) Policy 1: requiring serum Cr assay

(b) Policy 2: requiring serum Cr assay and abandoning dipstick test

* Cr stands for creatinine

Figure 2 Budget impacts

D. 考察

本研究の結果としてもっとも着目すべきことは、特定腎機能検査を行わない場合と尿蛋白のみを行う場合の比較において、医療費の削減が生じていることが明らかにされたことである。この比較は、現行の尿蛋白のみを必須項目としている政策を反映しているものと捉えることができる。この意味では、現行の政策は医療費適正化へ貢献していると示唆される。

一方で、血清クレアチニンの必須項目化にともなっては、医療費の増大が見込まれた。ただし、この結果に基づいて直ちに特定健康診査で血清クレアチニンを行うべきではないとは言えないことに注意しなければならない。既述のように特定健康診査で血清クレアチニンを行うことついては費用効果分析によって「支払いに見合う価値」があることが示されている。また、本研究班が取り組んでいる保健指導と連結した効果的な慢性腎臓病（CKD）対策のような効果の大きな早期治療法の開発が進めば、血清クレアチニンについても尿蛋白のように財源影響が負に転じていく可能性は小さくない。さらに現在検討が進められている「かかりつけ医/非腎臓専門医と腎臓専門医の協力を促進する慢性腎臓病患者の重症化予防のための診療システムの有用性を検討する研究」（FROM-J）や腎専門医での大規模な慢性腎臓病の疫学研究である日本CKDコホート研究（CKD-JAC）の結果が明らかとなることにより、CKDの長期的予後改善可能な治療法が確立されれば、健診項目の財源影響にとどまらず、特定健診全体に対する医療経済的に良好な効果が期待される。

本研究の最大の限界は、経済モデルに依存していることである。しかし、健康診断による早期発見早期治療の財源影響を検討するにあたってフィールドで前向き研究を行うことは著しく困難であるうえに、数（十）年後に結果が得られたとしても、時機を得た政策決定に資することは不可能である。こうした観点から経済モデルに依存したアプローチは正当化できるだろう。

E. 結論

特定健康診査による腎機能検査項目に着目して CKD 早期発見早期治療の財源影響に関する研究を行ったところ、現行の尿蛋白のみを必須項目としている政策では医療費の削減が生じ

ていることが明らかになった。

本研究は3年計画の1年目であるので次年度以降の研究計画にふれておく。2年目では、保健指導と連結した効果的な慢性腎臓病（CKD）対策の医療経済面を研究する。この研究に関しては、平成24年3月に終了した厚生労働科学研究費補助金（腎疾患対策研究事業）「かかりつけ医/非腎臓専門医と腎臓専門医の協力を促進する慢性腎臓病患者の重症化予防のための診療システムの有用性を検討する研究」（FROM-J）から報告される臨床エビデンスなどを利用する予定である。3年目では、本研究班の先行研究である平成 20-22 年度厚生労働科学省科学研究費補助金（循環器疾患等生活習慣病総合研究事業）「今後の特定健康診査・保健指導における慢性腎臓病（CKD）の位置付けに関する検討」で構築した全国の約 58 万人のコホート群の追跡データから報告される臨床エビデンスなどを利用して、地域連携システムの制度設計の医療経済面の研究を行う予定である。

G. 研究発表

1．論文発表

Kondo M, Yamagata K, Hoshi SL, Saito C, Asahi K, Moriyama T, Tsuruya K, Yoshida H, Iseki K, Watanabe T. Cost-effectiveness of chronic kidney disease mass screening test in Japan. ***Clin Exp Nephrol.*** 2012;16(2):279-91.

2．学会発表　　なし。

H. 知的財産権の出願・登録状況

1．特許取得　　なし。

2．実用新案登録　なし。

3．その他　　なし。

研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Yano Y, Sato Y, Fujimoto S, Konta T, Iseki K, Moriyama T, Yamagata K, Tsuruya K, Yoshida H, Asahi K, Kurahashi I, Ohashi Y, Watanabe T	Association of high pulse pressure with proteinuria in subjects with diabetes, prediabetes, or normal glucose tolerance in a large Japanese general population sample.	Diabetes Care	35	1310-1315	2012
Sato Y, Yano Y, Fujimoto S, Konta T, Iseki K, Moriyama T, Yamagata K, Tsuruya K, Yoshida H, Asahi K, Kurahashi I, Ohashi Y, Watanabe T	Glycohemoglobin not as predictive as fasting glucose as a measure of prediabetes in predicting proteinuria.	Nephrol Dial Transplant	27	862-868	2012
Yano Y, Fujimoto S, Asahi K, Watanabe T	Prevalence of chronic kidney disease in China.	Lancet	380	213-214	2012
Konta T, Fujimoto S, Iseki K, Moriyama T, Yamagata K, Tsuruya K, Yoshida H, Asahi K, Kurahashi I, Ohashi Y, Watanabe T	Blood pressure control in a Japanese population with chronic kidney disease: A baseline survey of a nationwide cohort	Am J Hypertens	25	342-347	2012
Yano Y, Fujimoto S, Sato Y, Konta T, Iseki K, Moriyama T, Yamagata K, Tsuruya K, Yoshida H, Asahi K, Kurahashi I, Ohashi Y, Watanabe T	Association between prehypertension and chronic kidney disease in the Japanese general population.	Kidney Int	81	293-299	2012
Kondo M, Yamagata K, Hoshi X, Saito C, Asahi K, Moriyama T, Tsuruya K, Yoshida H, Iseki K, Watanabe T	Cost-effectiveness of chronic kidney disease mass screening test in Japan	Clin Exp Nephrol	16	279-291	2012
Wakasugi M, Narita I, Iseki K, Moriyama T, Yamagata K, Tsuruya K, Yoshida H, Fujimoto S, Asahi K, Kurahashi I, OhashiY, Watanabe T	Weight gain after 20 years of age is associated with prevalence of chronic kidney disease	Clin Exp Nephrol	16	259-268	2012
Iseki K, Asahi K, Moriyama T, Yamagata K, Tsuruya K, Yoshida H, Fujimoto S, Konta T, Kurahashi I, Ohashi Y, Watanabe T	Risk factor profiles based on estimated glomerular filtration rate and dipstick proteinuria among participants of the Specific Health Check and Guidance	Clin Exp Nephrol	16	244-249	2012
旭　浩一、井関邦敏、鶴屋和彦、山縣邦弘、守山敏樹、藤元昭一、吉田英昭、渡辺　毅	慢性腎臓病（CKD）におけるメタボリックシンドローム(MetS)・脂質異常症の実態と意義ー特定健診受診者コホートにおける横断的解析ー	Therapeutic Research	33	16-19	2012

