Table 2. Risks for the development of cardiovascular disease, total stroke and coronary heart disease according to smoking status

	Events/ population	Age- and sex-adjusted			Multivariate-adjusted		
		HR	95% CI	p	HR	95% CI	p
Cardiovascular disease							
Never smoker	137/1,477	1.00			1.00		
Former smoker	50/332	1.26	0.83–1.91	0.29	1.25	0.80–1.93	0.32
Current smoker (<20 cigarettes/day)	54/348	1.60	1.09–2.34	0.02	1.80	1.21–2.66	0.004
Current smoker (≥20 cigarettes/day)	40/264	1.88	1.20–2.95	0.006	2.04	1.29–3.24	0.003
Total stroke							
Never smoker	104/1,477	1.00			1.00		
Former smoker	34/332	1.52	0.91–2.52	0.11	1.53	0.90–2.61	0.12
Current smoker (<20 cigarettes/day)	34/348	1.70	1.07–2.71	0.02	1.90	1.18–3.06	0.009
Current smoker (≥20 cigarettes/day)	22/264	1.87	1.05–3.32	0.03	2.01	1.11–3.65	0.02
Coronary heart disease							
Never smoker	43/1,477	1.00			1.00		
Former smoker	23/332	1.19	0.63–2.26	0.60	1.10	0.56–2.15	0.78
Current smoker (<20 cigarettes/day)	25/348	1.61	0.88–2.93	0.12	1.88	1.02–3.47	0.04
Current smoker (≥20 cigarettes/day)	21/264	2.07	1.07–4.01	0.03	2.31	1.17–4.57	0.02

Multivariate-adjusted: adjusted for age, sex, systolic blood pressure, diabetes, total cholesterol, body mass index, electrocardiogram abnormalities, alcohol intake and regular exercise.

Table 3. Risks for the development of stroke subtypes according to smoking status

	Events/ population	Age- and sex-adjusted			Multivariate-adjusted		
		HR	95% CI	p	HR	95% CI	p
Ischemic stroke							
Never smoker	69/1,477	1.00			1.00		
Former smoker	26/332	1.72	0.95–3.12	0.08	1.70	0.90–3.20	0.10
Current smoker	37/612	1.78	1.05–3.01	0.03	2.03	1.18–3.49	0.01
Intracerebral hemorrhage							
Never smoker	24/1,477	1.00			1.00		
Former smoker	7/332	1.00	0.34–2.91	>0.99	1.11	0.37–3.33	0.85
Current smoker	12/612	1.20	0.48–3.00	0.70	1.21	0.47–3.15	0.70
Subarachnoid hemorrhage							
Never smoker	11/1,477	1.00			1.00		
Former smoker	1/332	0.86	0.09–8.32	0.89	0.92	0.09–9.08	0.95
Current smoker	7/612	3.39	1.00–11.54	0.051	3.85	1.05–14.13	0.04

Multivariate-adjusted: adjusted for age, sex, systolic blood pressure, diabetes, total cholesterol, body mass index, electrocardiogram abnormalities, alcohol intake and regular exercise.

cholesterolemia significantly increased the risks of total stroke and CHD, and their interactions were statistically significant. In regard to stroke subtypes, similar findings were observed in the risks of ischemic stroke and subarachnoid hemorrhage, although interaction was significant only for subarachnoid hemorrhage.

Discussion

In the present study of a population-based cohort in Japan, current smoking was an independently significant risk factor for the development of stroke and CHD. In regard to stroke subtypes, current smoking was clear-

Table 4. Combined and separate effects of smoking and each risk factor on the development of cardiovascular disease

	Events/ population	Multivariate-adjusted		
		HR	95% CI	p
Hypercholesterolemia				
Current smoking (–)/hypercholesterolemia (–)	108/1,099	1.00		
Current smoking (–)/hypercholesterolemia (+)	79/710	1.08	0.80–1.47	0.60
Current smoking (+)/hypercholesterolemia (–)	57/435	1.36	0.96–1.93	0.08
Current smoking (+)/hypercholesterolemia (+)	37/177	2.68	1.81–3.95	<0.001
p for interaction				0.001
Hypertension				
Current smoking (–)/hypertension (–)	67/1,103	1.00		
Current smoking (–)/hypertension (+)	120/706	1.87	1.36–2.57	<0.001
Current smoking (+)/hypertension (–)	44/388	1.83	1.22–2.76	0.003
Current smoking (+)/hypertension (+)	50/224	2.97	1.98–4.45	<0.001
p for interaction				0.22
Diabetes				
Current smoking (–)/diabetes (–)	142/1,602	1.00		
Current smoking (–)/diabetes (+)	45/207	1.74	1.23–2.46	0.002
Current smoking (+)/diabetes (–)	73/524	1.70	1.24–2.34	0.001
Current smoking (+)/diabetes (+)	21/88	2.83	1.73–4.63	<0.001
p for interaction				0.82
Obesity				
Current smoking (–)/obesity (–)	139/1,348	1.00		
Current smoking (–)/obesity (+)	48/461	0.93	0.66–1.30	0.66
Current smoking (+)/obesity (–)	68/480	1.49	1.07–2.07	0.02
Current smoking (+)/obesity (+)	26/132	2.10	1.34–3.28	0.001
p for interaction				0.07
Alcohol intake				
Current smoking (–)/alcohol intake(–)	138/1,402	1.00		
Current smoking (–)/alcohol intake (+)	49/407	0.81	0.55–1.19	0.29
Current smoking (+)/alcohol intake (–)	39/250	1.19	0.79–1.80	0.40
Current smoking (+)/alcohol intake (+)	55/362	1.15	0.75–1.75	0.52
p for interaction				0.58
Regular exercise				
Current smoking (–)/regular exercise (–)	166/1,622	1.00		
Current smoking (–)/regular exercise (+)	20/185	0.81	0.51–1.29	0.38
Current smoking (+)/regular exercise (–)	89/556	1.83	1.36–2.48	<0.001
Current smoking (+)/regular exercise (+)	5/56	0.57	0.23–1.42	0.23
p for interaction				0.08

Current smoking (–) includes both never and former smoking. Multivariate-adjusted: adjusted for age, sex, systolic blood pressure, diabetes, total cholesterol, body mass index, electrocardiogram abnormalities, alcohol intake and regular exercise. The variable relevant to the subgroup was excluded from each model.

ly associated with the development of ischemic stroke and subarachnoid hemorrhage, but not with intracerebral hemorrhage. These findings are concordant with previously reported meta-analyses based mainly on Caucasian populations [1, 2]. In addition, we demonstrated that hypercholesterolemia strengthened the harmful effects of smoking on these outcomes, but such effects were not observed for other risk factors: hypertension, diabetes, obesity, alcohol intake and regular exercise.

