表1 入院医療費

(丹波市)

危険因子	性別		対象者	平均値	標準偏差	最小値	最大値	医療費増加比	医療費差額(円)	過剰医療費割合(%)	保健指導後の有病率(%)	改善後過剰医療費割合(%)
肥満	男性	なし	1625	79,566	258,774	0	3,048,863					
		あり	558	73,125	240,321	0	2,508,013	0.92	0	0.0	50	0.0
	女性	なし	2173	57,500	225,365	0	3,264,240					
		あり	637	77,158	231,221	0	2,345,095	1.34	19,658	7.2	50	3.6
高コレステロール血症を除いた脂質異常症	男性	なし	1518	74,862	233,872	0	2,520,593					
		あり	665	84,899	295,334	0	3,048,863	1.13	10,037	3.9	50	2.0
	女性	なし	2274	61,751	233,136	0	3,264,240					
		あり	536	62,823	197,955	0	2,046,513	1.02	1,072	0.3	50	0.2
高血圧	男性	なし	697	55,897	206,126	0	2,114,073					
		あり	1486	88,249	273,237	0	3,048,863	1.58	32,352	28.3	50	14.1
	女性	なし	1033	47,929	189,495	0	3,264,240					
		あり	1777	70,110	245,602	0	2,630,698	1.46	22,181	22.6	50	11.3
高血糖	男性	なし	1425	66,721	217,277	0	2,131,860					
		あり	758	98,972	310,952	0	3,048,863	1.48	32,251	14.4	50	7.2
	女性	なし	1887	56,538	210,558	0	3,264,240					
		あり	923	73,033	256,633	0	2,802,093	1.29	16,495	8.7	50	4.4
高コレステロール血症	男性	なし	1597	81,279	259,100	0	2,520,593					
		あり	586	68,763	240,101	0	3,048,863	0.85	0	0.0	50	0.0
	女性	なし	1460	57,273	197,464	0	2,117,233					
		あり	1350	67,021	254,757	0	3,264,240	1.17	9,748	7.6	50	3.8
喫煙	男性	なし	747	71,759	231,770	0	3,048,863					
		あり	1436	81,124	265,061	0	2,737,245	1.13	9,365	7.9	50	4.0
	女性	なし	2720	62,479	226,980	0	3,264,240					
		あり	90	46,162	222,385	0	2,046,513	0.74	0	0.0	50	0.0

注意:医療費差額、過剰医療費割合、保健指導後の有病率、改善後過剰医療費割合は、医療費増加比が1未満のときは計算せず、0とした。

表2 入院外医療費

(丹波市)

危険因子	性別		対象者数	平均値	標準偏差	最小値	最大値	医療費増加比	医療費差額(円)	過剰医療費割合(%)	保健指導後の有病率(%)	改善後過剰医療費割合(%)
肥満	男性	なし	1625	124,305	271,833	0	9,145,488					
		あり	558	136,091	145,902	0	1,104,275	1.09	11,786	2.4	50	1.2
	女性	なし	2173	119,967	115,884	0	1,799,895					
		あり	637	156,786	115,788	0	767,413	1.31	36,819	6.5	50	3.3
高コレステロール血症を除いた脂質異常症	男性	なし	1518	130,125	265,633	0	9,145,488					
		あり	665	120,910	193,406	0	3,201,385	0.93	0	0.0	50	0.0
	女性	なし	2274	126,076	115,900	0	1,799,895					
		あり	536	137,806	120,516	0	1,496,858	1.09	11,730	1.7	50	0.9
高血圧	男性	なし	697	86,857	107,302	0	814,103					
		あり	1486	146,296	286,894	0	9,145,488	1.68	59,439	31.8	50	15.9
	女性	なし	1033	108,809	127,528	0	1,799,895					
		あり	1777	139,652	108,629	0	838,670	1.28	30,843	15.2	50	7.6
高血糖	男性	なし	1425	119,746	278,807	0	9,145,488					
		あり	758	141,552	166,518	0	2,162,718	1.18	21,806	5.9	50	3.0
	女性	なし	1887	121,599	113,321	0	1,496,858					
		あり	923	142,042	122,715	0	1,799,895	1.17	20,443	5.2	50	2.6
高コレステロール血症	男性	なし	1597	130,452	276,909	0	9,145,488					
		あり	586	118,776	127,303	0	1,104,275	0.91	0	0.0	50	0.0
	女性	なし	1460	129,880	116,718	0	1,496,858					
		あり	1350	126,620	117,040	0	1,799,895	0.97	0	0.0	50	0.0
喫煙	男性	なし	747	127,127	133,112	0	1,104,275					
		あり	1436	127,417	287,606	0	9,145,488	1.00	290	0.1	50	0.1
	女性	なし	2720	129,260	116,854	0	1,799,895					
		あり	90	99,718	114,104	0	772,595	0.77	0	0.0	50	0.0

注意:医療費差額、過剰医療費割合、保健指導後の有病率、改善後過剰医療費割合は、医療費増加比が1未満のときは計算せず、0とした。

表3 入院外医療費＋保険調剤費

(丹波市)

危険因子	性別		対象者数	平均値	標準偏差	最小値	最大値	医療費増加比	医療費差額(円)	過剰医療費割合(%)	保健指導後の有病率(%)	改善後過剰医療費割合(%)
肥満	男性	なし	1625	166,181	300,883	0	9,295,305					
		あり	558	195,474	216,915	0	1,466,515	1.18	29,293	4.3	50	2.2
	女性	なし	2173	160,521	157,630	0	1,848,648					
		あり	637	206,808	151,474	0	819,523	1.29	46,287	6.1	50	3.1
高コレステロール血症を除いた脂質異常症	男性	なし	1518	177,815	300,194	0	9,295,305					
		あり	665	164,202	235,398	0	3,318,070	0.92	0	0.0	50	0.0
	女性	なし	2274	168,243	155,817	0	1,848,648					
		あり	536	182,769	163,711	0	1,790,863	1.09	14,526	1.6	50	0.8
高血圧	男性	なし	697	120,882	154,687	0	1,287,423					
		あり	1486	198,427	322,113	0	9,295,305	1.64	77,545	30.4	50	15.2
	女性	なし	1033	142,451	160,866	0	1,848,648					
		あり	1777	187,617	153,006	0	1,806,468	1.32	45,166	16.7	50	8.4
高血糖	男性	なし	1425	162,713	306,858	0	9,295,305					
		あり	758	194,265	226,998	0	2,198,938	1.19	31,552	6.3	50	3.2
	女性	なし	1887	161,801	151,967	0	1,790,863					
		あり	923	189,848	166,545	0	1,848,648	1.17	28,047	5.4	50	2.7
高コレステロール血症	男性	なし	1597	177,679	311,093	0	9,295,305					
		あり	586	162,737	180,363	0	1,426,695	0.92	0	0.0	50	0.0
	女性	なし	1460	174,436	163,905	0	1,806,468					
		あり	1350	167,313	150,080	0	1,848,648	0.96	0	0.0	50	0.0
喫煙	男性	なし	747	176,611	191,282	0	1,426,695					
		あり	1436	172,138	319,277	0	9,295,305	0.97	0	0.0	50	0.0
	女性	なし	2720	172,049	157,676	0	1,848,648					
		あり	90	139,718	147,111	0	781,683	0.81	0	0.0	50	0.0

注意:医療費差額、過剰医療費割合、保健指導後の有病率、改善後過剰医療費割合は、医療費増加比が1未満のときは計算せず、0とした。

表4 医療費総額

(丹波市)

危険因子	性別		対象者数	平均値	標準偏差	最小値	最大値	医療費増加比	医療費差額(円)	過剰医療費割合(%)	保健指導後の有病率(%)	改善後過剰医療費割合(%)
肥満	男性	なし	1625	245,747	447,599	0	10,349,853					
		あり	558	268,598	365,513	0	2,927,405	1.09	22,851	2.3	50	1.2
	女性	なし	2173	218,021	309,389	0	4,650,740					
		あり	637	283,966	301,213	0	2,715,865	1.30	65,945	6.4	50	3.2
高コレステロール血症を除いた脂質異常症	男性	なし	1518	252,677	426,192	0	10,349,853					
		あり	665	249,101	432,906	0	4,469,508	0.99	0	0.0	50	0.0
	女性	なし	2274	229,994	314,453	0	4,650,740					
		あり	536	245,592	283,145	0	2,552,613	1.07	15,598	1.3	50	0.6
高血圧	男性	なし	697	176,780	298,471	0	2,856,780					
		あり	1486	286,676	473,015	0	10,349,853	1.62	109,896	29.7	50	14.9
	女性	なし	1033	190,380	290,685	0	4,650,740					
		あり	1777	257,728	316,217	0	3,775,585	1.35	67,348	18.3	50	9.1
高血糖	男性	なし	1425	229,434	420,466	0	10,349,853					
		あり	758	293,236	439,505	0	3,396,950	1.28	63,802	8.8	50	4.4
	女性	なし	1887	218,339	283,224	0	3,448,145					
		あり	923	262,881	353,532	0	4,650,740	1.20	44,542	6.3	50	3.1
高コレステロール血症	男性	なし	1597	258,959	459,790	0	10,349,853					
		あり	586	231,500	326,240	0	3,332,198	0.89	0	0.0	50	0.0
	女性	なし	1460	231,708	287,821	0	3,775,585					
		あり	1350	234,334	329,974	0	4,650,740	1.01	2,626	0.5	50	0.3
喫煙	男性	なし	747	248,370	334,240	0	3,332,198					
		あり	1436	253,262	469,739	0	10,349,853	1.02	4,892	1.3	50	0.6
	女性	なし	2720	234,528	309,647	0	4,650,740					
		あり	90	185,879	277,359	0	2,197,745	0.79	0	0.0	50	0.0