Association of High Pulse Pressure With Proteinuria in Subjects With Diabetes, Prediabetes, or Normal Glucose Tolerance in a Large Japanese General Population Sample

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OBJECTIVE—To examine whether there is a difference in the association between high pulse pressure and proteinuria, independent of other blood pressure (BP) indices, such as systolic or diastolic BP, among subjects with diabetes, prediabetes, or normal glucose tolerance.

RESEARCH DESIGN AND METHODS—Using a nationwide health checkup database of 228,778 Japanese aged ≥20 years (mean 63.2 years; 39.3% men; none had pre-existing cardiovascular disease), we examined the association between high pulse pressure, defined as the highest quintile of pulse pressure (≥63 mmHg, n = 40,511), and proteinuria (≥1+ on dipstick, n = 12,090) separately in subjects with diabetes (n = 27,913), prediabetes (n = 100,214), and normal glucose tolerance (n = 100,651).

RESULTS—The prevalence of proteinuria was different among subjects with diabetes, prediabetes, and normal glucose tolerance (11.3 vs. 5.0 vs. 3.9%, respectively; $P < 0.001$). In subjects with diabetes, but not those with prediabetes or normal glucose tolerance, high pulse pressure was associated with proteinuria independently of significant covariates, including systolic BP (odds ratio 1.15 [95% CI 1.04–1.28]) or diastolic or mean BP (all $P < 0.01$). In patients with diabetes, a +1 SD increase of pulse pressure (+13 mmHg) was associated with proteinuria, even after adjustment for systolic BP (1.07 [1.00–1.13]) or diastolic or mean BP (all $P < 0.05$).

CONCLUSIONS—Among the Japanese general population, there was a significant difference in the association between high pulse pressure and proteinuria among subjects with diabetes, prediabetes, and normal glucose tolerance. Only in diabetes was high pulse pressure associated with proteinuria independent of systolic, diastolic, or mean BP levels.

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In the systemic circulation, the kidney has unique features: vascular resistance in the glomerular afferent arterioles is low, and the myogenic response of the glomerular arterioles is insensitive to changes in the other BP indices of systolic blood pressure (BP), including pulse pressure (1–3). These characteristics suggest that pressure pulsatility may contribute to barotrauma-induced renal microvascular injury, and in turn causes glomerular ultrastructural changes (e.g., podocyte loss and glomerular basement membrane thickness) (1–6).

In fact, several cross-sectional studies performed in general or hypertensive populations have demonstrated a significant association between pulse pressure and albuminuria (7,8), and some longitudinal studies have underscored the importance of pulse pressure as a risk factor for increased albuminuria in general or hypertensive populations (9,10); however, few studies have directly examined the impact of high pulse pressure on albuminuria with adjustment for other BP components, such as systolic BP, diastolic BP, and/or mean BP levels. Since renal autoregulation is particularly impaired in patients with diabetes (1–3,11–13), we hypothesized that the association between high pulse pressure and albuminuria would be more prominent in patients with diabetes than in subjects without diabetes (14–16); as of yet, however, there have been no studies examining this hypothesis directly in a large database. Furthermore, the association of pulse pressure with albuminuria has never been explored in prediabetics, who are classified as being at an intermediate stage between normal glucose tolerance and diabetes (17), but prediabetics have been shown to have a significantly increased risk of developing not only diabetes but also cardiovascular disease (18).

In the current study, therefore, we examined the association of high pulse pressure with proteinuria separately in each of subjects with diabetes, prediabetes, and normal glucose tolerance, using a large nationwide

database of subjects recruited from the national health checkup system in Japan.

RESEARCH DESIGN AND METHODS

Study population

This study was performed as a part of the prospective ongoing "Research on the Positioning of Chronic Kidney Disease in Specific Health Check and Guidance in Japan" project. A new annual health check program, "The Specific Health Check and Guidance in Japan", was started by the Japanese government in 2008, targeting early diagnosis and intervention for metabolic syndrome. The target population comprises Japanese citizens between the ages of 40 and 74 years. In Japan, there are 47 administrative divisions (prefectures), and 13 of these prefectures (Yamagata, Miyagi, Fukushima, and Niigata from the Tohoku region in northeastern Japan; Tokyo, Kanagawa, and Ibaraki from the Kanto region in central Japan; Osaka, Okayama, and Kochi from the Kansai, Tyugoku, or Shikoku region in western Japan; and Fukuoka, Miyazaki, and Okinawa from the Kyushu region in southern Japan), which were randomly distributed across Japan, agreed with the aims of this study and performed data collection prospectively from 2008 to 2009. Data were sent to an independent data center, the nonprofit organization Japan Clinical Research Support Unit after anonymization in a linkable fashion, and verified by trained staff (K.I. and Y.O.). After that, the database was locked with a security password, which contained the participant's information managed by a research ID number but did not contain the participant's name, and was sent to each investigator on a recordable compact disc.