Several injurious effects of cigarette smoking on arteries have been demonstrated. Smoking causes direct injury to endothelial cells [16], oxidation of low-density lipoprotein [17], and acceleration of thrombus formation through increased plasma fibrinogen [18], increased platelet aggregability [19] and decreased fibrinolytic ac-

Table 5. Combined and separate effects of smoking and hypercholesterolemia on the development of stroke and coronary heart disease

	Events/ population	Multivariate-adjusted		
		HR	95% CI	p
Total stroke				
Current smoking (–)/hypercholesterolemia (–)	83/1,099	1.00		
Current smoking (–)/hypercholesterolemia (+)	55/710	0.92	0.65–1.31	0.64
Current smoking (+)/hypercholesterolemia (–)	36/435	1.34	0.87–2.06	0.19
Current smoking (+)/hypercholesterolemia (+)	20/177	2.08	1.25–3.45	0.005
p for interaction				0.048
Ischemic stroke				
Current smoking (–)/hypercholesterolemia (–)	54/1,099	1.00		
Current smoking (–)/hypercholesterolemia (+)	41/710	1.14	0.74–1.74	0.55
Current smoking (+)/hypercholesterolemia (–)	23/435	1.37	0.80–2.33	0.25
Current smoking (+)/hypercholesterolemia (+)	14/177	2.24	1.21–4.14	0.01
p for interaction				0.15
Intracerebral hemorrhage				
Current smoking (–)/hypercholesterolemia (–)	19/1,099	1.00		
Current smoking (–)/hypercholesterolemia (+)	12/710	0.87	0.41–1.85	0.72
Current smoking (+)/hypercholesterolemia (–)	10/435	1.29	0.55–3.03	0.56
Current smoking (+)/hypercholesterolemia (+)	2/177	0.86	0.19–3.80	0.84
p for interaction				0.83
Subarachnoid hemorrhage				
Current smoking (–)/hypercholesterolemia (–)	10/1,099	1.00		
Current smoking (–)/hypercholesterolemia (+)	2/710	0.25	0.05–1.15	0.08
Current smoking (+)/hypercholesterolemia (–)	3/435	1.54	0.35–6.72	0.57
Current smoking (+)/hypercholesterolemia (+)	4/177	5.31	1.52–18.54	0.009
p for interaction				0.005
Coronary heart disease				
Current smoking (–)/hypercholesterolemia (–)	34/1,099	1.00		
Current smoking (–)/hypercholesterolemia (+)	32/710	1.59	0.96–2.65	0.07
Current smoking (+)/hypercholesterolemia (–)	26/435	1.63	0.95–2.81	0.08
Current smoking (+)/hypercholesterolemia (+)	20/177	3.72	2.09–6.63	<0.001
p for interaction				0.01

Current smoking (–) includes both never and former smoking. Multivariate-adjusted: adjusted for age, sex, systolic blood pressure, diabetes, body mass index, electrocardiogram abnormalities, alcohol intake and regular exercise.

tivity [20], all of which are associated with the development of atherosclerotic diseases such as ischemic stroke and CHD. Smoking is also considered to cause the formation, growth and rupture of intracranial aneurysms [21, 22], probably due to an elastase/α_2-antitrypsin imbalance in the artery wall [23], leading to an elevated risk of subarachnoid hemorrhage [21, 22, 24].

While smoking is an established risk factor for CHD [4, 5], there is no consensus on whether or not smoking raises the risk of ischemic stroke in Japanese [4–8]. Using the first cohort of the Hisayama study, established in 1961, we previously reported that smoking was not a risk factor for ischemic stroke [4]. Similarly, no obvious relationship between smoking and ischemic stroke was observed in some old cohort studies in Japan that started their follow-up in the 1960s [6, 7]. On the other hand, some other recent cohort studies in Japan [5, 8], as well as our present study, showed statistical associations between smoking and the risk of ischemic stroke. We consider that these different conclusions can be explained in 2 possible ways. One is a secular change in the prevalence of hypercholesterolemia. According to our cross-sectional surveys in Hisayama, the prevalence of hypercholesterolemia was very low in 1961 (2.8% in men, 6.6% in women) but increased greatly in the following 4 decades (to 25.8% in men and 41.6% in women in 2002) [25]. Therefore, the harmful effect of smoking on the development of ischemic stroke might be obscured in studies in which the

population prevalence of hypercholesterolemia was low. The other possible reason is a change in the distribution of ischemic stroke subtypes. In Hisayama, while the proportion of lacunar infarctions among all ischemic stroke events has decreased during the past 4 decades, the proportions of atherothrombotic and cardioembolic stroke have increased [25]. These changes might affect the influence of smoking on the development of ischemic stroke.

In previous studies, the relationship between smoking and the risk of intracerebral hemorrhage has been reported to be inconsistent. A few cohort studies [26, 27] showed that current smoking increased the risk of intracerebral hemorrhage, while other studies [5–8, 12, 28], including a meta-analysis [1] and ours, found no discernible association between the two. The reasons for these inconsistent conclusions are unknown. However, because smoking increases hypercoagulability rather than bleeding tendency [18–20], the effect of smoking on the risk of intracerebral hemorrhage seems to be weak, if any.

Because smoking oxidizes low-density lipoprotein [17], it is reasonable to think that the combination of smoking and hypercholesterolemia may accelerate the progression of atherosclerosis and the development of ischemic stroke and CHD. Some studies have evaluated the interaction between smoking and hypercholesterolemia in relation to CVD outcomes. However, the conclusions have not been consistent [4, 9–13]. In the present study, the synergistic effect of smoking and hypercholesterolemia on the development of CHD was significant, and a similar tendency was observed for ischemic stroke. Another Japanese cohort study [9] also demonstrated positive interactions between smoking and cholesterol for ischemic stroke and CHD mortality. On the other hand, the first cohort of the Hisayama study, established in 1961 [4], as well as the Asia Pacific Cohort Studies Collaboration [10], confirmed a positive interaction for CHD but not for ischemic stroke. Two Korean cohort studies [11, 12] and a meta-analysis of mainly Caucasian studies [13] did not find any interactions for CVD outcomes. These inconsistent conclusions may be explained in part by ethnicity and differences in average cholesterol levels. The effects of smoking and cholesterol on CVD outcomes may differ between Asians and Caucasians. Among Asian studies, the average cholesterol levels were lower in the first cohort of Hisayama [4], Pacific Cohort Studies Collaboration [10] and 2 Korean studies [11, 12] compared with the present study. We have no clear explanation of the synergistic effect of smoking and hypercholesterolemia on the risk of subarachnoid hemorrhage. In any case, we cannot draw any conclusion from the present results because of the small number of subarachnoid hemorrhages in our study. Our finding should be confirmed in larger cohort studies.

The advantages of the present analyses include accurate measurement of risk factors at baseline, the longitudinal population-based study design, the long duration of follow-up, perfect follow-up of study subjects and accurate diagnoses of CVD. However, a possible limitation should be discussed. Because we did not consider changes in smoking habits and other risk factors or treatments that occurred during the follow-up, our results may underestimate the effects of smoking and other risk factors on the risk of CVD.

In conclusion, we demonstrated that current smoking increases the risk of ischemic stroke, subarachnoid hemorrhage and CHD, especially in individuals with hypercholesterolemia. Although the smoking rates in Japanese men and women have been decreasing in the past 4 decades [25], Japanese men still have a higher smoking rate than people in Western countries [3]. Our findings highlight the importance of smoking cessation to reduce the burden of CVD in Japan, where the prevalence of hypercholesterolemia is escalating rapidly [25].

Acknowledgments

We thank the residents of Hisayama and the staff of the Division of Health and Welfare of Hisayama for their cooperation in this study. This study was supported in part by Grants-in-Aid for Scientific Research C (20591063, 21590698 and 22590892) from the Ministry of Education, Culture, Sports, Science and Technology of Japan, and by a Health and Labour Sciences Research Grant from the Ministry of Health, Labour and Welfare of Japan (Comprehensive Research on Aging and Health: H20-Chouju-004).