注意:医療費差額、過剰医療費割合、保健指導後の有病率、改善後過剰医療費割合は、医療費増加比が1未満のときは計算せず、0とした。

表5 肥満および危険因子の集積と医療費との関連

（介護市）

分類	肥満	性別	危険因子	対象者数（人）	平均値	標準偏差	最小値	最大値	医療費増加比	医療費差額（円）	過剰医療費割合（%）	保健指導後の有病率（%）	改善後過剰医療費（%）	保健指導での改善が必要な対象者数（人）	期待される医療費減少割合（%）
入院医療費	なし	男性	0	91	36,982	119,541	0	778,055							
			1	372	67,607	216,155	0	2,044,810	1.83	30,625	6.7	50	3.3		
			2以上	1,162	86,729	278,193	0	3,048,863	2.35	49,747	34.0	50	17.0		
		女性	0	326	33,917	121,783	0	1,455,600							
			1	760	62,390	240,825	0	3,264,240	1.84	28,473	12.4	50	6.2		
			2以上	1,087	61,153	237,507	0	2,802,093	1.80	27,236	17.0	50	8.5		
	あり	男性	0	10	40,140	126,934	0	401,400	1.09	3,158					
			1	77	59,130	145,952	0	826,348	1.60	22,148	1.0	50	0.5		
			2以上	471	76,113	254,219	0	2,508,013	2.06	39,131	10.8	50	5.4		
		女性	0	37	101,861	179,701	0	550,695	3.00	67,944					
			1	181	46,266	163,956	0	1,413,598	1.36	12,349	1.3	50	0.6		
			2以上	419	88,321	257,676	0	2,345,095	2.60	54,404	13.1	50	6.5		
入院外医療費	なし	男性	0	91	105,457	118,016	1,145	549,205							
			1	372	103,412	110,497	0	861,320	0.98	0	0.0	50	0.0		
			2以上	1,162	132,470	313,282	0	9,145,488	1.26	27,013	11.3	50	5.6		
		女性	0	326	93,140	101,261	0	593,848							
			1	760	119,557	117,747	0	1,496,858	1.28	26,417	5.6	50	2.8		
			2以上	1,087	128,300	117,534	0	1,799,895	1.38	35,160	10.6	50	5.3		
	あり	男性	0	10	122,753	247,999	4,553	814,103	1.16	17,296					
			1	77	132,854	124,577	0	600,848	1.26	27,397	0.8	50	0.4		
			2以上	471	136,903	146,747	0	1,104,275	1.30	31,446	5.3	50	2.7		
		女性	0	37	164,409	147,246	6,323	626,998	1.77	71,269					
			1	181	142,362	118,773	0	767,413	1.53	49,222	2.5	50	1.2		
			2以上	419	162,344	111,043	0	671,018	1.74	69,204	8.0	50	4.0		
入院外医療費＋保険調剤費	なし	男性	0	91	154,098	195,987	1,145	1,287,423	−						
			1	372	143,191	159,064	0	981,688	0.93	0	0.0	50	0.0		
			2以上	1,162	174,487	339,589	0	9,295,305	1.13	20,389	6.2	50	3.1		
		女性	0	326	121,320	128,108	0	620,118	−						
			1	760	160,839	161,646	0	1,790,863	1.33	39,519	6.3	50	3.1		
			2以上	1,087	172,055	161,018	0	1,848,648	1.42	50,735	11.5	50	5.7		
	あり	男性	0	10	152,112	306,835	4,553	1,008,918	0.99	0					
			1	77	190,151	183,227	0	854,288	1.23	36,053	0.7	50	0.4		
			2以上	471	197,264	220,187	0	1,466,515	1.28	43,166	5.4	50	2.7		
		女性	0	37	216,810	198,915	6,323	692,060	1.79	95,490					
			1	181	186,772	152,612	0	786,008	1.54	65,452	2.5	50	1.2		
			2以上	419	214,579	145,707	0	819,523	1.77	93,259	8.1	50	4.1		
医療費総額	なし	男性	0	91	191,080	251,931	1,145	1,523,573	−						
			1	372	210,799	314,303	0	2,856,780	1.10	19,719	1.3	50	0.7		
			2以上	1,162	261,216	492,837	0	10,349,853	1.37	70,136	14.8	50	7.4		
		女性	0	326	155,237	196,242	0	1,823,220	−						
			1	760	223,229	314,016	0	3,448,145	1.44	67,992	7.9	50	3.9		
			2以上	1,087	233,208	331,014	0	4,650,740	1.50	77,971	12.9	50	6.5		
	あり	男性	0	10	192,252	432,073	4,553	1,410,318	1.01	1,172					
			1	77	249,282	285,058	0	1,577,120	1.30	58,202	0.8	50	0.4	38.5	0.4
			2以上	471	273,377	376,042	0	2,927,405	1.43	82,297	7.1	50	3.5	235.5	3.5
		女性	0	37	318,671	347,598	6,323	1,183,243	2.05	163,434					
			1	181	233,038	246,858	0	1,538,363	1.50	77,801	2.2	50	1.1	90.5	1.1
			2以上	419	302,901	315,928	0	2,715,865	1.95	147,664	9.5	50	4.7	209.5	4.7
保健指導での改善が必要な対象者数			肥満者	1,195	人中									574	人
その肥満者に占める割合														48	%
期待される医療費減少割合(%)			男性												3.9
			女性												5.8

注意：医療費差額、過剰医療費割合、保健指導後の有病率、改善後過剰医療費割合は、医療費増加比が1未満のときは計算せず、0とした。

5. 久山町研究

分担研究者：清原　裕　九州大学大学院医学研究院環境医学分野教授
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研究要旨

久山町研究は、福岡県久山町において1961年より継続されている脳卒中をはじめとする心血管病の前向きコホート研究である。平成19年度は、久山町の剖検例における成績をもとに、血圧と腎細動脈硬化との間に有意な直線的関連が存在し、前高血圧症(120-139/80-89mmHg)から腎細動脈硬化を有するリスクが高くなることを明らかにした。また、久山町における追跡調査の成績をもとに、メタボリック・シンドロームが心血管病発症の有意な危険因子となることを報告した。

A. 研究目的

久山町研究の目的は、様々な危険因子と生活習慣病との関連を検討し、久山町住民のみならず、国民全体の健康増進に有用なエビデンスを提供することである。本年度は、どの血圧レベルから動脈硬化が進展するかを明らかにするために、久山町一般住民における連続剖検例の成績を用いて、高血圧が腎細動脈硬化に及ぼす影響について検討した。また、日本の一般住民におけるメタボリック・シンドローム(MetS)と心血管病発症との関連を明らかにするために、久山町における追跡調査の成績を用いて、MetSが心血管病発症に及ぼす影響を検証した。

B. 研究方法

久山町研究は、福岡県久山町において1961年より継続しておこなわれてきた前向きコホート研究である。40歳以上の一般住民を対象とし、病歴調査（既往歴、家族歴など)、生活習慣調査（飲酒、喫煙など)、身体計測、血圧測定、多項目の血液検査、尿検査、心電図検査などを含む包括的な健診を行ってきた。特に、平成19年度は、5年に一度行っている一斉健診の年にあたり、久山町住民（40歳以上）の75%以上の方に受診していただいた。通常の健診でも病歴調査、生活習慣調査、身体計測、血圧測定、血液検査、75g経口糖負荷試験、尿検査、心電図検査などを含む包括的な健診を行っているが、この健診ではさらに家庭血圧測定、脈波検査(Augmentation Index)、頸動脈エコー検査、うつ症状評価などの健診項目を追加した。従来、75g経口糖負荷試験では、空腹時および負荷120分後に血液検査を実施していたが、本年度は負荷30分後にも血液検査を実施した。久山町研究では、同時に健診受診者を追跡し、心血管病の発症や死因別死亡などに関する調査を継続してきた。心血管病発症が疑われる者に対しては、研究スタッフが往診し、病歴、理学所見、検査所見などから診断を確定している。ま