There were a total of 346,942 subjects (mean age, 63.4 years; 41% [n = 141,938] men) for whom information on age, sex, BP, BMI, habitual smoking or drinking, use of antihypertensive drugs, and previous history of cardiovascular diseases (i.e., stroke and cardiac diseases such as angina and myocardial infarction) were available, as well as data on the serum creatinine level and dipstick urine test for proteinuria (19). Some of the regions participating in our project (i.e., Okinawa and Osaka) concomitantly performed regular health checkups for employees as legally mandated in Japan; as a result, the database used in the present analysis also included subjects aged 20–39 years (n = 2,025). Among the 346,942 subjects, 29,820 subjects with a previous history of cardiovascular disease, 243 subjects with chronic kidney disease stage 5 (estimated glomerular filtration rate [eGFR] <15 mL/min/1.73m^2), and 47 subjects with both were excluded from the present analysis. Moreover, 88,101 subjects with insufficient blood sampling data of glucose and lipid parameters were excluded. Supplementary Table 1 shows the differences in clinical characteristics between subjects who were included in the present analysis (n = 228,778) and those who had missing data (n = 88,101).

The study was conducted according to the guidelines of the Declaration of Helsinki and Ethical Guidelines for Epidemiological Research (1 November 2007, Ministry of Education, Culture, Sports, Science, and Technology and Ministry of Health, Labor, and Welfare of Japan). Ethical approval from the respective institutional review boards was also granted.

Baseline measurement

All subjects completed a self-administered questionnaire to document their medical history, current medications, smoking habits (current smoker or not), and alcohol intake (daily drinker or not). The study physicians performed a physical examination of each subject and rechecked their medical history to improve the precision of the information. Body height and weight were measured in light clothing without shoes, and the BMI was calculated (kg/m^2). BP measurement and blood and urine sampling were performed at each local medical institution to cooperate with the nationwide medical checkup. According to the recommendations of the Japanese Ministry of Health, Labor, and Welfare (http://www.mhlw.go.jp/bunya/shakaihosho/iryouseido01/info03a.html), BP was measured by medical staff using a standard sphygmomanometer or an automated device on the right arm after the subject had rested for 5 min in a seated position with the legs not crossed. Conversation as well as alcohol/caffeine consumption was also avoided before measurement. Pulse pressure was calculated as systolic BP − diastolic BP, and mean BP was calculated as diastolic BP + (pulse pressure/3).

Blood samples were collected after an overnight fast and were assayed within 24 h with an automatic clinical chemical analyzer. All measurements were conducted locally rather than at a central laboratory without calibration among different laboratories, despite the fact that beginning several years ago, standardized methods to measure laboratory data were recommended and widely adopted by the activity of the Japan Society of Clinical Chemistry.

The value for hemoglobin A_{1c} (HbA_{1c}) was estimated as a National Glycohemoglobin Standardization Program equivalent value calculated with the following equation (20): HbA_{1c} (%) = HbA_{1c} (Japan Diabetes Society) (%) + 0.4%.

Diabetes was defined in accordance with American Diabetes Association guidelines (17) as a fasting glucose concentration of 126 mg/dL or higher, HbA_{1c} 6.5% or higher, or self-reported use of antihyperglycemic drugs. Diagnosis of prediabetes was based on the new American Diabetes Association criterion of impaired fasting glucose (fasting plasma glucose 100–125 mg/dL) or HbA_{1c} 5·7–6·4%, or both (17).

Urinalysis by the dipstick method was performed on a single spot urine specimen collected in the early morning after overnight fasting. Urine dipstick results are interpreted by the medical staff in each local medical institution and recorded as −, ±, 1+, 2+, and 3+. In Japan, it is recommended and widely adopted by the activity of the Japanese Committee for Clinical Laboratory Standards (http://jccls.org/) that all urine dipstick tests be manufactured so that a urine dipstick result of 1+ will correspond to a urinary protein level of 30 mg/dL. In the current study, proteinuria was defined as 1+ or more. eGFR was derived using the following equation (21): eGFR (mL/min/1.73 m^2) = 194 × age (years)$^{-0.287}$ × serum creatinine (mg/dL)$^{-1.094}$ (if women ×0.739).

Statistical analysis

All statistical analyses were performed with SPSS version 18.0 J software (SPSS, Chicago, IL). Data were expressed as the means ± SD (age, BMI, eGFR, and BP values) or median and interquartile range (glucose and lipid parameters). Clinical parameters and BP or metabolic values according to the presence of diabetes or prediabetes were compared using ANOVA, and categorical parameters were compared with the χ^2 test. We subdivided the study population according to the quintiles of pulse pressure, and the prevalence of proteinuria (≥1+) was compared by χ^2 test among each group of the quintiles of pulse pressure separately in subjects with diabetes, prediabetes, or normal glucose tolerance, respectively. The highest quintile of pulse pressure (≥63 mmHg, n = 40,511) was defined as the high pulse pressure group in the present analysis.

Next, we used a multivariable logistic regression analysis to examine the independent

association of high pulse pressure with proteinuria (≥1+) separately in subjects with diabetes, prediabetes, or normal glucose tolerance, respectively. In the initial model (Model 1), these associations were assessed with adjustment for age, sex, BMI, current smoking and daily drinking, the presence of antihypertensive medications, and eGFR. Extended models were used to assess whether the association of high pulse pressure with proteinuria (≥1+) was attenuated by the potential confounding effects of glucose and lipid parameters (Model 2) and systolic BP (Model 3). In addition, to minimize the influence of systolic BP in the association between pulse pressure and proteinuria, we examined the association only in patients with diabetes whose systolic BP was within the normal BP range (i.e., <130 mmHg) (22). Finally, we examined the association of a +1 SD increase of pulse pressure (+13 mmHg), rather than pulse pressure as a dichotomous variable, with proteinuria in patients with diabetes by a multivariable logistic regression analysis. Statistical significance was defined as $P < 0.05$.