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〈原　著〉

地域一般住民高齢者・非高齢者における腹部肥満の糖尿病発症リスクに関する検討—端野・壮瞥町研究—

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要　約　**目的**：地域一般住民における腹部肥満と糖尿病発症との関連について高齢者と非高齢者での影響の違いを，端野・壮瞥町住民健診受診者のデータから検討した．**方法**：1994年に住民健診を受診し，かつ2003年または2004年にも健診を受診した1,023名中，データ欠損者，1994年の時点での糖尿病者（空腹時血糖値≧126 mg/d *l* または糖尿病治療中の者）を除いた827名を対象とした．1994年のデータに基づいて65歳以上の高齢者群，65歳未満の非高齢者群に分け，さらに日本のメタボリックシンドローム診断基準に基づいて腹部肥満群と非腹部肥満群に分けた．上記4群において，2003・04年の受診時点での糖尿病発症者の頻度を比較検討した．**結果**：非高齢者群においては非腹部肥満群に対し腹部肥満群からの糖尿病発症が有意に高率であったが，高齢者群において統計学的有意差は認められなかった．非高齢者・高齢者で糖尿病発症を従属変数とし，年齢，性別，総コレステロール，収縮期血圧値，喫煙の有無，糖尿病発症家族歴有無，空腹時血糖110 mg/d *l* の有無で調整したロジスティック回帰分析では，高齢者群において腹部肥満は関連要因とはならず，非高齢者群ではオッズ比2.68で糖尿病発症の有意なリスクとなった．腹部肥満の有無と血圧高値，血糖高値，脂質異常症の危険因子集積の有無を同時にモデルにいれたロジスティック回帰分析では，非高齢者群で腹部肥満が3.10，危険因子集積が3.00とそれぞれ独立して新規糖尿病発症の有意なリスクとなったが，高齢者群では，危険因子集積のみが3.70と新規糖尿病発症の有意なリスクとなった．**結論**：65歳未満の非高齢者において青壮年期からの腹部肥満への介入が重要であるのはもちろんのこと，高齢者においては腹部肥満なしと判定される者の中でも危険因子集積者は糖尿病のハイリスクであるため，生活習慣見直し等の介入が必要となる可能性が示唆された．

Key words：高齢者，腹部肥満，糖尿病，インスリン抵抗性，端野・壮瞥町研究

（日老医誌　2011；48：71–77）

緒　言

糖尿病患者は世界的に増加傾向にあり，2000年の1億7,100万人から2030年には3億6,600万人に増加すると推計されており，特に65歳以上の高齢糖尿病者の増加が懸念されている[1)]．またアジア地域では肥満者の増加と共に糖尿病患者が急増しており[2)]，日本でも生活習慣の欧米化により糖尿病患者は増加傾向で，厚生労働省の調査では2002年の740万人から2007年では890万人へと増加している．特に高齢者において糖尿病とその予備群の増加が顕著であり，高齢者における糖尿病予防対策は極めて重要であると考えられる．

近年，内臓脂肪の蓄積から動脈硬化危険因子が個人に集積する病態としてメタボリックシンドロームが注目され，心血管疾患イベントのみならず糖尿病発症と密接に関係するという報告がされている[3)4)]．わが国において2008年度より開始された特定健診・特定保健指導においてはメタボリックシンドロームが重要な骨子として採用されており[5)]，心血管疾患や糖尿病も含めた種々の生活習慣病の予防対策としてメタボリックシンドロームに該当する者やその予備群に積極的に介入を行うことになっている．その中でも腹囲径によって判定される腹部肥満は保健指導対象者の階層化の最初のステップであり，現在の腹部肥満の基準が将来の生活習慣病罹患に与える影響を検討することは重要である．

高齢者の糖尿病発症は，耐糖能異常からの発症が多く[6)]，その原因としては加齢によるインスリン抵抗性の増大や内臓脂肪の蓄積といった体組成の変化などが知ら

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3）H. Ohnishi, S. Saitho, K. Shimamoto：札幌医科大学医学部内科学第二講座
受付日：2010.7.5，採用日：2010.10.6

れているが，腹囲径によって判定される腹部肥満が糖尿病発症に与える影響に関する報告は少ない．特に，特定健診・特定保健指導では生活習慣改善による予防効果は若年の方が高いという理由から，65歳以上の高齢者に対しては，積極的支援の対象になった場合でも動機付け支援に留めることとなっている．よって階層化の最初のステップとなる腹部肥満が将来の糖尿病の罹患に与える影響について高齢者と非高齢者での影響の違いを検討することは非常に重要である．

今回我々は端野・壮瞥町住民健診受診者を対象に地域一般住民における高齢者と非高齢者における腹部肥満の糖尿病罹患に与える影響について検討を行った．

方　法

端野・壮瞥町研究は1976年に札幌医大第二内科で開始された疫学研究である[6][7]．今回は1994年の受診者1,934名から2003年あるいは2004年にも受診した1,023名中，体重，腹囲，血圧などのデータ欠損者および1994年の時点での糖尿病者（空腹時血糖値（FPG）≧126 mg/d*l*または糖尿病治療中の者）を除いた827名（男性347名：平均年齢59.6±9.0歳，女性480名：平均年齢58.3±8.5歳）が解析対象となった．

早朝空腹時に身長，体重，臍周囲腹囲径，安静坐位にて血圧値（収縮期血圧（SBP），拡張期血圧（DBP））を測定し，採血にて血糖値，総コレステロール値（T. chol），中性脂肪値（TG），HDLコレステロール値（HDL-C）を測定した．服薬状況や喫煙状況，糖尿病家族歴に関しては保健師の問診により確認した．

1994年の健診データに基づいて65歳未満の非高齢者群と65歳以上の高齢者群の2群に分け，さらにわが国のメタボリックシンドローム診断基準[8]に基づいて腹部肥満（AO）群と非腹部肥満（Non-AO）群の2群に分け，高齢者・非高齢者別にAO，Non-AOからの2003・04年の健診時の新規糖尿病者（FPG≧126 mg/d*l*または1994年から2003・04年までの間に糖尿病治療が開始となった者）の割合を比較した．また血圧高値（SBP≧130 mmHgかつ/またはDBP≧85 mmHgかつ/または高血圧治療中），血糖高値（110 mg/d*l*≦FPG＜126 mg/d*l*），脂質代謝異常（TG≧150 mg/d*l*かつ/またはHDL-C＜40 mg/d*l*かつ/または脂質異常症治療中）の危険因子のうち二つ以上をもつ者を集積群，二つ未満を非集積群とし，初年度の危険因子の集積の有無が糖尿病罹患に与える影響についても高齢者・非高齢者別に検討を行った．

また2003・04年の健診では空腹時血漿インスリン値（FIRI）も測定しているため，断面成績の結果から腹部肥満の有無とHOMA-R（＝FPG×FIRI/405）を指標としたインスリン抵抗性との関連を高齢者・非高齢者別に検討した．なおこの解析においては治療中の者も含めた糖尿病者を除外して検討を行っている．インスリン抵抗性の評価としては教室既報の結果より[9]HOMA-R≧1.73をインスリン抵抗性あり，HOMA-R＜1.73をインスリン抵抗性なしと判定し，高齢者・非高齢者群，AO・Non-AO群でのインスリン抵抗性者の頻度を比較検討した．

統計解析はIBMSPSS ver. 17.0を使用した．統計学的有意水準は$p<0.05$とし，値は平均値±標準偏差で表した．連続変数の差の検定にはunpaired　t-testを，頻度の差の検定にはχ^2検定を用いた．また2003・04年の健診時の新規糖尿病の有無を従属変数としたロジスティック回帰分析を用いて，腹部肥満や危険因子集積の有無のオッズ比を算出した．交絡要因としては年齢，性別，喫煙，糖尿病家族歴，T. chol，SBPを考慮した．

本研究は札幌医科大学倫理委員会の承認を得ており，また健診受診者全員に研究内容を説明の上，文書による同意が得られた者のみを対象とした．

結　果

Non-AO群とAO群別の高齢者・非高齢者の背景を示す（表1）．Non-AO群では年齢以外にSBP，DBP，FPGが高齢者において非高齢者に比べて有意に高値であった．AO群では高齢者・非高齢者間で年齢以外の項目に有意な差はみられなかった．