た、死亡例に対しては、80%において剖検を施行し、死因、臓器病変を特定している。このような徹底した追跡調査システムを用いることにより、追跡脱落率は0.2%以下と極めて低く抑えられている。

1. 高血圧が腎細動脈硬化に及ぼす影響に関する検討

1962年1月から1994年12月までの久山町連続剖検例1,394名(剖検率80%)のうち、死亡7年以内に循環器健診を受診していない者、評価可能な腎組織が保存されていない者、降圧薬服薬者を除いた652名(男性362例、女性290例)を対象とした。腎中小動脈硬化は、各剖検組織切片内のすべての中小動脈について血管狭窄度を算出し、半定量化した。腎動脈硝子化は、各組織切片内の50個の細動脈について硝子化度を算出し、半定量化した。血圧レベルは米国合同委員会の第7次報告に基づいて分類した。解析にはロジスティック回帰モデルを用いた。

2. メタボリック・シンドロームが心血管病発症に及ぼす影響に関する検討

脳卒中および心筋梗塞の既往がない40歳以上の男女2,452名(男性 1,050名、女性1,402名)を1988年より14年間追跡した。MetSの診断には、腹囲基準をAsia-Pacific基準(男性>90cm、女性>80cm)で修正した National Cholesterol Education Program Adult Treatment Panel III (NCEP)の基準を用いた。心血管病は、脳卒中および虚血性心疾患(心筋梗塞、1時間以内の心臓突然死、冠動脈形成術)と定義した。

(倫理面への配慮)

久山町研究は、文部科学省・厚生労働省の「疫学研究に関する倫理指針」に準拠して行われており、九州大学医学研究院等倫理委員会の承認を得ている。

C. 研究結果

1. 高血圧が腎細動脈硬化に及ぼす影響に関する検討

血圧レベル別にみた腎中小動脈硬化の頻度は血圧レベルが高くなるほど上昇し、正常血圧(<120/80mmHg)に対し前高血圧症(120-139/80-89mmHg)から有意に高かった。また、血圧レベルと腎細動脈硝子化の頻度との間にも正の関連があり、前高血圧症のレベルから有意差を認めた。これらの関連は、多変量解析により死亡時年齢、性、血清コレステロール、耐糖能異常、body mass index、飲酒、喫煙を調整しても変わらなかった。標的臓器障害(心電図異常、慢性腎臓病および脳卒中・虚血性心疾患の既往)の有無別に血圧レベルと腎中小動脈硬化の関連を検討したところ、標的臓器障害の有無にかかわらず、腎中小動脈硬化を有する相対危険(多変量調整)は、血圧レベルが高くなるほど直線的に上昇した。

2. メタボリック・シンドロームが心血管病発症に及ぼす影響に関する検討

1988年の集団におけるMetSの頻度は、男性21%、女性30%であった。追跡期間中に心血管病307例(男性158例、女性149例)、脳卒中209例(男性94例、女性115例)、虚血性心疾患125例(男性78例、女性47例)の発症をみた。男女において、心血管病

発症率は、非MetS者に比べMetS群で有意に高かった。MetSの心血管病発症に対する多変量調整相対危険は、男性で1.9、女性で1.7と有意に上昇していた。心血管病発症率は、MetSの構成因子が集積するほど上昇し、構成因子が3個以上集積した群で構成因子がない群に比べ有意差を認めた。 脳卒中および虚血性心疾患における解析でも同様の関連を認めた。

D. 考察

1. 高血圧が腎細動脈硬化に及ぼす影響に関する検討

久山町一般住民の剖検例における検討では、血圧レベルと腎細動脈硬化の程度の間に有意な直線的関係が存在した。血圧レベル別の検討では、正常血圧に対し前高血圧症から腎細動脈硬化を有するリスクが高かった。つまり、従来考えられていたよりも低い血圧レベルから、腎細動脈硬化を有するリスクが高いことがうかがえる。

2. メタボリック・シンドロームが心血管病発症に及ぼす影響に関する検討

本報告は、わが国の一般住民を対象とした前向きコホート研究において、MetSが心血管病発症に及ぼす影響を検討した数少ない研究である。本研究により、日本の一般住民においてもMetSが心血管病発症の有意な危険因子となることが明らかになった。わが国における心血管病の予防戦略を構築するうえで、MetSを早期発見し、生活習慣の修正および適切な治療を働きかけていくことが重要と考えられる。

E. 結論

1. 高血圧が腎細動脈硬化に及ぼす影響に関する検討

久山町一般住民の剖検例では、血圧レベルと腎細動脈硬化の程度の間に有意な直線的関係が存在し、前高血圧症から腎細動脈硬化を有するリスクが高かった。この関連は標的臓器障害の有無にかかわらず認められた。

2. メタボリック・シンドロームが心血管病発症に及ぼす影響に関する検討

日本の一般住民において、MetSは心血管病発症の有意な危険因子であった。

G. 研究発表

1. 論文発表

1. Ninomiya T, Kubo M, Doi Y, Yonemoto K, Tanizaki Y, Tsuruya K, Sueishi K, Tsuneyoshi M, Iida M, Kiyohara Y. Prehypertension increases the risk for renal arteriosclerosis in autopsies: the Hisayama Study. J Am Soc Nephrol. 2007;18:2135-2142.
2. Ninomiya T, Kubo M, Doi Y, Yonemoto K, Tanizaki Y, Rahman M, Arima H, Tsuryuya K, Iida M, Kiyohara Y. Impact of metabolic syndrome on the development of cardiovascular disease in a general Japanese population: the Hisayama Study. Stroke. 2007;38:2063-2069.

論文要約 1

論文題名	Prehypertension increases the risk for renal arteriosclerosis in autopsies: the Hisayama Study.
著者名	Ninomiya T, Kubo M, Doi Y, Yonemoto K, Tanizaki Y, Tsuruya K, Sueishi K, Tsuneyoshi M, Iida M, Kiyohara Y.
書誌情報	J Am Soc Nephrol. 2007;18:2135-2142.

目的	高血圧は腎硬化症を引き起こし、慢性腎臓病や末期腎不全の危険因子となる。しかし、どの血圧レベルから腎動脈硬化が進展するかは必ずしも明らかではない。そこで本報告では、久山町一般住民における連続剖検例の成績を用いて、高血圧が腎細動脈硬化に及ぼす影響について検討した。
研究デザイン	後向きコホート研究。 1962 年 1 月-1994 年 12 月の久山町連続剖検例。
セッティング	福岡県糟屋郡久山町
対象者	1962 年 1 月から 1994 年 12 月の間に、久山町住民の死亡者 1,394 名を剖検した(剖検率 80%)。このうち死亡 7 年以内に循環器健診を受診していない者、評価可能な腎組織が保存されていない者、降圧薬服薬者を除いた 652 名(男性 362 例、女性 290 例)を本研究の対象者とした。
エンドポイント	・腎中小動脈硬化は、各剖検組織切片内のすべての中小動脈について血管狭窄度を算出し、半定量化した。 ・腎動脈硝子化は、各組織切片内の 50 個の細動脈について硝子化度を算出し、半定量化した。
統計解析	腎中小動脈硬化および腎動脈硝子化の頻度を算出した。頻度の比較検定および相対危険の算出には、ロジスティック回帰モデルを用いた。
主な結果	・血圧レベル別にみた腎中小動脈硬化の頻度は血圧レベルが高くなるほど上昇し、正常血圧に対し前高血圧症から有意に高かった。 ・血圧レベル別にみた腎細動脈硝子化の頻度は血圧レベルが高くなるほど上昇し、正常血圧に対し前高血圧症から有意に高かった。 ・これらの関連は、多変量解析により、死亡時年齢、性、血清コレステロール、耐糖能異常、BMI、飲酒、喫煙を調整しても変わらなかった。 ・標的臓器障害(心電図異常、慢性腎臓病および脳卒中・虚血性心疾患の既往)の有無別に血圧レベルと腎中小動脈硬化の関連を検討したところ、標的臓器障害の有無にかかわらず、腎中小動脈硬化を有する多変量調整相対危険は、血圧レベルが高くなるほど直線的に上昇した。
結論	久山町一般住民の剖検例では、血圧レベルと腎細動脈硬化の程度の間に有意な直線的関係が存在し、前高血圧症から腎細動脈硬化を有するリスクが高かった。この関連は標的臓器障害の有無にかかわらず認められた。

Prehypertension Increases the Risk for Renal Arteriosclerosis in Autopsies: The Hisayama Study