RESULTS

Clinical characteristics of the study population

The mean age ± SD of the 228,778 subjects was 63.2 ± 8.9 years, and 89,877 of the subjects (39.3%) were men. There were 27,913 subjects (12.2% of the total subject population) with diabetes, of whom 10,980 subjects (39.1%) were taking antihyperglycemic medications. There were 100,214 subjects (43.8%) with prediabetes. The clinical characteristics according to the presence of diabetes or prediabetes are shown in Table 1. Compared with subjects with normal glucose tolerance (as a reference), the odds ratio (OR) for the increased risk of proteinuria (≥ 1+) in diabetes itself was 2.14 (95% CI 2.03–2.25), and that in prediabetes was 1.10 (1.05–1.14), even after adjustment for significant covariates, such as age, sex, BMI, current smoking and daily drinking, the presence of antihypertensive medications, and systolic BP level (both $P < 0.001$).

Pulse pressure and proteinuria

Clinical characteristics and metabolic or BP parameters according to the quintile of pulse pressure are shown in Supplementary Table 2. The increasing prevalence of proteinuria (≥1+) in accordance with the increasing pulse pressure was more prominent in subjects with diabetes than those without diabetes (Fig. 1). Supplementary Table 3 shows the prevalence of proteinuria subdivided by the dipstick positive scale according to the quintile of pulse pressure with or without diabetes.

Next, a multivariable logistic regression analysis was performed to examine the independent association between the highest quintile of pulse pressure and proteinuria, separately in subjects with diabetes, prediabetes, and normal glucose tolerance. In patients with diabetes, the highest quintile of pulse pressure (≥63 mmHg) was positively associated with proteinuria, independently of significant covariates, including systolic BP (Models 1–3 in Table 2). When we examined the association between pulse pressure and proteinuria only in patients with diabetes whose systolic BP was within the normal range (i.e., <130 mmHg, n = 11,074 [39.7%]), the highest quintile of pulse pressure still remained significantly associated with proteinuria (OR 1.46 [95% CI 1.03–2.08]; $P = 0.04$, respectively), even after adjustment for significant covariates, as shown in Model 2 in Table 2. When diastolic BP or mean BP was entered into Model 3 in Table 3 in place of systolic BP, the association between the highest quintile of pulse pressure and proteinuria still remained significant (1.61 [1.49–1.75] and 1.42 [1.31–1.55]; both $P < 0.001$, respectively). In contrast, the highest quintile of pulse pressure in subjects with prediabetes or normal glucose tolerance was not associated with proteinuria independently of systolic BP (Model 3 in Table 2). When

Table 1—*Characteristics of the study population according to the presence of diabetes or prediabetes*

	Diabetes (n = 27,913)	Prediabetes (n = 100,214)	Normal glucose tolerance (n = 100,651)	P value
Age (years)	65.2 ± 7.3	64.2 ± 7.9	61.6 ± 9.8	<0.001
Men, n (%)	14,626 (52.4)	40,077 (40.0)	35,174 (34.9)	<0.001
BMI (kg/m^2)	24.1 ± 3.7	23.3 ± 3.3	22.5 ± 3.1	<0.001
Current smoker, n (%)	4,846 (17.4)	12,960 (12.9)	13,971 (13.9)	<0.001
Daily drinker, n (%)	7,162 (25.7)	22,825 (22.8)	21,521 (21.4)	<0.001
eGFR (mL/min/1.73 m^2)	76.2 ± 17.8	74.7 ± 15.6	76.1 ± 15.9	<0.001
Proteinuria (≥1+), n (%)	3,164 (11.3)	5,013 (5.0)	3,913 (3.9)	<0.001
Glucose and lipid parameters				
Fasting glucose (mg/dL)*	125.0 (100.0–143.0)	98.0 (90.0–105.0)	89.0 (84.0–93.0)	<0.001
HbA_{1c} (%)*	6.2 (5.6–6.9)	5.4 (5.3–5.6)	5.0 (4.8–5.1)	<0.001
Triglycerides (mg/dL)*	112.0 (79.0–162.0)	101.0 (74.0–142.0)	91.0 (67.0–127.0)	<0.001
LDL (mg/dL)*	123.0 (104.0–145.0)	127.0 (108.0–148.0)	124.0 (105.0–144.0)	<0.001
HDL (mg/dL)*	57.0 (48.0–68.0)	60.0 (51.0–72.0)	63.0 (53.0–75.0)	<0.001
Antihypertensive drugs, n (%)	11,101 (39.8)	29,157 (29.1)	21,410 (21.3)	<0.001
Antihyperlipidemic drugs, n (%)	6,823 (24.4)	17,440 (17.4)	12,233 (12.2)	<0.001
Antihyperglycemic drugs, n (%)	10,980 (39.1)	0 (0)	0 (0)	<0.001
BP parameters				
Systolic BP (mmHg)	133.4 ± 17.5	129.7 ± 17.0	125.7 ± 17.2	<0.001
Diastolic BP (mmHg)	77.1 ± 10.8	76.8 ± 10.5	75.1 ± 10.7	<0.001
Pulse pressure (mmHg)	56.2 ± 13.4	52.9 ± 12.4	50.6 ± 12.2	<0.001

Data are expressed as the means ± SD or percentage. P values were obtained by ANOVA or χ^2 test. *Variables with skewed distribution are expressed as median (interquartile range).