高齢者・非高齢者別に初年度の腹部肥満の有無からの糖尿病発症頻度を比較したところ，非高齢者群においてはNon-AO群に対しAO群からの糖尿病発症頻度が有意に高率であった（Non-AO群5.4% vs. AO群16.9%，$p<0.0001$）が，高齢者群においてはNon-AO群に対してAO群からの糖尿病発症頻度は高い傾向にはあったが統計学的有意差は認められなかった（Non-AO群7.1% vs.AO群12.7%）（図1）．

また初年度の腹囲径と新規糖尿病発症との関連を検討すると，非高齢者では腹囲径の増大とともに糖尿病発症頻度が増加し（男性：p for trend＝0.008，女性：p for trend＝0.021），80 cm以上になると増加する傾向にあるが，高齢者では特に女性において80 cm未満の低い腹囲径からすでに糖尿病発症者の増加がみられ，統計的には有意な傾向は認められなかった（図2）．さらに新規糖尿病発症を従属変数としたロジスティック回帰分析において，年齢，性別，T. chol，SBP，喫煙の有無，糖尿病家族歴の有無，初年度の血糖高値の有無で調整すると，

表1　対象背景（1994年）

Non-AO群では年齢以外にSBP，DBP，FPGが高齢者において非高齢者に比べて有意に高値であり，AO群では高齢者・非高齢者間では年齢以外の項目に有意差を認めなかった．

	Non-AO (n=654)		AO (n=173)	
	非高齢者 n=484	高齢者 n=170	非高齢者 n=118	高齢者 n=55
Age	54.9±7.0	68.6±3.2**	56.5±7.2	69.2±4.1**
Male/Female	136/348	65/105	103/15	43/12
WC（cm）	74.5±6.8	76.3±6.5**	91.8±5.6	91.8±4.9
SBP（mmHg）	128.7±17.3	140.9±19.1**	135.9±16.8	139.6±18.9
DBP（mmHg）	76.5±9.6	79.0±8.7**	82.0±8.7	79.9±9.3
T.chol（mg/dl）	194.0±33.1	192.1±30.1	192.1±30.5	189.0±25.2
TG（mg/dl）	117.8±81.3	125.4±79.0	167.3±130.7	153.4±83.1
HDL-C（mg/dl）	57.8±13.4	56.0±4.0	50.3±12.1	49.5±13.8
FPG（mg/dl）	92.2±9.0	93.8±9.5*	98.2±9.4	97.5±10.5

*p<0.05，**p<0.01 vs. 非高齢者

WC：腹囲，SBP：収縮期血圧，DBP：拡張期血圧，T.chol：総コレステロール，TG：トリグリセリド，HDL-C：HDLコレステロール，FPG：空腹時血糖値

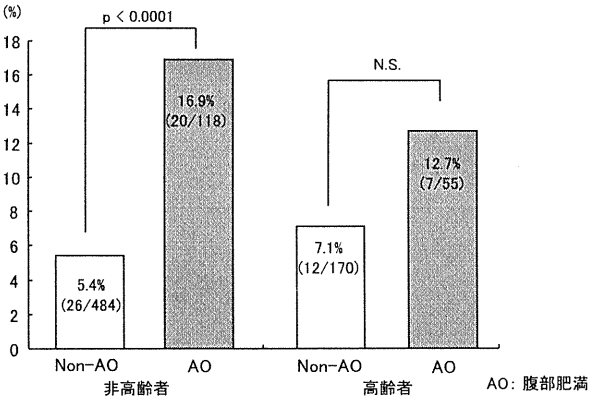

図1　高齢者・非高齢別の腹部肥満の有無での糖尿病発症頻度の比較

非高齢者群においてはNon-AO群に対しAO群からの糖尿病発症頻度が有意に高率であったが，高齢者群においてはNon-AO群に対してAO群からの糖尿病発症頻度は高い傾向にはあったが有意差は認められなかった

高齢者群において腹部肥満は有意なリスクとはならず，非高齢者群ではオッズ比2.68（95%CI：1.05～6.90）と新規糖尿病発症リスクとなった（表2）．

また腹部肥満の有無と危険因子集積の有無を同時にモデルに入れた場合，年齢，性別，T. chol，喫煙の有無，糖尿病家族歴の有無で調整したオッズ比は，非高齢者群においては腹部肥満で3.10（95%CI：1.26～7.63），危険因子集積が3.00（95%CI：1.89～4.76）とそれぞれ独立して有意な糖尿病発症のリスクとなったが，高齢者群において腹部肥満は有意なリスクとはならず，危険因子集積のみが3.70（95%CI：1.65～8.72）と糖尿病発症の有意なリスクとなった（表3）．

高齢者と非高齢者での腹部肥満の糖尿病罹患に対する影響の違いの原因を検討する目的で，2003・04年の断面調査からNon-AO・AO別に高齢者・非高齢者群におけるインスリン抵抗性者の頻度を比較検討すると，Non-AO群では非高齢者に比べ高齢者でのインスリン抵抗性者の頻度が有意に高値を示したが（高齢者8.6%vs非高齢者2.8%，p=0.015），AO群では高齢者において非高齢者よりも頻度は高い傾向にあるものの，統計学的に有意な差は認められなかった（高齢者23.8% vs. 非高齢者19.4%）（図3）．

考　察

今回の検討において，非高齢者では日本基準の腹部肥満が糖尿病のリスクとなるが，高齢者では有意なリスクとはならなかった．これまで腹部肥満を糖尿病のリスクとして多民族・人種間で検討した先行研究では，BMI25以下・25～30・30以上のいずれとも糖尿病は関係があったと報告[10]，またアジアでの糖尿病疫学研究では，2型糖尿病は短期間にその割合が増加し，欧米よりも比較的若年層からの発症や低いBMIからの発症が特徴であると報告されている[2]．両者とも年齢は直接的な要因ではなく，交絡要因として解析で調整されているため，高齢者と非高齢者で層別化して腹部肥満の影響度の違いを検討した報告はほとんどみられない．