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ABSTRACT

Information regarding the association between prehypertension BP level and renal arteriosclerosis is limited. In 652 consecutive population-based autopsy samples without hypertension treatment before death, the relationship between the severity of renal arteriosclerosis and BP levels classified according to the criteria of the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure was examined. The age- and gender-adjusted frequencies of renal arteriosclerosis linearly increased with elevating BP levels; both hypertensive and prehypertensive subjects had significantly higher frequencies of renal arteriosclerosis than subjects with normal BP (normal 11.9%; prehypertension 28.5%; stage 1 hypertension 32.9%; stage 2 hypertension 58.2%; all $P < 0.01$ *versus* normal). In a logistic regression model, prehypertension was significantly associated with renal arteriosclerosis after adjustment for other cardiovascular risk factors (prehypertension multivariate-adjusted odds ratio [mOR] 5.99 [95% confidence interval (CI) 2.20 to 15.97]; stage 1 hypertension mOR 6.99 [95% CI 2.61 to 18.72]; stage 2 hypertension mOR 22.21 [95% CI 8.35 to 59.08]). This significant association was observed for all renal arterial sizes. The similar association was also observed for arteriolar hyalinosis. When the subjects were divided into those with and those without target organ damage, the impact of prehypertension on renal arteriosclerosis was similar for both groups (subjects without target organ damage mOR 5.04 [95% CI 1.36 to 18.62]; subjects with target organ damage mOR 6.42 [95% CI 1.29 to 32.04]). These findings suggest that both hypertension and prehypertension are associated significantly with the severity of renal arteriosclerosis, regardless of the presence or absence of target organ damage.

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Hypertension has been recognized as one of the major risk factors for the development of ESRD.[1,2] Nephrosclerosis is characterized pathologically by focal or global glomerular sclerosis and renal arteriosclerosis and is frequently found in individuals with hypertension.[3–5] Meanwhile, several prospective studies have indicated that the impressive increase in the risk for cardiovascular disease or in the risk for progression to hypertension started at a BP level of ≥120/80 mmHg.[6–8] On the basis of these findings, the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7) introduced a "prehypertension" category in which BP is 120 to 139/80 to 89 mmHg and for which health-promoting lifestyle modifications are recommended to prevent cardiovascular disease.[9]

A prospective population-based study of cardiovascular disease has been carried out since 1961 in

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the town of Hisayama on Kyushu Island in southern Japan. The most characteristic feature of the Hisayama Study is that the cause of death has been verified by autopsy for approximately 80% of deceased subjects in the study population.[10–13] Our previous autopsy reports of Hisayama residents showed that systolic BP (SBP) was closely related to the progression of glomerular sclerosis, renal arteriolar hyalinosis, and renal arteriosclerosis.[12,13] To our knowledge, the Honolulu Heart Program is the only other population-based study that has examined this issue, although the autopsy rate was not high (20.6%).[14,15] Their findings also suggested that diastolic BP (DBP) was an independent predictor of glomerular sclerosis, renal arteriolar hyalinosis, and renal arteriosclerosis.[14,15] However, the association between categorized BP levels and renal vascular changes was not assessed in these studies or in ours. In this study, we examined the relationship between BP levels and renal arteriosclerosis, focusing on prehypertension, in population-based autopsy samples of the Hisayama Study, taking into account other cardiovascular risk factors as well as renal artery size.

RESULTS

The baseline characteristics of the 652 autopsy subjects are represented according to the BP levels in Table 1. The subjects with stage 1 or stage 2 hypertension were older than those with normal BP. The proportions of women gradually increased with elevating BP levels. The mean GFR values decreased significantly in stage 2 hypertension relative to normal BP level, whereas serum creatinine levels did not change across BP levels. The frequencies of proteinuria and history of cardiovascular disease were significantly higher in subjects with stage 2 hypertension, and that of electrocardiogram (ECG) abnormalities increased linearly with elevating BP levels. The mean values of total cholesterol were significantly higher in subjects with hypertensive or prehypertensive BP levels, whereas the frequency of glucose intolerance and the mean value of body mass index (BMI) did not change across BP levels. The frequency of current smoking decreased gradually with elevating BP levels, but no such tendency was observed for the frequency of alcohol intake.

Figure 1 presents the age- and gender-adjusted frequencies of renal arteriosclerosis, arteriolar hyalinosis, and glomerular sclerosis according to BP classification. The frequencies of renal arteriosclerosis and arteriolar hyalinosis linearly increased with elevating BP levels; not only hypertensive subjects but also prehypertensive subjects had a significantly higher frequency of renal arteriosclerosis and arteriolar hyalinosis compared with subjects with normal BP. Likewise, the age- and gender-adjusted mean values of the wall-lumen ratio of renal arteries decreased linearly (normal 5.10; prehypertension 4.16; stage 1 hypertension 3.96; stage 2 hypertension 3.47; all $P < 0.01$ *versus* normal), and those of the arteriolar hyalinosis index increased gradually with elevating BP levels (normal 1.21; prehypertension 1.29 [$P < 0.05$ *versus* normal]; stage 1 hypertension 1.29 [$P < 0.05$]; stage 2 hypertension 1.38 [$P < 0.01$]). The severity of glomerular sclerosis increased significantly in only stage 2 hypertension. The age- and gender-adjusted odds ratios (OR) of renal arteriosclerosis and arteriolar hyalinosis were significantly higher in prehypertension subjects and in hypertension subjects than in normal ones (Table 2). This association remained substantially unchanged even after adjustment for age at death, gender, total cholesterol, glucose intolerance, BMI, smoking habits, and alcohol intake. Furthermore, we di-

Table 1. Mean values or frequencies of potential risk factors and laboratory variables according to BP classification for 652 autopsy subjects[a]

Variables	BP Classification			
	Normal ($n = 106$)	Prehypertension ($n = 172$)	Stage 1 HT ($n = 176$)	Stage 2 HT ($n = 198$)
Age at death (yr)	70 ± 12	72 ± 13	75 ± 12[b]	79 ± 11[b]
Women (%)	37.7	40.7	43.2	52.5[c]
SBP (mmHg)	109 ± 8	129 ± 6[b]	148 ± 7[b]	179 ± 18[b]
DBP (mmHg)	66 ± 7	73 ± 10[b]	80 ± 11[b]	91 ± 13[b]
GFR (ml/min per 1.73 m^2)	77.1 ± 15.8	75.5 ± 18.8	76.3 ± 20.6	70.2 ± 19.5[c]
Serum creatinine (μmol/L)	83.5 (57.3 to 121.8)	85.4 (54.7 to 133.4)	84.0 (51.5 to 137.2)	88.2 (49.0 to 158.7)
Proteinuria (%)	9.2	6.8	10.8	23.4[b]
History of cardiovascular disease (%)	4.7	11.6	9.1	12.1[c]
Electrocardiogram abnormalities (%)	6.8	15.4[c]	25.7[b]	40.8[b]
Total cholesterol (mmol/L)	4.25 ± 1.07	4.67 ± 1.07[b]	4.60 ± 1.22[c]	4.63 ± 1.10[c]
Glucose intolerance (%)	13.2	21.5	18.2	22.2
BMI (kg/m^2)	20.2 ± 2.8	20.7 ± 3.2	20.7 ± 3.3	20.7 ± 3.1
Smoking habits (%)	47.6	41.3	39.7	35.4[c]
Alcohol intake (%)	24.0	32.6	31.2	30.6

[a]Data are means ± SD or percentage. GFR determined by Modification of Diet in Renal Disease Study Group formula. Glomerular filtration rate and serum creatinine were measured in 442 subjects who died after 1977. Geometric mean values and 95% confidence intervals (CI) of serum creatinine are shown because of the skewed distribution. BMI, body mass index; DBP, diastolic BP; HT, hypertension; SBP, systolic BP.
[b]$P < 0.01$, [c]$P < 0.05$ *versus* normal.