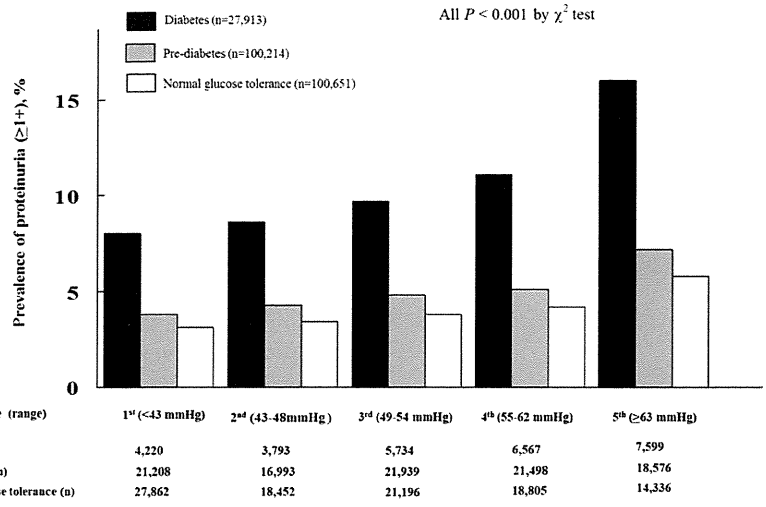

Figure 1—*Prevalence of proteinuria according to the quintile of pulse pressure in subjects with diabetes, prediabetes, or normal glucose tolerance. The prevalence of proteinuria (≥1+) was calculated among each group of the quintiles of pulse pressure separately in subjects with diabetes, prediabetes, or normal glucose tolerance, respectively. The* P *value was obtained by a* χ^2 *test among each group of the quintiles of pulse pressure.*

we examined the risk of the highest quintile of pulse pressure on proteinuria among subjects without antihypertensive medications (n = 167,110), the conclusion remained unchanged (Model 4 in Table 2). Use of antihyperglycemic or antihyperlipidemic drugs did not influence any of the above results (data not shown). In contrast, systolic BP, used as an adjusted factor in Model 3 in Table 2, showed significant associations with proteinuria in subjects with diabetes, prediabetes, and normal glucose tolerance (data not shown).

Finally, we analyzed the association of a +1 SD increase of pulse pressure (+13 mmHg), rather than pulse pressure as a dichotomous variable, with proteinuria in patients with diabetes. We found that a +1 SD increase of pulse pressure was associated with proteinuria independently of significant covariates, including systolic BP (Table 3), diastolic BP, or mean BP (data not shown).

CONCLUSIONS—In this nationwide study of 228,778 Japanese people (mean age 63.2 years) who had no known cardiovascular disease, we demonstrated for the first time that there was a significant difference in the association between the highest quintile of pulse pressure (≥63 mmHg) and proteinuria (≥1+ on dipstick) among subjects with diabetes, prediabetes, and normal glucose tolerance. The cross-sectional design of the current study did not allow us to elucidate the pathophysiological pathway linking high pulse pressure and proteinuria (≥1+). However, there are some possible explanations for the observed association.

Pulse pressure, proteinuria, and patients with diabetes

Since the glomerular afferent arterioles provide relatively low resistance, the glomerulus is susceptible to barotrauma if the pulse pressure is elevated (1–6). In fact, prior studies have demonstrated an association of high pulse pressure with microalbuminuria even in subjects without diabetes (7,8). In the current study, we examined the possible association of high pulse pressure and proteinuria (≥1+), i.e., macroalbuminuria, and found that this association was not significant independently of systolic BP in subjects without diabetes. In contrast, systolic BP was significantly associated with proteinuria in these subjects. Although the usefulness of the urine dipstick test for risk stratification of renal and cardiovascular disease has been recognized, this method is a less sensitive measure of albuminuria compared with the measurement of urinary albumin excretion (23–26). Accordingly, we cannot deny the possibility of an association between high pulse pressure and microalbuminuria in subjects without diabetes.

Table 2—*OR for the highest quintile of pulse pressure in the association of proteinuria (≥1+) according to the presence of diabetes or prediabetes*

Model	Adjusted covariates	OR (95% CI)		
Overall (n = 228,778)		Diabetes (n = 27,913)	Prediabetes (n = 100,214)	Normal glucose tolerance (n = 100,651)
Model 1	Age + sex + BMI + current-smoking + daily drinking + antihypertensive medications + eGFR	1.72 (1.59–1.87)‡	1.45 (1.35–1.55)‡	1.48 (1.37–1.61)‡
Model 2	Model 1 + fasting glucose + triglycerides + HDL + LDL	1.63 (1.50–1.77)‡	1.41 (1.31–1.50)‡	1.48 (1.36–1.60)‡
Model 3	Model 2 + systolic BP	1.16 (1.05–1.29)†	0.97 (0.89–1.05)	1.08 (0.98–1.20)
Subjects without antihypertensive medications (n = 167,110)		Diabetes (n = 16,812)	Prediabetes (n = 71,057)	Normal glucose tolerance (n = 79,241)
Model 4	Age + sex +BMI + current smoking + daily drinking + eGFR + fasting glucose + triglycerides + HDL + LDL + systolic BP	1.21 (1.03–1.43)*	1.09 (0.97–1.23)	1.13 (0.98–1.29)

OR (95% CI) of proteinuria (≥1+) was calculated for highest quintile of pulse pressure (≥63 mmHg, n = 40,511) vs. lower quintiles of pulse pressure (<63 mmHg) in each model. Statistical significance was defined as $P < 0.05$. *$P < 0.05$. †$P < 0.01$. ‡$P < 0.001$.