また今回の解析において非高齢者では腹囲径の増大と

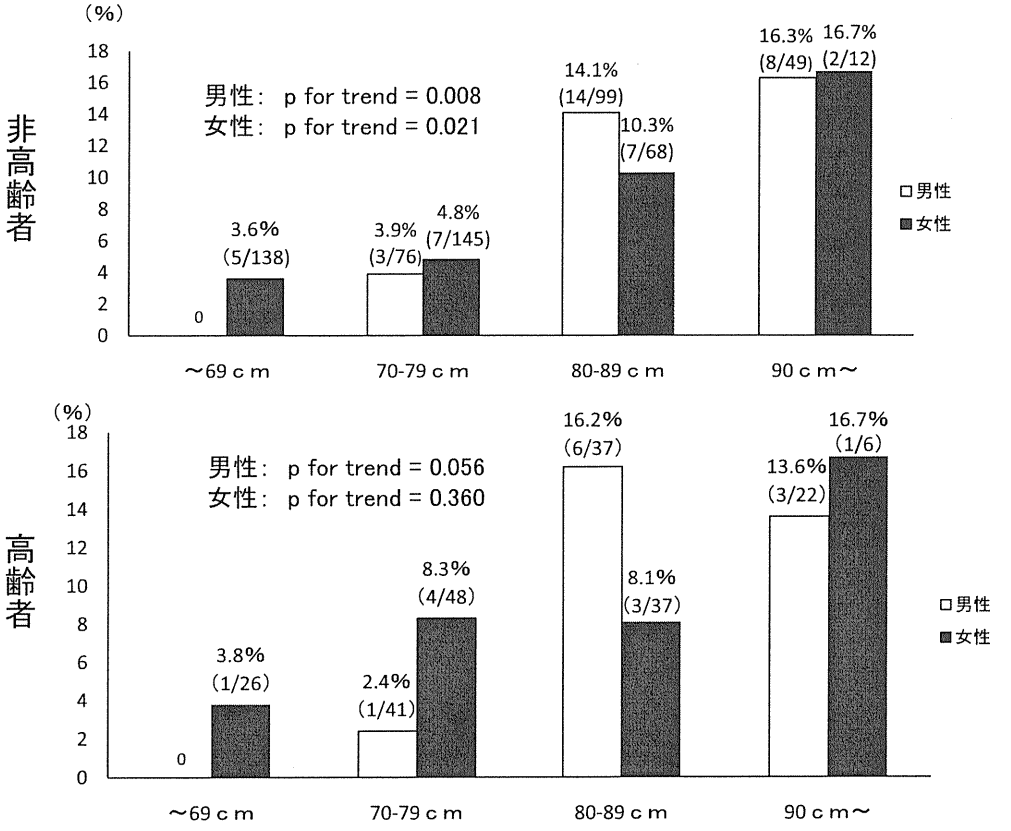

図2　高齢者・非高齢者別の各腹囲区分からの糖尿病発症頻度

初年度の腹囲径からの新規糖尿病発症の関連を検討すると，非高齢者では腹囲径の増大とともに糖尿病発症頻度が増加し，80 cm 以上になると増加する傾向にあるが，高齢者では特に女性において 80 cm 未満の低い腹囲径からすでに糖尿病発症者の増加がみられた

表2　ロジスティック回帰分析による高齢者・非高齢者別の腹部肥満の糖尿病発症に対するオッズ比

新規糖尿病発症を従属変数としたロジスティック回帰分析において，年齢，性別，T. chol，SBP，喫煙の有無，糖尿病家族歴の有無，初年度の血糖高値の有無で調整すると，高齢者群において腹部肥満は有意なリスクとはならず，非高齢者群では有意な新規糖尿病発症リスクとなった．

	Model 1	Model 2	Model 3
非高齢者	3.67** (1.67 ～ 8.27)	3.72** (1.59 ～ 8.67)	2.68* (1.05 ～ 6.90)
高齢者	1.47 (0.47 ～ 4.59)	1.60 (0.49 ～ 5.19)	0.67 (0.16 ～ 2.84)

*p＜0.05，**p＜0.01，（　）は 95% 信頼区間
T. chol：総コレステロール，SBP：収縮期血圧，FPG：空腹時血糖値
Model 1：年齢，性別で調整
Model 2：Model 1＋T. chol，SBP，喫煙，糖尿病家族歴で調整
Model 3：Model 2＋FPG≧110 mg/dl の有無で調整

ともに糖尿病発症頻度が増加するが，高齢者では特に女性においてはより低い腹囲径から糖尿病発症者の増加が認められた．すなわち高齢者では現在の腹囲基準で腹部肥満と判定されない群からも糖尿病発症が非高齢者より

表3　ロジスティック回帰分析による高齢者・非高齢者の腹部肥満と危険因子集積の糖尿病発症に対するオッズ比
腹部肥満の有無と危険因子集積の有無を同時にモデルに入れたロジスティック回帰分析では年齢，性別，T. chol，喫煙の有無，糖尿病家族歴の有無で調整したオッズ比は，非高齢者群においては腹部肥満，危険因子集積でそれぞれ独立して有意な糖尿病発症のリスクとなったが，高齢者群において腹部肥満は有意なリスクとはならず，危険因子集積のみが新規糖尿病発症の有意なリスクとなった．

		Model 1	Model 2
非高齢者	腹部肥満	2.54* (1.07 ～ 6.02)	3.10* (1.26 ～ 7.63)
	危険集積	2.68** (1.72 ～ 4.17)	3.00** (1.89 ～ 4.76)
高齢者	腹部肥満	0.84 (0.23 ～ 3.11)	0.81 (0.22 ～ 3.08)
	危険集積	3.72** (1.69 ～ 8.19)	3.70** (1.65 ～ 8.72)

*$p<0.05$，**$p<0.01$，（　）は95%信頼区間
T. chol：総コレステロール
Model 1：年齢，性別で調整
Model 2：Model 1＋T. chol，喫煙，糖尿病家族歴で調整

も多く認められる結果であった．

日本人糖尿病患者を対象とした先行研究では，高齢者では非肥満者においてもインスリン抵抗性者の頻度や危険因子集積者の頻度の増加が報告されている[11]．この中で腹部肥満とインスリン抵抗性の増大について年齢に伴う増加がみられ，腹囲とインスリン抵抗性に明確な関係があった．ただしインスリン抵抗性の増大は腹囲のみならず，メタボリックシンドロームを構成する危険因子集積があり腹部肥満がない事例でもみられたと報告している．本研究においても，腹部肥満群においては非高齢者も高齢者も確かにインスリン抵抗性が増大しているが，非腹部肥満群であっても高齢者では加齢による影響もありインスリン抵抗性を背景として危険因子が集積している者が非高齢者よりも多く含まれる結果であったことから，前述の報告を支持するものと考えられた．

またメタボリックシンドロームは内臓脂肪蓄積を上流にインスリン抵抗性を一つの背景として動脈硬化危険因子が集積する病態であり，心血管疾患イベントのリスクのみならず糖尿病発症のリスクとなることも報告されている[3]．久山町研究では，メタボリックシンドロームが空腹時血糖高値とは独立した糖尿病発症の予測因子として有用であると報告している[4]．この報告で使用されたメタボリックシンドロームの診断基準はATP-IIIであり腹囲基準は必須ではなくリスクの1つとして定義されている．本研究において危険因子集積が糖尿病発症の予測因子となったことは，この結果に矛盾しないものと考えられる．

非高齢者においては腹部肥満が有意な糖尿病発症予測因子であったのに対し，高齢者においては有意な予測因子とはならなかった理由として，一つには高齢者においては腹部肥満なしと判定される者にもインスリン抵抗性を背景とした危険因子集積者が非高齢者に比べて多く含まれており，腹部肥満の有無で2群に分けた場合，非腹部肥満群でも腹部肥満群と同程度に糖尿病リスクが高くなるために2群の差が薄まって有意な差として認められなかった可能性が考えられる．また，もう一つの可能性として，今回の検討において初年度にすでに糖尿病のため除外した者のうち約6割が65歳以上の高齢者であり，さらにその約半数が腹部肥満者であったことから，腹部肥満者は青壮年期から肥満傾向を認めておりそのような糖尿病発症のハイリスク者は65歳までには多くが糖尿病を発症しているため，65歳の時点で糖尿病でない腹部肥満者のその後の糖尿病発症リスクはそれほど高くならなかった可能性も考えられる．

三つ目の理由として，高齢者の体組成の変化として，筋肉等の除脂肪体重の減少に加え，脂肪組織でも皮下脂肪が相対的に減少して内臓脂肪が増加するという変化を示す[12)～14)]ことから，今回の検討での高齢者の非腹部肥満群の中には，腹囲径としては基準に該当しないものの相対的に内臓脂肪蓄積量が多い者が含まれるために，非腹部肥満群と腹部肥満群との間に有意な差が認められなかった可能性も考えられる．