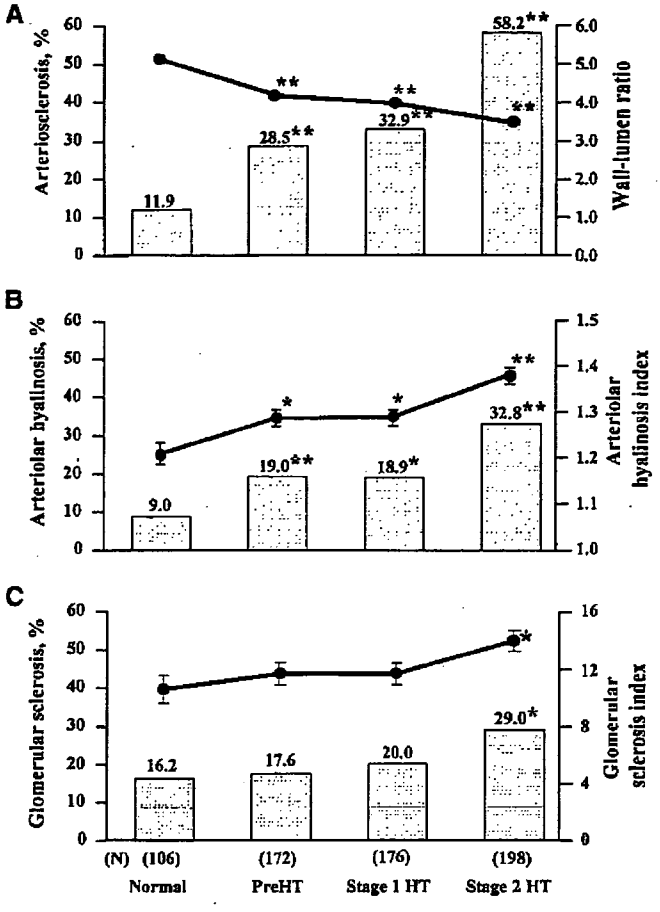

Figure 1. Age- and gender-adjusted frequencies of renal arteriosclerosis (A), arteriolar hyalinosis (B), and glomerular sclerosis (C) according to BP classification among 652 autopsy subjects. Solid lines indicate age- and gender-adjusted mean values of wall-lumen ratio, arteriolar hyalinosis index, and glomerular sclerosis, respectively. PreHT, prehypertension; HT, hypertension. *$P < 0.05$, **$P < 0.01$ *versus* normal.

vided prehypertension into two subcategories—BP 120 to 129/80 to 84 mmHg and BP 130 to 139/85 to 89 mmHg—and examined the association between BP level and renal arteriosclerosis. As a result, the risk for having renal arteriosclerosis was significantly increased in both BP subcategories even after adjustment for the previously mentioned cardiovascular risk factors (BP 120 to 129/80 to 84 mmHg OR 5.93 [95% confidence interval (CI) 2.08 to 16.91; $P < 0.01$]; BP 130 to 139/85 to 89 mmHg OR 5.92 [95% CI 2.02 to 17.29; $P < 0.01$]).

We examined whether the association between BP and renal arteriosclerosis differs by the presence or absence of target organ damage. As shown in Figure 2A, the age- and gender-adjusted frequencies of renal arteriosclerosis were higher in the group with target organ damage than in the group without it, regardless of BP level. In both groups, however, the frequencies of renal arteriosclerosis increased significantly with elevating BP levels; the difference was significant between the normal and both the prehypertension and hypertension categories. Likewise, the mean values of the wall-lumen ratio of renal arteries were significantly lower in BP levels of prehypertension and hypertension than in normal BP level for both the target-organ-damaged and target-organ-undamaged groups (Figure 2B). As shown in Table 3, the impact of prehypertension on renal arteriosclerosis was similar for both the damaged and undamaged groups after adjustment for the previously mentioned cardiovascular risk factors (without target organ damage OR 5.04 [95% CI 1.36 to 18.62; $P < 0.05$]; with target organ damage OR 6.42 [95% CI 1.29 to 32.04; $P < 0.05$]).

Finally, we examined the associations between BP levels and renal arteriosclerosis by the size of renal arteries using logistic regression analysis (Table 4). After adjustment for the previously mentioned cardiovascular risk factors, both prehypertension and hypertension significantly increased the risk for having renal arteriosclerosis in all arterial sizes. For smaller arteries (<300 μm), the risk for arteriosclerosis significantly and linearly increased with elevating BP levels, whereas this linear association was diminished for larger arteries (≥300 μm).

DISCUSSION

In this population-based autopsy survey, we histopathologically examined the relationship between categorized BP levels classified according to the JNC-7 criteria and renal arteriosclerosis. The results showed that both hypertension and prehypertension were associated significantly with renal arteriosclerosis, without regard for the presence or absence of target organ damage or for the size of intrarenal arteries. The relationships between BP and renal histopathologic changes also have been reported in the several biopsy-based studies of living subjects. Lhotta *et al.*[16] showed in patients who underwent biopsy that SBP was associated significantly with the frequencies of glomerular sclerosis and arteriolar hyalinosis. According to the study for patients with biopsy-proven IgA nephropathy, patients with hypertension, defined as BP ≥140/90 mmHg, had more severe glomerular sclerosis, interstitial fibrosis/tubular atrophy, interstitial infiltration, and atherosclerosis compared with those without hypertension.[17] In a similar biopsy study for IgA nephropathy, prehypertension (BP 120 to 139/80 to 89 mmHg) was associated significantly with the severity of mesangial proliferation and arteriolar changes, including intimal thickening, intimal duplication or hyalinosis, but not glomerular sclerosis.[18] These findings are in accordance with those of our study.

Several recent reports have shown that the risk for the development of cardiovascular disease or the risk for the progression to hypertension initiates an increase in BP levels of ≥120/80 mmHg. A meta-analysis of individual data for 1 million adults in 61 prospective studies indicated that the mortality from both ischemic heart disease and stroke increased progressively and linearly from BP levels as low as SBP of 115 mmHg and DBP of 75 mmHg in middle and old age.[6] In addi-

Table 2. Age- and gender-adjusted or multivariate-adjusted OR for renal arteriosclerosis, arteriolar hyalinosis, and glomerular sclerosis according to BP classification among 652 autopsy subjects

Parameter	BP Classification			
	Normal	Prehypertension	Stage 1 HT	Stage 2 HT
Arteriosclerosis				
age and gender adjusted				
OR[b]	1.00	4.21[d]	4.97[d]	16.57[d]
CI	Reference	1.85 to 9.60	2.20 to 11.21	7.41 to 37.05
multivariate adjusted				
OR[c]	1.00	5.99[d]	6.99[d]	22.21[d]
CI	Reference	2.20 to 15.97	2.61 to 18.72	8.35 to 59.08
Arteriolar hyalinosis				
age and gender adjusted				
OR[b]	1.00	2.70[e]	2.59[e]	5.84[d]
CI	Reference	1.19 to 6.13	1.14 to 5.89	2.65 to 12.88
multivariate adjusted				
OR[c]	1.00	2.36[e]	2.19	5.42[d]
CI	Reference	1.01 to 5.50	0.93 to 5.16	2.37 to 12.38
Glomerular sclerosis				
age and gender adjusted				
OR[b]	1.00	1.03	1.24	2.06[e]
CI	Reference	0.50 to 2.12	0.62 to 2.49	1.06 to 4.02
multivariate adjusted				
OR[c]	1.00	1.01	1.21	2.21[e]
CI	Reference	0.46 to 2.21	0.56 to 2.61	1.06 to 4.64

[a]OR odds ratio.
[b]Adjusted for age at death and gender.
[c]Adjusted for age at death, gender, total cholesterol, glucose intolerance, BMI, smoking habit, and alcohol intake.
[d]$P < 0.01$, [e]$P < 0.05$ *versus* normal.

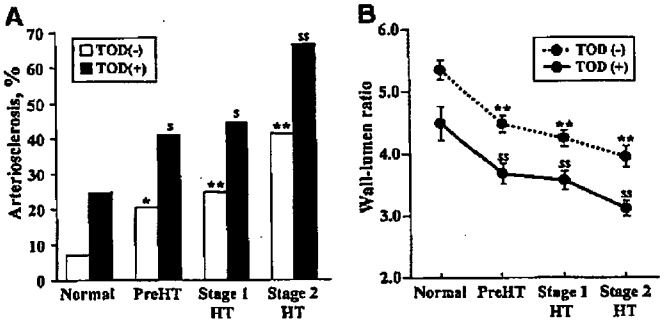

Figure 2. Age- and gender-adjusted frequencies of renal arteriosclerosis (A) and mean values of wall-lumen ratio of the renal arteries (B) according to BP classification by the presence or absence of target organ damage among 652 autopsy subjects. TOD, target organ damage; $^{*}P < 0.05$, $^{**}P < 0.01$ *versus* normal in target organ damage (−); $^{\$}P < 0.05$, $^{\$\$}P < 0.01$ *versus* normal in target organ damage (+).

tion, longitudinal data that were obtained from the Framingham Heart Study indicated that high-normal BP and normal BP, defined by JNC-6, were associated with the occurrence of cardiovascular disease.[7] Moreover, according to the randomized, controlled trial conducted in the Modification of Diet in Renal Disease (MDRD) study, low target BP (mean BP <92 mmHg, equivalent to a BP <125/75 mmHg) reduced the risk for developing kidney failure by approximately 30% compared with the usual target BP (mean BP <107 mmHg, equivalent to a BP <140/90 mmHg).[19] Our findings also showed that prehypertension levels were significantly associated with renal arteriosclerosis and arteriolar hyalinosis. It may be reasonable to suppose that prehypertension promotes systemic arteriosclerosis including renal vascular changes and causes cardiovascular disease and renal dysfunction.