Table 3—*OR (95% CI) for proteinuria in diabetes* (n = 27,913)

Model	OR (95% CI)	*P* value
Age (+9 years)*	0.94 (0.89–1.00)	0.04
Sex (0, men; 1, women)	0.55 (0.50–0.60)	<0.001
BMI (+3 kg/m^2)*	1.18 (1.14–1.22)	<0.001
Current smoking (0, no; 1, yes)	1.49 (1.35–1.65)	<0.001
Daily drinking (0, no; 1, yes)	0.90 (0.82–0.99)	0.04
Antihypertensive medications (0, no; 1, yes)	0.59 (0.54–0.64)	<0.001
eGFR (+16 mL/min/1.73 m^2)*	0.76 (0.73–0.79)	<0.001
Fasting glucose (+21 mg/dL)*	1.20 (1.18–1.22)	<0.001
Triglycerides (+78 mg/dL)*	1.06 (1.03–1.09)	<0.001
LDL (+30 mg/dL)*	1.07 (1.03–1.11)	<0.001
HDL (+16 mg/dL)*	1.02 (0.98–1.07)	0.39
Systolic BP (+17 mmHg)*	1.27 (1.20–1.36)	<0.001
Pulse pressure (+13 mmHg)*	1.08 (1.01–1.14)	0.02

Statistical significance was defined as $P < 0.05$. *The OR (95% CI) of proteinuria (≥1+) was calculated for a +1 SD increase of each indicated variable as well as dichromatic variables.

In spite of the strict collinearity between systolic BP and pulse pressure, the OR of high pulse pressure to proteinuria was reduced but remained significant even after adjustment for systolic BP in patients with diabetes (Table 2). Table 3 also shows that a +1 SD increase of systolic BP and a +1 SD increase of pulse pressure were associated with proteinuria independently of each other, with the OR of the systolic BP increase on proteinuria being higher than that of the pulse pressure increase. These findings indicate that high systolic BP showed a confirmed association with proteinuria and is an important confounder explaining the association between high pulse pressure and proteinuria; however, even after adjustment for systolic BP, the pulsatile component of BP itself was still significantly associated with proteinuria in patients with diabetes. Intriguingly, even in the patients with diabetes who were within the normal range of systolic BP values, high pulse pressure was associated with proteinuria. Some possible explanations for these findings exist. First, since renal autoregulation is impaired in diabetes (1–3,11–13), it may be possible that when pulse pressure is elevated, more barotrauma-induced glomerular ultrastructural changes leading to albuminuria occur in subjects with diabetes than in those without diabetes (1–5). Second, much as in the previous reports (27,28), higher pulse pressure was observed in diabetes than nondiabetes (Table 1), suggesting the possibility that diabetes accelerates aortic and large arterial stiffness (29). Aortic stiffness itself has a potential etiologic role in the causation and progression of renal dysfunction (30–32), because loss of the damping of ventricular ejection in the stiffened aortae could lead to an increase in the transmission of these pressure changes to the renal microcirculation. In the current study, however, we did not use any measure of vascular stiffness more direct than pulse pressure, such as pulse wave velocity, and thus the potential efficacy of such measures will need to be investigated in the future. Third, overt proteinuria in patients with diabetes, which is observed in long-standing diabetes, together with hypertension and increased arterial stiffness, is a surrogate marker not only for renal structural damages but also generalized vascular damages (3,6,24,25). Therefore, we speculate that patients with diabetes with proteinuria are likely to have systemic vasculopathy, and as a consequence, they have high pulse pressure. Lastly, since the current study is a cross-sectional analysis, we have to pay attention to another possibility that diabetic renal disease indicated by greater proteinuria raises systolic BP as well as pulse pressure rather than the reverse in patients with diabetes.

Pulse pressure, proteinuria, and prediabetes

The current study provided the first examination of the association of pulse pressure with proteinuria in prediabetes using a large sample size. Understanding such risk estimates is important, given the increases in the prevalence of prediabetes that have occurred in many populations in conjunction with the increasing prevalence of obesity, particularly in Asian populations (33,34). In the current study, the prevalence of prediabetes was substantially high (44%). Another Japanese study performed in healthy Japanese people (n = 6,636, mean age 50 years) demonstrated that the prevalence of prediabetes was 32% (35). This survey was performed between 1997 and 2003, and since the prevalence of diabetes in Asian populations has increased rapidly in recent years (33,34), the high prevalence of prediabetes in the current study was not entirely unexpected.

Several limitations of our study should be mentioned. First, single-measurement readings of BP, fasting glucose or HbA_{1c}, and proteinuria cannot be considered fully accurate. In particular, some of the dipstick-positive proteinuria could have been transient, and thus could not be taken as definitive evidence of the presence of persisting proteinuria. These factors may introduce a source of variability that could have led to a tendency to underestimate the true association between pulse pressure and proteinuria. Second, we could not separate diabetes into type 1 or type 2 diabetes. However, the incidence of type 1 diabetes is extremely low (approximately two cases/year/100,000 individuals), and Japan has one of the lowest incidence rates of type 1 diabetes in the world (36). Third, we could not assess the diabetes- and atherosclerosis-related information, such as the duration of diabetes and the presence of diabetes complications (e.g., neuropathy), which would be informative and extend the knowledge achieved in the current study. Lastly, we could not assess what kinds of antihypertensive drugs had been prescribed in treated hypertensive subjects. Some antihypertensive drugs (e.g., angiotensin receptor blockers or angiotensin enzyme–converting inhibitors) have more favorable effects on vascular and renal protection (37). Therefore, their use was potentially confounding, although our conclusions remained unchanged when we analyzed our data while excluding the subjects with antihypertensive medications.

In conclusion, among the Japanese general population, high pulse pressure, particularly in individuals with diabetes, was associated with proteinuria, and this information has the potential to supplement other BP indices. To confirm our findings, a prospective study as well as interventions that examine whether or not reduction of pulse pressure can enhance nephron-protective benefits in diabetes will be required.