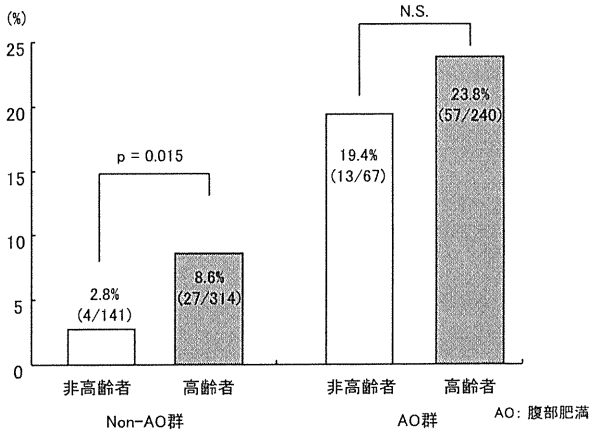

図3　HOMA-R≧1.73で判定したインスリン抵抗性の頻度2003・04年の断面調査からNon-AO・AO別に高齢者・非高齢者群におけるインスリン抵抗性者の頻度を比較検討すると，Non-AO群では非高齢者に比べ高齢者でのインスリン抵抗性者の頻度が有意に高値を示したが，AO群では高齢者において非高齢者よりも頻度は高い傾向にあるものの，統計学的に有意な差は認められなかった

本研究の限界について述べる．今回は1994年と2003・04年の両年受診者を解析対象としたため，解析対象とならなかった2003・04年受診なし群と今回の解析対象との間で初年度特性の比較をしたところ，2003・04年受診なし群において男性の比率が高く（2003・04受診あり群男/女：412/621，なし群男/女：427/484），平均年齢（2003・04受診あり群58.1±9.5，なし群63.0±13.2，$p<0.01$），SBP（2003・04受診あり群132.8±19.7，なし群140.0±21.9，$p<0.01$），DBP（2003・04受診あり群77.8±9.7，なし群79.6±10.1，$p<0.01$），FPG（2003・04受診あり群95.3±14.7，なし群101.4±39.7，$p<0.01$）が有意に高い傾向を示していた．よって，より高齢あるいは動脈硬化危険因子が重症な者ほど，死亡や入院あるいは医療機関での厳格な管理が必要となって10年後の健診を受診できなかった可能性が考えられ，今回の結果は10年後も健診を受診できる比較的健康状態がよく，また定期的に検診を受ける健康意識の高い者が中心となる対象での解析であり，結果を過小評価している可能性が考えられた．

また，今回は初年度の腹囲径と10年後の糖尿病罹患との関連を示したが，途中の時点での腹囲径は測定されておらず，腹囲径の変化がその後の糖尿病の罹患に与える影響については検討できなかった．本研究は観察研究であるが，腹囲径の変化がその後の糖尿病罹患に与える影響を検討することは重要であり，今後の検討課題であると考えられる．

結論として，非高齢者においては腹部肥満が強い糖尿病発症リスクとなることから青壮年期からの腹部肥満への介入が重要である．また特定健診・特定保健指導では65歳以上の前期高齢者においてはメタボリックシンドローム該当者にも動機付け支援を行うこととなっているが，今回の検討においては腹部肥満に該当しない高齢者にも将来の糖尿病のハイリスク者が非高齢者と比較して多く含まれていたことから，糖尿病予防の観点からは，高齢者の危険因子集積者においては例え腹部肥満の基準を満たさなくとも糖尿病予防のためのライフスタイル改善の指導が重要となる可能性が示唆された．

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Comparison of the effect of abdominal obesity on new onset of type 2 diabetes in a general Japanese elderly population with that in a non-elderly population-The Tanno and Sobetsu study

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Abstract

Aim: We investigated the effect of abdominal obesity (AO) on new onset of type 2 diabetes (NODM) in a general Japanese elderly population compared with that in a non-elderly population.

Methods: The subjects were 827 people aged 29-84 who underwent medical examinations in the towns of Tanno and Sobetsu in Hokkaido, first in 1994 and subsequently in either 2003 or 2004, after the exclusion of individuals with preexisting type 2 diabetes at baseline. The subjects were divided into 2 groups according to waist circumference (WC) at baseline: an AO (WC ≥85 cm for men and ≥90 cm for women) group and a non-AO group. The percentages of subjects with NODM recorded in either in 2003 or 2004 were compared between these 2 groups, and the AO odds ratio in NODM was calculated separately for elderly (≥65 years) and non-elderly (<65 years) subjects, using multiple logistic regression analysis.

Results: The percentage of non-elderly subjects with NODM was significantly higher in the AO group than in the non-AO group (16.9% vs. 5.4%, $p<0.0001$), but there was no statistically significant difference in the elderly subjects. Multiple logistic regression analysis showed that there was a significant relationship between AO and NODM (AO odds ratio in NODM = 2.68, 95% confidence interval (CI): 1.05-6.90) in the non-elderly subjects, but not in the elderly subjects.

Conclusion: Consideration of the different effects of AO on NODM in elderly and non-elderly people may be important for the prevention of type 2 diabetes.

Key words: *Elderly, Diabetes mellitus, Abdominal obesity, Insulin resistance, Tanno and Sobetsu study*
(Nippon Ronen Igakkai Zasshi 2011; 48: 71-77)

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Journal of Human Hypertension (2011), 1–9

www.nature.com/jhh

ORIGINAL ARTICLE

Matsuda–DeFronzo insulin sensitivity index is a better predictor than HOMA-IR of hypertension in Japanese: the Tanno–Sobetsu study

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Here we examined whether the Matsuda–DeFronzo insulin sensitivity index (ISI-M) is more efficient than the homeostasis model assessment of insulin resistance (HOMA-IR) for assessing risk of hypertension. Cross-sectional and longitudinal analyses were conducted using normotensive subjects who were selected among 1399 subjects in the Tanno–Sobetsu cohort. In the cross-sectional analysis ($n=740$), blood pressure (BP) level was correlated with HOMA-IR and with ISI-M, but correlation coefficients indicate a tighter correlation with ISI-M. Multiple linear regression analysis adjusted by age, sex, body mass index (BMI) and serum triglyceride level (TG) showed contribution of ISI-M and fasting plasma glucose, but not of HOMA-IR. In the longitudinal analysis ($n=607$), 241 subjects (39.7%) developed hypertension during a 10-year follow-up period, and multiple logistic regression indicated that age, TG, systolic BP and ISI-M, but not HOMA-IR, were associated with development of hypertension. In subjects <60 years old, odds ratio of new-onset hypertension was higher in the low ISI-M group (ISI-M, less than the median) than in the high ISI-M group for any tertile of BMI. In conclusion, ISI-M is a better predictor of hypertension than is HOMA-IR. Non-hepatic IR may be a determinant, which is independent of TG, BP level and BMI, of the development of hypertension.
Journal of Human Hypertension advance online publication, 17 March 2011; doi:10.1038/jhh.2011.23

Keywords: insulin resistance; Matsuda–DeFronzo insulin sensitivity index; HOMA-IR; epidemiology

Introduction

Hypertension, diabetes and dyslipidemia are life-threatening risk factors of cardiovascular events worldwide[1–4] and these lifestyle-related diseases tend to co-exist in the same individuals.[5–7] Insulin resistance (IR) is not only a hallmark of type 2 diabetes mellitus and metabolic syndrome but also frequently present in non-diabetic patients with hypertension. Accumulating evidence to date indicates that IR significantly contributes to accelerated atherosclerosis and development of cardiovascular events.[8–12] However, in contrast to its role in atherosclerosis, the role of IR in development of hypertension remains unclear. Acute hyperinsulinemic glucose clamp has been shown to induce sodium retention and activation of the sympathetic nervous system and renin–angiotensin system in humans.[13–15] However, results regarding the association of IR with hypertension in previous population studies are inconsistent.[16–25]

Although the inconsistency cannot be easily explained, use of different indices for assessment of IR might be responsible for the apparent contradiction between results of earlier studies. Insulin resistance in skeletal muscle is thought to contribute to the development of hypertension.[26–31] On the other hand, recent studies have shown that IR can occur separately in the liver and in skeletal muscles.[32] Current clinical indexes of insulin sensitivity (IS) are not specific to IS in the liver or that in the skeletal muscle.