It is possible that prehypertension is not the cause of renal arteriosclerosis but the result of renal vascular changes or organ damages by other cardiovascular risk factors. In this study, however, prehypertension was clearly associated with renal arteriosclerosis, regardless of the presence or absence of target organ damage, and this association was significant even after adjustment for other cardiovascular risk factors. This suggests that a slight increase in BP to prehypertension levels was associated independently with the severity of renal arteriosclerosis. Therefore, it is possible that antihypertensive treatment with BP-lowering <120/80 mmHg prevents the progression of renal arteriosclerosis, regardless of the presence or absence of target organ damage.

In our study, the relationship between BP levels and renal arteriosclerosis differed somewhat according to the size of renal arteries; the risk for renal arteriosclerosis increased significantly and linearly with elevating BP levels in smaller arteries (<300 μm), including arterioles, whereas this phenomenon was diminished in larger arteries (≥300 μm). Instead, the impact of total cholesterol levels was reinforced with elevating renal arterial size in our subjects (data not shown). In autopsy

Table 3. Multivariate-adjusted OR for renal arteriosclerosis according to BP classification by the presence or absence of target organ damage.

Parameter	BP Classification			
	Normal	Prehypertension	Stage 1 HT	Stage 2 HT
Target organ damage (−)[a]				
population at risk	83	109	103	70
OR[b]	1.00	5.04[c]	6.05[d]	18.81[d]
95% CI	Reference	1.36 to 18.62	1.65 to 22.20	4.98 to 71.01
Target organ damage (+)[a]				
population at risk	23	63	73	128
OR[b]	1.00	6.42[c]	7.21[c]	18.02[d]
95% CI	Reference	1.29 to 32.04	1.46 to 35.65	3.75 to 86.47

[a]Target organ damage was defined as the presence of preexisting cardiovascular disease, electrocardiogram abnormalities, proteinuria, or GFR <60 ml/min per 1.73 m^2.
[b]Adjusted for age at death, gender, total cholesterol, glucose intolerance, BMI, smoking habits, and alcohol intake.
[c]$P < 0.05$, [d]$P < 0.01$ *versus* normal.

Table 4. Multivariate-adjusted OR for renal arteriosclerosis according to BP classification by the size of renal arteries among 652 autopsy subjects

Size of Renal Arteries (μm)	BP Classification			
	Normal	Prehypertension	Stage 1 HT	Stage 2 HT
60 to 149				
OR[a]	1.00	4.01[b]	4.13[b]	12.00[b]
95% CI	Reference	1.59 to 10.10	1.64 to 10.39	4.84 to 29.68
150 to 299				
OR[a]	1.00	2.39[c]	4.27[b]	9.94[b]
95% CI	Reference	1.13 to 5.07	2.05 to 8.89	4.77 to 20.72
300 to 499				
OR[a]	1.00	4.21[b]	2.73[c]	6.21[b]
95% CI	Reference	1.68 to 10.60	1.06 to 6.99	2.49 to 15.47
≥500				
OR[a]	1.00	3.80[c]	2.59	3.08
95% CI	Reference	1.09 to 13.30	0.72 to 9.34	0.86 to 11.04

[a]Adjusted for age at death, gender, total cholesterol, glucose intolerance, BMI, smoking habits, and alcohol intake.
[b]$P < 0.01$, [c]$P < 0.05$ *versus* normal.

findings from the Honolulu Heart Program, BP was associated strongly with the intimal thickness of renal arteries with an outer diameter of 80 to 300 μm, but there were no correlations between the intimal thickness of these renal arteries and other cardiovascular risk factors, such as total cholesterol, triglycerides, blood glucose, and smoking.[14] It is feasible to speculate that the degree of the atherogenic effects of risk factors varies according to artery size and that hypertension affects small arteries notably.

Several limitations of our study should be discussed. First, our findings might be biased by the exclusion of 187 subjects who were taking antihypertensive medications. The mean values of SBP, DBP, serum creatinine, and total cholesterol and the frequencies of proteinuria, ECG abnormalities, glucose intolerance, and history of cardiovascular disease were significantly higher and the mean values of wall-lumen ratio were significantly lower in subjects who were taking antihypertensive medications than in the 652 subjects without antihypertensive medications in the present study. This bias has the potential to underestimate the impact of hypertension or other cardiovascular risk factors on renal arteriosclerosis. However, it is unlikely that this bias affects the association between prehypertension and renal arteriosclerosis, because prehypertensive subjects did not use antihypertensive medication. Second, only a single BP measurement was obtained at the baseline examination in the recumbent position. This imperfect measurement of BP might have resulted in a misclassification of our study subjects into different BP categories and a consequent dilution of our estimates of BP's impact on renal arteriosclerosis. Third, this is a cross-sectional study. Therefore, it is difficult to infer causality between prehypertension and risk for progression of renal arteriosclerosis, because it may be presumed that BP increased as a result of renal ischemia by preexisting renal arteriosclerosis, acting mainly through the renin-angiotensin system. In any case, our findings suggest that subjects with prehypertension should be considered as those with more progressive renal arteriosclerosis. Fourth, several variables used in this study were less accurate. We used the MDRD equation to estimate GFR; this formula is notoriously inaccurate in patients with normal kidney function. Proteinuria was established as 1+ or more on the dipstick; this would have missed all subjects with microalbuminuria. In addition,

the definition of glucose tolerance varied depending on when the examination was done. These facts might lead to the misclassification of a normal subgroup without any risk factor and affect the cutoff value of each histologic parameter. However, it seems to be unlikely that this limitation distorted the associations between BP levels and severity of renal arteriosclerosis, because BP levels showed the dosage-dependent association with the continuous values of wall-lumen ratio. Finally, this study is based on autopsy and the proportion of aged people is extremely high. Therefore, its findings cannot be applied to the overall living population. However, we believe that our findings provide useful information toward a better understanding of the pathogenesis of renal arteriosclerosis.

CONCLUSION

Prehypertension level classified by JNC-7 was associated significantly with the severity of renal arteriosclerosis. Therefore, prehypertensive individuals should be considered a high-risk population, regardless of the presence or absence of target organ damage. Our findings emphasize the need to determine whether the lowering of goal BP in hypertension management can prevent the progression of renal and systemic arteriosclerosis.

CONCISE METHODS

Study Population

The population of the town of Hisayama is approximately 7500, and data from the national census show it to be representative of Japan as a whole.[10,11] The study design and characteristics of the subject population have been described in detail elsewhere.[12,13] Briefly, from January 1962 to December 1994, a total of 1742 Hisayama residents of all age groups died, 1394 (80.0%) of whom underwent autopsy. The autopsy rate was not different between men (78.7%) and women (81.6%). Among these consecutive autopsy subjects, 1168 participated in at least one of the six health examinations conducted in 1961, 1967, 1974, 1978, 1983, and 1988. For every examination, the participation rate exceeded >80% of all Hisayama residents 40 yr or older. After exclusion of 98 subjects who lacked preserved renal tissues, 33 with degenerated or small renal tissues, 80 who underwent autopsy at other hospitals, 118 who had no health examination data within 7 yr before death, and 187 who had been treated with antihypertensive medications, 652 subjects (362 men and 290 women) were included in this study. The mean period from the most recent health examination to death was 3.6 ± 1.8 yr.

Morphologic Examination of Renal Tissue

The methods of morphologic examination of renal tissue have been described in detail elsewhere.[13] Briefly, for light microscopic study, paraffin-embedded renal tissues that were obtained by standard autopsy methods were cut at a 2-μm thickness and stained with periodic acid-Schiff reagent. The wall-lumen ratio was evaluated as the severity of arteriosclerosis by the method of Kernohan *et al.*[20] For each specimen, all arteries with an outer diameter >60 μm were examined using an eyepiece micrometer. The outer diameter and the lumen diameter of the least axis of the elliptic profile were directly measured. The wall-lumen ratio was calculated in each artery as lumen diameter/(outer diameter − lumen diameter)/2, and the mean value for all arteries in all subjects was used as the index of arteriosclerosis. We further classified all arteries into four categories according to the outer diameters of the renal arteries—60 to 149, 150 to 299, 300 to 499, and ≥500 μm—and calculated the mean values of the wall-lumen ratio by the previously mentioned categories.

The severity of arteriolar hyalinosis was assessed semiquantitatively by the method of Barder *et al.*[21] For each tissue specimen, 50 arterioles were examined and the severity of the lesion in each arteriole was graded from 1+ to 4+ according to the extent of arteriolar hyalinosis. The arteriolar hyalinosis index was calculated by the following formula: Arteriolar hyalinosis index = $(n_1 \times 1 + n_2 \times 2 + n_3 \times 3 + n_4 \times 4)/50$. Here, n_1, n_2, n_3, and n_4 indicate the number of arterioles showing hyalinosis scores of 1+ to 4+, respectively.