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No potential conflicts of interest relevant to this article were reported.

Y.Y. and Y.S. analyzed the data. S.F. designed the study, collected data, and wrote the paper. T.K. and K.I. designed the study and collected data. T.M., K.Y., K.T., H.Y., K.A., I.K., Y.O., and T.W. designed the study, collected data, supervised the study, and revised the manuscript. S.F. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. Loutzenhiser R, Bidani A, Chilton L. Renal myogenic response: kinetic attributes and physiological role. Circ Res 2002;90:1316–1324
2. O'Rourke MF, Safar ME. Relationship between aortic stiffening and microvascular disease in brain and kidney: cause and logic of therapy. Hypertension 2005;46:200–204
3. Ito S, Nagasawa T, Abe M, Mori T. Strain vessel hypothesis: a viewpoint for linkage of albuminuria and cerebro-cardiovascular risk. Hypertens Res 2009;32:115–121
4. Hostetter TH, Rennke HG, Brenner BM. The case for intrarenal hypertension in the initiation and progression of diabetic and other glomerulopathies. Am J Med 1982; 72:375–380
5. Anderson S. Relevance of single nephron studies to human glomerular function. Kidney Int 1994;45:384–389
6. Satchell SC, Tooke JE. What is the mechanism of microalbuminuria in diabetes: a role for the glomerular endothelium? Diabetologia 2008;51:714–725
7. Pedrinelli R, Dell'Omo G, Penno G, et al. Microalbuminuria and pulse pressure in hypertensive and atherosclerotic men. Hypertension 2000;35:48–54
8. Cirillo M, Stellato D, Laurenzi M, Panarelli W, Zanchetti A, De Santo NG; The GUBBIO Study Collaborative Research Group. Pulse pressure and isolated systolic hypertension: association with microalbuminuria. Kidney Int 2000;58:1211–1218
9. Farasat SM, Valdes C, Shetty V, et al. Is longitudinal pulse pressure a better predictor of 24-hour urinary albumin excretion than other indices of blood pressure? Hypertension 2010;55:415–421
10. Tsakiris A, Doumas M, Lagatouras D, et al. Microalbuminuria is determined by systolic and pulse pressure over a 12-year period and related to peripheral artery disease in normotensive and hypertensive subjects: the Three Areas Study in Greece (TAS-GR). Angiology 2006;57:313–320
11. Parving HH, Kastrup H, Smidt UM, Andersen AR, Feldt-Rasmussen B, Christiansen JS. Impaired autoregulation of glomerular filtration rate in type 1 (insulin-dependent) diabetic patients with nephropathy. Diabetologia 1984;27:547–552
12. Christensen PK, Hansen HP, Parving HH. Impaired autoregulation of GFR in hypertensive non-insulin dependent diabetic patients. Kidney Int 1997;52:1369–1374
13. Carmines PK. The renal vascular response to diabetes. Curr Opin Nephrol Hypertens 2010;19:85–90
14. Knudsen ST, Poulsen PL, Hansen KW, Ebbehøj E, Bek T, Mogensen CE. Pulse pressure and diurnal blood pressure variation: association with micro- and macrovascular complications in type 2 diabetes. Am J Hypertens 2002;15:244–250
15. Palmas W, Moran A, Pickering T, et al. Ambulatory pulse pressure and progression of urinary albumin excretion in older patients with type 2 diabetes mellitus. Hypertension 2006;48:301–308
16. Knudsen ST, Laugesen E, Hansen KW, Bek T, Mogensen CE, Poulsen PL. Ambulatory pulse pressure, decreased nocturnal blood pressure reduction and progression of nephropathy in type 2 diabetic patients. Diabetologia 2009;52:698–704
17. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2010;33(Suppl. 1):S62–S69
18. DeFronzo RA, Abdul-Ghani M. Assessment and treatment of cardiovascular risk in prediabetes: impaired glucose tolerance and impaired fasting glucose. Am J Cardiol 2011;108(Suppl. 3):3B–24B
19. Yano Y, Fujimoto S, Sato Y, et al. Association between prehypertension and chronic kidney disease in the Japanese general population. Kidney Int 2012;81:293–299
20. The Committee of Japan Diabetes Society on the Diagnostic Criteria of Diabetes Mellitus. Report of the Committee on the classification and diagnostic criteria of diabetes mellitus. J Japan Diab Soc 2010; 53:450–467
21. Matsuo S, Imai E, Horio M, et al.; Collaborators developing the Japanese equation for estimated GFR. Revised equations for estimated GFR from serum creatinine in Japan. Am J Kidney Dis 2009;53:982–992
22. American Diabetes Association. Standards of medical care in diabetes—2010. Diabetes Care 2010;33(Suppl. 1):S11–S61
23. Iseki K, Ikemiya Y, Iseki C, Takishita S. Proteinuria and the risk of developing end-stage renal disease. Kidney Int 2003; 63:1468–1474
24. Levey AS, de Jong PE, Coresh J, et al. The definition, classification, and prognosis of chronic kidney disease: a KDIGO Controversies Conference report. Kidney Int 2011;80:17–28
25. de Zeeuw D, Raz I. Albuminuria: a great risk marker, but an underestimated target in diabetes. Diabetes Care 2008;31(Suppl. 2): S190–S193
26. de Jong PE, van der Velde M, Gansevoort RT, Zoccali C. Screening for chronic kidney disease: where does Europe go? Clin J Am Soc Nephrol 2008;3:616–623
27. Benetos A, Waeber B, Izzo J, et al. Influence of age, risk factors, and cardiovascular and renal disease on arterial stiffness: clinical applications. Am J Hypertens 2002;15: 1101–1108
28. Schram MT, Kostense PJ, Van Dijk RA, et al. Diabetes, pulse pressure and cardiovascular mortality: the Hoorn Study. J Hypertens 2002;20:1743–1751
29. Dart AM, Kingwell BA. Pulse pressure—a review of mechanisms and clinical relevance. J Am Coll Cardiol 2001;37:975–984
30. Ford ML, Tomlinson LA, Chapman TP, Rajkumar C, Holt SG. Aortic stiffness is independently associated with rate of renal function decline in chronic kidney disease stages 3 and 4. Hypertension 2010;55: 1110–1115
31. Briet M, Collin C, Karras A, et al.; Nephrotest Study Group. Arterial remodeling associates with CKD progression. J Am Soc Nephrol 2011;22:967–974
32. Bouchi R, Babazono T, Mugishima M, et al. Arterial stiffness is associated with incident albuminuria and decreased glomerular filtration rate in type 2 diabetic patients. Diabetes Care 2011;34:2570–2575
33. Chan JC, Malik V, Jia W, et al. Diabetes in Asia: epidemiology, risk factors, and pathophysiology. JAMA 2009;301:2129–2140
34. Hu FB. Globalization of diabetes: the role of diet, lifestyle, and genes. Diabetes Care 2011;34:1249–1257
35. Heianza Y, Hara S, Arase Y, et al. HbA1c 5·7-6·4% and impaired fasting plasma glucose for diagnosis of prediabetes and risk of progression to diabetes in Japan (TOPICS 3): a longitudinal cohort study. Lancet 2011;378:147–155
36. Neville SE, Boye KS, Montgomery WS, Iwamoto K, Okamura M, Hayes RP. Diabetes in Japan: a review of disease burden and approaches to treatment. Diabetes Metab Res Rev 2009;25:705–716
37. Paulis L, Unger T. Novel therapeutic targets for hypertension. Nat Rev Cardiol 2010;7:431–441