The aim of the present study was to determine whether the Matsuda–DeFronzo index (ISI-M)[33] is a better predictor of hypertension than the homeostasis model assessment of IR (HOMA-IR).[33] To this end, we performed both a cross-sectional analysis and a longitudinal analysis using the same Japanese cohort, Tanno–Sobetsu cohort.[12,34–37] HOMA-IR[38] is easily calculated from fasting insulin and glucose levels and has thus been used in numerous clinical and epidemiological studies. However, this index basically represents IS of the liver and possibly underestimates IR of the skeletal muscle. On the

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Received 8 September 2010; revised 16 January 2011; accepted 15 February 2011

other hand, ISI-M incorporates plasma insulin and glucose levels after oral glucose loading, both of which depend on not only hepatic but also skeletal glucose disposition. We postulated that IR detected by ISI-M is more closely associated with elevation of blood pressure (BP) than is that by HOMA-IR. Results of the present study suggest that ISI-M is a better index of IR in terms of prediction of new-onset hypertension and that its contribution to development of hypertension is independent of serum triglyceride (TG) and BP level *per se*.

Subjects and methods

Study subjects

The protocol of the present study was approved by the Ethics Committee of Sapporo Medical University, and all of the study subjects gave informed consent for inclusion in the present investigation.

A total of 1399 residents of the towns of Tanno and Sobetsu in Hokkaido, Japan, who underwent health examinations in 1991 or 1992, (Residents of Tanno and those of Sobetsu attended the examinations in 1991 and 1992, respectively.) participated in the present protocol. To examine the relationship between IR and new-onset hypertension, we excluded subjects receiving treatment for hypertension, diabetes or dyslipidemia and those with untreated hypertension at the baseline examination. Hypertension was defined by criteria described below (BP determination and diagnosis of hypertension). An additional 10 subjects whose serum TG level at the baseline examination was $>400\,mg\,dl^{-1}$ were excluded, because that level of TG makes calculation of low-density lipoprotein cholesterol (LDL-C) concentration, by use of the Friedewald equation, invalid.[39] After the exclusion, 740 subjects remained and their data were used for cross-sectional analyses in the present study.

The study cohort was followed up by biannual health examinations, and data at 10 years after the baseline examination (that is, data in 2001 or 2002) were used for longitudinal analyses of new onset of hypertension and associated factors. As 133 subjects did not show up to receive a health examination at the 10-year follow-up, data from 607 subjects (254 males and 353 females, aged 57.6 ± 10.3 years) were used for the longitudinal analysis.

Blood pressure determination and diagnosis of hypertension

After a 5-min rest, BP was measured twice in the sitting position using a mercury sphygmomanometer. Patients were advised to refrain from smoking before BP determination and blood sampling. The average of two measurements was used for analysis. Subjects with systolic BP (SBP) $\geqslant 140$ mm Hg and/or diastolic BP (DBP) $\geqslant 90$ mm Hg or those who were treated for hypertension were defined as individuals with hypertension. This definition was used for diagnosis of hypertension at the baseline examination and during a 10-year follow-up. Information on medications, which study subjects were taking, was thoroughly collected by public nurses.

Oral glucose tolerance test and blood analyses

In the morning after a 10- to 12-h overnight fast, all participants underwent a 75-g oral glucose tolerance test (OGTT). Blood samples were taken for the determination of plasma glucose and insulin concentrations before and at 60 and 120 min after taking 75 g glucose solution (TRELAN-G75, 225 ml, Ajinomoto Pharmaceutical Co. Ltd., Tokyo, Japan). Plasma glucose and insulin levels were measured using the glucose oxidase method and the RIA beads method (Dainippon Sumitomo Pharma, Osaka, Japan), respectively. Fasting levels of serum total cholesterol, high-density lipoprotein-cholesterol and TG were determined by the cholesterol-oxidase-dimethoxy-aniline hydroxy-3-sulfopropyl (DAOS) method, dextran-sulfate magnesium-hydrochloride precipitation method and glycerol-3-phosphate-oxidase-DAOS method, respectively. LDL-C was calculated from the Friedewald equation.

Indices of insulin resistance

HOMA-IR[38] was calculated using the equation HOMA-IR = fasting glucose [mmol dl^{-1}] × fasting insulin [mU l^{-1}]/22.5. ISI-M[33] was calculated based on the results of OGTT: $ISI\text{-}M = 10\,000/(G_0 \times I_0 \times G_{mean} \times I_{mean})^{1/2}$, where G and I represents plasma glucose [mmol dl^{-1}] and insulin [mU l^{-1}] concentrations, respectively, and '0' and 'mean' indicates fasting value and mean value during OGTT, respectively.

Statistical analysis

Statistical analyses were conducted using JMP software version 7.0.1 for Windows (SAS Institute, Cary, NC, USA) and SPSS ver.12.0J for Windows (SPSS, Chicago, IL, USA). Numerical values are presented as means ± s.d.'s. Pearson correlation coefficient was calculated to evaluate correlations between the two variables. Differences in parameters between two study groups were tested by use of the unpaired *t*-test. The Meng–Rosenthal–Rubin method was used for testing difference in correlation coefficients between HOMA-IR and BP and those between ISI-M and BP. In cross-sectional analysis of the data, multiple linear regression analysis was carried out to assess the relationships between BP and IR indices. In longitudinal analysis of the data, odds ratio (OR) of new-onset hypertension was calculated by multiple logistic regression analysis. The χ^2-test was used for analyzing trend of incidence of hypertension across quartiles of HOMA-IR or ISI-M and between subgroups of HOMA-IR or ISI-M. Because of the skewed distribution of data, natural

logarithmic transformation was performed for glucose concentrations, insulin concentrations, HOMA-IR, ISI-M, and TG, high-density lipoprotein-cholesterol and LDL-C levels for regression analysis. *P*-values <0.05 were considered to be statistically significant.

Results

Cross-sectional analyses

Baseline characteristics of the study subjects are shown in Table 1. There was no significant difference between the male and female subjects in body mass index (BMI), HOMA-IR or ISI-M ($P=0.9$, 0.7 and 0.06, respectively), whereas levels of high-density lipoprotein-cholesterol and LDL-C were lower, and TG level was higher in the male subjects than in the female subjects. BMI values were low by Western standards but were comparable with BMI values in earlier population studies in Japan.[40,41] As shown in Figure 1, both SBP and DBP were significantly correlated with HOMA-IR ($r=0.12$ and $r=0.21$, $P<0.01$ for both) and with ISI-M ($r=-0.18$ and $r=-0.25$, $P<0.01$ for both). However, absolute values of correlation coefficients were significantly larger for ISI-M than for HOMA-IR (by Fisher's *z*-transformation; *z* values = 5.21 and 7.40 for SBP and DBP, respectively). SBP had significant correlation also with the level of fasting plasma glucose (FPG) ($r=0.16$, $P<0.0001$), plasma glucose at 120 min after glucose loading ($r=0.19$, $P<0.001$), fasting plasma insulin (FPI) ($r=0.09$, $P=0.02$) and plasma insulin at 120 min after glucose loading ($r=0.11$, $P=0.004$). In multiple linear regression analysis adjusted by age, sex, BMI and TG (Table 2), there was a weak association between SBP and ISI-M, but there was no significant association between SBP and HOMA-IR. A stronger association was observed between DBP and both ISI-M and HOMA-IR. A significant contribution to SBP and/or DBP variations was detected also for fasting plasma glucose, plasma glucose at 120 min after glucose loading and FPI but not for plasma insulin at 120 min after glucose loading.