The semiquantitative score was used to evaluate the severity of glomerular sclerosis by the method of Raij *et al.*[22] For each tissue specimen, 100 glomeruli from the superficial to deep cortex were examined uniformly, and the severity of the lesion in each glomerulus was graded from 0 to 4+ according to the percentage of glomerular sclerosis. The glomerular sclerosis index was calculated by the following formula: Glomerular sclerosis index = $(n_0 \times 0 + n_1 \times 1 + n_2 \times 2 + n_3 \times 3 + n_4 \times 4)/4$. Here, n_0, n_1, n_2, n_3, and n_4 indicate the number of glomeruli showing sclerotic lesion scores of 0 to 4+, respectively.

Definition of Renal Arteriosclerosis, Arteriolar Hyalinosis, and Glomerular Sclerosis

To differentiate the effects of cardiovascular risk factors from age-related changes, we selected 103 subjects who had none of the following characteristics: Proteinuria, kidney failure, hypertension, glucose intolerance, or primary renal disease at autopsy. Using this subgroup, the cutoff limits were defined as below the 10th percentile or above the 90th percentile of each histologic parameter distribution; that is, renal arteriosclerosis, arteriolar hyalinosis, and glomerular sclerosis were defined as a wall-lumen ratio <3.37, an arteriolar hyalinosis index >1.44, and a glomerular sclerosis index >17.0, respectively. In the analysis by the size of renal arteries, furthermore, renal arteriosclerosis was defined as below the lower 10th percentile for mean values of the wall-lumen ratio by size (60 to 149 μm: wall-lumen ratio <3.56; 150 to 299 μm: wall-lumen ratio <2.65; 300 to 499 μm: wall-lumen ratio <2.64; ≥500 μm: wall-lumen ratio <2.44).

Risk Factors

BP was measured three times after a single rest period of at least 5 min using a standard mercury sphygmomanometer with the subject in the recumbent position. The mean of the three measurements was used for the analysis. BP levels were categorized according to the criteria recommended by JNC-7[9] (normal: SBP <120 mmHg and DBP <80 mmHg; prehypertension: SBP 120 to 139 mmHg or DBP 80 to 89 mmHg; stage 1 hypertension: SBP 140 to 159 mmHg or DBP 90 to 99

mmHg; stage 2 hypertension: SBP ≥160 mmHg or DBP ≥100 mmHg).

Glucose intolerance was defined by an oral glucose tolerance test in the subjects with glycosuria in 1961 and 1967; by fasting and postprandial glucose concentrations in 1974, 1978, and 1983; and by a 75-g oral glucose tolerance test in 1988, in addition to medical history of diabetes. ECG abnormalities were defined as Minnesota codes 3-1 and/or 4-1, -2, -3. Serum total cholesterol levels were measured by the Zak-Henly method with a modification by Yoshikawa in 1961 and 1967, by the Zurkowski method in 1974, and by the enzymatic method after 1978. Serum creatinine concentration was measured by the Jaffe method after 1974, and GFR was calculated by the MDRD Study Group formula.[23] Freshly voided urine samples were tested by the sulfosalicylic acid method in 1961 and 1967 and by the dipstick method after 1974. Proteinuria was defined as 1+ or more. Body height and weight were measured in light clothing without shoes, and the BMI (kg/m^2) was calculated. Information on antihypertensive medication, alcohol intake, and smoking habits was obtained through a standard questionnaire and classified as current habitual use or a lack thereof. All available information about potential cardiovascular diseases, including stroke, myocardial infarction, and coronary intervention, was gathered and reviewed by a panel of physician members of the Hisayama Study to determine the occurrence of cardiovascular disease under the standard criteria. A history of cardiovascular disease was determined on the basis of this information. Target organ damage was defined as the presence of ECG abnormalities, proteinuria, GFR <60 ml/min per 1.73 m^2, or a history of cardiovascular disease.

Statistical Analyses

SAS software (SAS Institute, Cary, NC) was used to perform all statistical analyses. The crude or age- and gender-adjusted mean values and frequencies of variables were compared among BP levels using Dunnett *t* test or logistic regression analysis as appropriate. The age- and gender-adjusted or multivariate-adjusted OR and 95% CI were calculated by a logistic regression analysis. $P < 0.05$ was considered statistically significant in all analyses.

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DISCLOSURES

None.

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論文要約 2

論文題名	Impact of metabolic syndrome on the development of cardiovascular disease in a general Japanese population: the Hisayama Study.
著者名	Ninomiya T, Kubo M, Doi Y, Yonemoto K, Tanizaki Y, Rahman M, Arima H, Tsuryuya K, Iida M, Kiyohara Y.
書誌情報	Stroke. 2007;38:2063-2069.

目的	メタボリック・シンドロームは心血管病との関連が指摘されている。しかし、アジアの一般住民において、メタボリック・シンドロームの心血管病発症に与える影響を検討した疫学研究は少ない。そこで本報告では、福岡県久山町における追跡調査の成績をもとに、メタボリック・シンドロームが心血管病発症に及ぼす影響を検討した。
研究デザイン	前向きコホート研究。 1988 年にベースライン調査、その後 2002 年 11 月まで追跡。
セッティング	福岡県糟屋郡久山町
対象者	40 歳以上の男女を対象に健診を実施し 2,736 名が受診（受診率 81%)。そのうち脳卒中および心筋梗塞の既往がない 2,452 名(男性 1,050 名、女性 1,402 名)を本研究の対象者とした。
エンドポイント	・心血管病(脳卒中+冠動脈疾患)発症。 ・脳卒中発症。病歴、神経学的所見、CT 検査・剖検所見をもとに診断した。 ・虚血性心疾患発症。心筋梗塞発症と 1 時間以内の心臓突然死を虚血性心疾患と定義した。病歴、心筋由来の血液酵素学的変化、心電図、心エコー検査・心臓カテーテル検査・剖検による形態学的変化をその診断の根拠とした。
統計解析	発症率の算出には人年法を用いた。発症率の比較検定および相対危険の算出には、Cox 比例ハザードモデルを用いた。
主な結果	・メタボリック・シンドローム(National Cholesterol Education Program Adult Treatment Panel III [NCEP]の基準による)の頻度は、男性で 21%、女性で 30%であった。 ・追跡期間中に心血管病 307 例(男性 158 例、女性 149 例)、脳卒中 209 例(男性 94 例、女性 115 例)、虚血性心疾患 125 例(男性 78 例、女性 47 例)の発症をみた。 ・男女において、心血管病発症率は、メタボリック・シンドロームのない者に比べメタボリック・シンドロームのある者で有意に高かった。 ・メタボリック・シンドロームの心血管病発症に対する多変量調整相対危険は、男性で 1.9、女性で 1.7 と有意に上昇していた。 ・心血管病発症率は、メタボリック・シンドロームの構成因子が集積するほど上昇し、構成因子が 3 個以上集積した群で構成因子がない群に比べ有意差を認めた。 ・脳卒中および虚血性心疾患における解析でも同様の関連を認めた。
結論	日本の一般住民において、メタボリック・シンドロームは心血管病発症の有意な危険因子であった。

Impact of Metabolic Syndrome on the Development of Cardiovascular Disease in a General Japanese Population

The Hisayama Study

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Background and Purpose—The metabolic syndrome (MetS) is associated with an increased risk of cardiovascular disease (CVD) events in general populations. However, well-designed prospective studies in Asian populations are very limited.

Methods—We prospectively evaluated a total of 2452 community-dwelling Japanese individuals aged 40 years or older from 1988 to 2002 and examined the effects of MetS defined by the modified National Cholesterol Education Program Adult Treatment Panel III criteria on incident CVD.

Results—The prevalence of the MetS was 21% in men and 30% in women at baseline. During the follow up, 307 CVD events occurred. Compared with those without MetS, the age-adjusted incidence of CVD (per 1000 person-years) was significantly higher in subjects with the MetS in both men (21.8 versus 11.6, $P<0.01$) and women (12.9 versus 6.5, $P<0.01$). The risk of CVD events was significantly higher even after adjusting for the following confounding factors: age, proteinuria, electrocardiographic abnormalities, serum total cholesterol, smoking habits, alcohol intake, and regular exercise (hazard ratio, 1.86; 95% CI, 1.32 to 2.62 in men and hazard ratio, 1.70; 95% CI, 1.22 to 2.36 in women). The risk of incident CVD was found to increase with the number of components of MetS and became significantly predictive when the number of components reached 3. Similar associations were also observed when CVD was divided into coronary heart disease and stroke.