17. Takayama T, Nagata M, Ichiyama A, Ozono S. Primary hyperoxaluria type 1 in Japan. *Am J Nephrol* 2005; 25: 297–302
18. Cochat P, Liutkus A, Fargue S *et al.* Primary hyperoxaluria type 1: still challenging! *Pediatr Nephrol* 2006; 21: 1075–1081
19. Beck BB, Hoppe B. Is there a genotype–phenotype correlation in primary hyperoxaluria type 1? *Kidney Int* 2006; 70: 984–986
20. Fargue S, Harambat J, Gagnadoux MF *et al.* Effect of conservative treatment on the renal outcome of children with primary hyperoxaluria type 1. *Kidney Int* 2009; 76: 767–773
21. Monico CG, Rossetti S, Schwanz HA *et al.* Comprehensive mutation screening in 55 probands with type 1 primary hyperoxaluria shows feasibility of a gene-based diagnosis. *J Am Soc Nephrol* 2007; 18: 1905–1914
22. Rumsby G, Williams E, Coulter-Mackie M. Evaluation of mutation screening as a first line test for the diagnosis of the primary hyperoxalurias. *Kidney Int* 2004; 66: 959–963
23. Santana A, Salido E, Torres A, Shapiro LJ. Primary hyperoxaluria type 1 in the Canary Islands: a conformational disease due to I244T mutation in the P11L-containing alanine:glyoxylate aminotransferase. *Proc Natl Acad Sci USA* 2003; 100: 7277–7282
24. Cellini B, Montioli R, Paiardini A *et al.* Molecular defects of the glycine 41 variants of alanine glyoxylate aminotransferase associated with primary hyperoxaluria type I. *Proc Natl Acad Sci USA* 2010; 107: 2896–2901

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Glycohemoglobin not as predictive as fasting glucose as a measure of prediabetes in predicting proteinuria

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Abstract

Background. There is little data on the assessment of prediabetes with proteinuria.

Methods. This is a cross-sectional cohort study assessing prediabetes with proteinuria in a large Japanese population. Using a nationwide health checkup database of 228 778 Japanese aged ≥20 years (median 66 years; 39.3% were men; none had pre-existing cardiovascular disease), we examined the association between prediabetes and proteinuria (≥1+ on dipstick) separately in prediabetes subjects diagnosed with the new hemoglobin A1c (HbA1c) criterion only (PD-A1c), the impaired fasting plasma glucose only (PD-IFG) and fulfilling both criteria (PD-Both).

Results. According to the American Diabetes Association's (ADA's) criterion of 5.7–6.4% HbA1c and/or 100–125 mg/dL fasting plasma glucose, 43.8% of the subjects were judged as having prediabetes. Prediabetes subjects were divided into subclasses of PD-A1c (53.7%), PD-IFG (21.7%) and PD-Both (24.5%), respectively. Therefore, 21.7% of prediabetes subjects were missed using the new HbA1c criterion only. Compared with subjects with normal glucose tolerance (as a reference), the odds ratio (OR) [95% confidence interval (95% CI)] for the increased risk of proteinuria (≥1+) in diabetes itself was 2.191 (2.081–2.307) and in whole prediabetes was 1.093 (1.046–1.142); when prediabetes was subdivided, the OR for proteinuria in PD-IFG was 1.217 (1.140–1.300) and that in PD-Both was 1.249 (1.174–1.329), but that in PD-A1c was not significant, even after adjustment for significant covariates, such as age, sex, body mass index, systolic blood pressure, antihypertensive medication, eGFR, lifestyle and lipid profile.

Conclusions. Prediabetes is a significant risk factor for proteinuria compared with completely normal glucose level, and subjects with prediabetes defined using IFG are at significantly higher risk for proteinuria than those defined by HbA1c only.

Keywords: odds ratio; prediabetes; proteinuria