Conclusions—Our findings suggest that MetS is a significant risk factor for the development of CVD in the Japanese middle-aged population. (***Stroke*. 2007;38:2063-2069.)**

Key Words: cardiovascular disease ■ epidemiology ■ metabolic syndrome ■ myocardial infarction ■ stroke

Metabolic syndrome (MetS), also known as syndrome X,[1] the insulin resistance syndrome,[2] and deadly quartet,[3] is a constellation of dyslipidemia, central obesity, elevated blood pressure, and impaired glucose tolerance. It is associated with high risk for the development of type 2 diabetes mellitus and cardiovascular disease (CVD).[4–7] In the past several years, a great deal of attention has been directed to it attributable to increases in its prevalence worldwide[6] and its association with CVD morbidity and mortality. Although each of the components of MetS has been shown to increase CVD risk,[8–12] the presence of MetS has been reported to identify additional risk.[7] Different prospective studies[7,13–25] based on the definitions from the National Cholesterol Education Program's (NCEP) Third Adult Treatment Panel Report III[5] and World Health Organization[26] showed that subjects with MetS are at increased risk of incident CVD, CVD mortality, and all-cause mortality in the general population with or without diabetes mellitus. However, most of these studies were based on Western populations, and well-designed prospective studies in Asian populations are very limited.[27–29] Thus, there is a dearth of literature regarding the relationship of MetS with incident CVD based on general population cohorts with a reasonable length of follow-up time in ethnic groups other than whites. In this study, we examined the impact of MetS on CVD events in a general Japanese population cohort based on 14-year prospective follow-up data.

Materials and Methods

Study Population

The Hisayama Study, an epidemiological study of cerebro- and cardiovascular diseases, was established in 1961 in Hisayama Town, a suburban community adjacent to Fukuoka City, a metropolitan area of Kyushu Island in southern Japan. The population of the town is

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approximately 7500, and full community surveys of the residents have been repeated since 1961.[30] In 1988, a screening survey for the present study was performed in the town. A detailed description of this survey was published previously.[31] Briefly, a total of 2736 residents aged 40 years or over (80.7% of the total population of this age group) consented to participate in the examination and underwent a comprehensive assessment. After excluding 102 subjects with a history of coronary heart disease or stroke, as determined by a questionnaire and medical records, one subject for whom no blood sample was obtained, 120 subjects with postprandial blood sample, and 61 subjects without the measurements of their waist circumferences, the remaining 2452 subjects (1050 men and 1402 women) were enrolled in this study.

Follow-Up Survey

The subjects were followed prospectively from December 1988 to November 2002 by repeated health examinations. Health status was checked yearly by mail or telephone for any subjects who did not undergo a regular examination or who had moved out of town. We also established a daily monitoring system among the study team and local physicians or members of the town's health and welfare office. When a subject died, an autopsy was performed at the Department of Pathology of Kyushu University. During the follow-up period, only one subject was lost to follow up and 479 subjects died, of whom 362 (75.6%) underwent autopsy.

Definition of Cardiovascular Events

CVD was defined as first-ever development of coronary heart disease (CHD) or stroke. The criteria for a diagnosis of CHD included first-ever acute myocardial infarction, silent myocardial infarction, sudden cardiac death within 1 hour after the onset of acute illness, or coronary artery disease followed by coronary artery bypass surgery or angioplasty.[32] Acute myocardial infarction was diagnosed when a subject met at least 2 of the following criteria: (1) typical symptoms, including prolonged severe anterior chest pain; (2) abnormal cardiac enzymes more than twice the upper limit of the normal range; (3) evolving diagnostic electrocardiographic changes; and (4) morphological changes, including local asynergy of cardiac wall motion on electrocardiography, persistent perfusion defect on cardiac scintigraphy, or myocardial necrosis or scars >1 cm long accompanied by coronary atherosclerosis at autopsy. Silent myocardial infarction was defined as myocardial scarring without any historical indication of clinical symptoms or abnormal cardiac enzyme changes. Stroke was defined as a sudden onset of nonconvulsive and focal neurological deficit persisting for >24 hours. The diagnosis of stroke and the determination of its pathological type were based on the clinical history, neurological examination, and all available clinical data, including brain CT/MRI and autopsy findings. Stroke was classified as either ischemic or hemorrhagic.[32]

Risk Factor Measurement

At the baseline examination, each participant completed a self-administered questionnaire covering medical history, exercise, treatment for hypertension or diabetes, smoking habits, and alcohol intake. The questionnaire was checked by trained interviewers at the screening. The subjects engaging in sports or other forms of exertion ≥3 times a week during their leisure time made up a regular exercise group. Smoking habits and alcohol intake were classified into currently habitual or not.

Blood pressure was measured 3 times using a standard mercury sphygmomanometer in the sitting position after rest for at least 5 minutes. The mean of the 3 measurements was used for the analysis. Hypertension was defined as blood pressure ≥140/90 mm Hg and/or current use of antihypertensive agents. The waist circumference was measured at the umbilical level in a standing position by a trained staff member. Body height and weight were measured in light clothing without shoes and the body mass index (kg/m^2) was calculated. Electrocardiographic abnormalities were defined as left ventricular hypertrophy (Minnesota code, 3 to 1) and/or ST depression (Minnesota code, 4 to 1, 2, or 3).

Blood samples were collected from an antecubital vein after an overnight fast for the determination of lipids and blood glucose levels. Serum total cholesterol, triglycerides, and high-density lipoprotein cholesterol concentrations were determined enzymatically. Fasting blood glucose levels were measured by the glucose oxidase method. Diabetes was defined as fasting blood glucose ≥126 mg/dL (7.0 mmol/L) and/or current use of insulin or oral medication for diabetes. Fresh voided urine samples were collected at the examination and proteinuria was defined as 1+ or more using a reagent strip.

Definition of Metabolic Syndrome

MetS was defined by using criteria recommended in the NCEP Adult Treatment Panel III guideline[5] with a modification. Specifically, abdominal obesity was defined as a waist circumference >90 cm in men and >80 cm in women according to International Obesity Task Force central obesity criteria for Asia.[33] Elevated blood pressure was defined as average systolic/diastolic blood pressures of ≥130/85 mm Hg and/or current use of antihypertensive medicine. Hypertriglyceridemia was defined as serum triglycerides of ≥1.69 mmol/L. Low high-density lipoprotein cholesterol was defined as serum high-density lipoprotein cholesterol levels of <1.03 mmol/L in men and of <1.29 mmol/L in women. Elevated blood glucose level was defined as fasting blood glucose of ≥6.10 mmol/L and/or current use of insulin or oral medication for diabetes. MetS was defined as the presence of 3 or more of these components.[5]

Statistical Analysis

The SAS software package (SAS Institute, Inc, Cary, NC) was used to perform all statistical analyses. Serum triglycerides were transformed into logarithms to improve the skewed distribution. The statistical significance of differences in mean values of continuous variables and frequencies of categorical variables was examined using the Student t test and χ^2 test as appropriate. The incidences were calculated by the person-year method. Differences in incidences between MetS status were tested by the Cox proportional hazards regression analysis after adjustment for age. The age- or multivariate-adjusted hazard ratios (HRs) and 95% CIs were also estimated with the use of the Cox proportional hazards model. $P<0.05$ was considered statistically significant in all analyses.

Results

The overall prevalence of MetS at baseline was 25.9%. The baseline characteristics on the basis of sex and MetS are shown in Table 1. Men with MetS had significantly higher mean values of blood pressures, waist circumference, body mass index, fasting blood glucose, and serum triglycerides and lower mean values of serum high-density lipoprotein cholesterol compared with those without MetS. Moreover, the frequencies of antihypertensive medication, hypertension, proteinuria, diabetes, and alcohol intake were higher in men with MetS than in those without MetS. A similar distribution was observed in women with MetS in terms of the previously mentioned variables except for alcohol intake. In addition, women with Mets were significantly older and had higher serum total cholesterol compared with those without MetS.

During the 14-year follow up, 307 first-ever CVD events (158 men and 149 women) occurred. Of these, there were 125 CHD (78 men and 47 women) and 209 stroke events (94 men and 115 women). The age-adjusted incidences of CVD were significantly higher in subjects with MetS compared with those without MetS for both sexes (men: 21.8 versus 11.6 per 1000 person-years, $P<0.01$; women: 12.9 versus 6.5, $P<0.01$) (Table 2). The same was true for CHD incidence in both sexes (men: 9.2 versus 5.7, $P<0.01$; women: 5.1 versus 1.5, $P<0.01$) and for stroke in men (14.1 versus 6.4, $P<0.01$). When we divided strokes into ischemic and hemorrhagic type, the age-adjusted incidences of ischemic stroke were