Longitudinal analyses

Table 3 shows a comparison of baseline parameters between subjects who developed hypertension during the 10-year follow-up period and those who remained normotensive during the follow-up period. New-onset hypertension during the follow-up period was observed in 241 subjects (39.1% of total subjects). Subjects who developed hypertension were significantly older and their BMI, SBP, DBP, LDL-C, plasma glucose at 120 min after glucose loading and FPI levels were higher at baseline examinations compared with those who remained normotensive. However, baseline plasma level of plasma insulin at 120 min after glucose loading was not different between the two groups. Both HOMA-IR and ISI-M indicate lower IS at the baseline examination in subjects who developed hypertension during the follow-up period than in those with normal BP. In contrast to elevation of SBP and DBP, changes in BMI and TG during the 10-year follow-up period were not different between the group of subjects with new-onset hypertension and the group of normotensives (Table 3). After adjustment for both age and sex, the difference in baseline HOMA-IR between the two groups was statistically insignificant, though inter-group differences in baseline ISI-M, BMI, SBP, DBP, FPI, ΔSBP and ΔDBP remained significant.

To examine the relationship between level of IR and risk of hypertension, we compared incidences of hypertension during the 10-year follow-up in

Table 1 Baseline characteristics of study subjects

	Cross-sectional analysis (n = *740*)	*Longitudinal analysis* (n = *607*)	*Male*[a]	*Female*[a]	P-*value*
Age, (years old)	58.0 ± 10.2	57.6 ± 10.3	58.7 ± 10.7	56.8 ± 10.2	0.02
Male/female	316:434	254:353			
BMI, kg m^{-2}	23.3 ± 2.7	23.1 ± 2.7	23.1 ± 2.6	23.1 ± 2.7	0.9
SBP, mm Hg	124.8 ± 16.0	119.2 ± 10.9	120.0 ± 10.7	118.9 ± 11.1	0.3
DBP, mm Hg	74.9 ± 9.1	72.5 ± 7.5	73.2 ± 7.8	72.0 ± 7.3	0.07
TG, mg dl^{-1}	126.3 ± 95.4	113.6 ± 57.2	124.7 ± 59.9	105.6 ± 53.9	<0.0001
HDL-C, mg dl^{-1}	55.6 ± 13.8	55.9 ± 13.9	52.4 ± 14.1	58.5 ± 13.2	<0.0001
LDL-C, mg dl^{-1}	109.2 ± 32.6	110.1 ± 28.2	103.8 ± 26.9	114.5 ± 28.3	<0.0001
FPG, mmol l^{-1}	4.88 ± 0.58	4.8 ± 0.6	4.9 ± 0.6	4.8 ± 0.6	0.03
PG_{120}, mmol l^{-1}	5.76 ± 1.06	5.7 ± 1.0	5.8 ± 1.1	5.6 ± 1.0	0.007
FPI, mU l^{-1}	5.6 ± 3.2	5.5 ± 3.2	5.4 ± 3.5	5.6 ± 3.1	0.4
PI_{120}, mU l^{-1}	27.5 ± 18.6	26.7 ± 18.2	24.6 ± 19.5	28.2 ± 17.0	0.02
HOMA-IR	1.23 ± 0.75	1.20 ± 0.75	1.19 ± 0.82	1.21 ± 0.69	0.7
ISI-M	11.4 ± 6.3	12.3 ± 6.7	13.0 ± 7.3	11.9 ± 6.3	0.06

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; FPG, fasting plasma glucose; FPI, fasting plasma insulin; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment index of insulin resistance; ISI-M, Matsuda–DeFronzo insulin sensitivity index; LDL-C, low-density lipoprotein cholesterol; PG_{120}, plasma glucose at 120 min after 75-g glucose loading; PI_{120}, plasma insulin level at 120 min after 75-g glucose loading; SBP, systolic blood pressure; TG, serum triglyceride.
All values are shown as mean ± s.d.
[a]Subgroups in Longitudinal analysis.

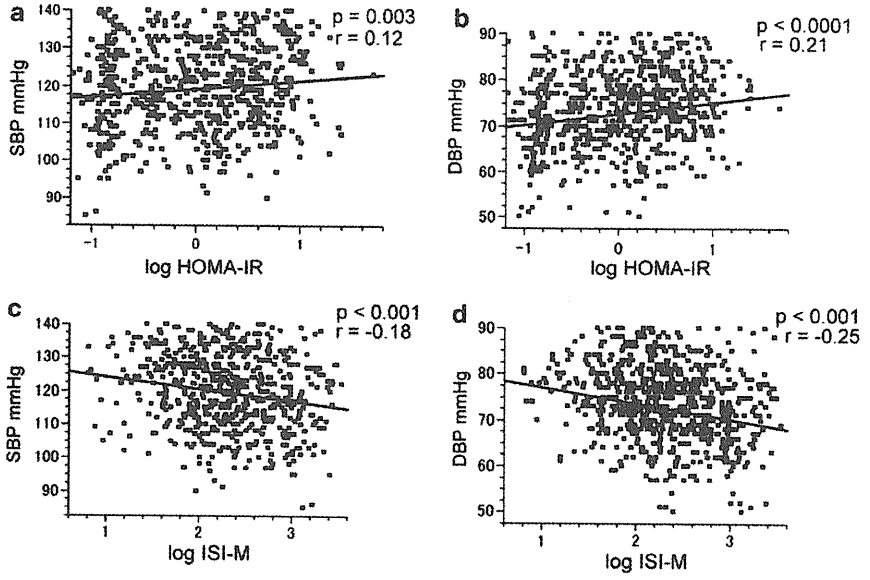

Figure 1 Relationship between blood pressure and an index of insulin sensitivity. Correlations between blood pressure levels with log HOMA-IR (panels **a**, **b**) and correlations between blood pressure levels with log ISI-M (panels **c**, **d**). DBP, diastolic blood pressure; HOMA-IR, homeostasis model assessment of insulin resistance; ISI-M, Matsuda–DeFronzo index; SBP, systolic blood pressure.

Table 2 Regression between blood pressure levels and indices of insulin sensitivity in multiple linear regression analysis adjusted by age, sex, BMI and TG in cross-sectional analysis ($n = 740$)

	SBP		*DBP*	
	β-*value*	P-*value*	β-*value*	P-*value*
FPG, mmol l^{-1}	0.12	0.006	0.06	0.03
PG_{120}, mmol l^{-1}	0.08	0.001	0.04	0.01
FPI, mU l^{-1}	0.05	0.7	0.20	0.04
PI_{120}, mU l^{-1}	0.01	0.6	0.02	0.2
HOMA-IR	0.72	0.3	1.42	0.006
ISI-M	−1.91	0.03	−2.13	0.001

Abbreviations: DBP, diastolic blood pressure; HOMA-IR, homeostasis model assessment index of insulin resistance; ISI-M, Matsuda–DeFronzo insulin sensitivity index; FPG, fasting plasma glucose; FPI, fasting plasma insulin; PG_{120}, plasma glucose at 120 min after 75-g glucose loading; PI_{120}, plasma insulin level at 120 min after 75-g glucose loading; SBP, systolic blood pressure; TG, serum triglyceride.

each quartile of HOMA-IR and ISI-M. As shown in Figure 2a, there was no significant difference in hypertension incidence between HOMA-IR subgroups. In contrast, incidences of hypertension were significantly higher in lower quartiles of ISI-M than in higher ISI-M quartiles (Figure 2b).

Multiple logistic regression analysis was used to identify factors significantly involved in the development of hypertension during the 10-year follow-up period. By use of the stepwise method, age, sex, TG and SBP, ISI-M, HOMA-IR and BMI were selected as independent variables from parameters that were significantly different between the groups with and without hypertension (Table 3) for the multiple logistic regression analysis. As IS is closely related to BMI, we used a model with an index of IS without BMI and a model with both an index of IS and BMI. In model 1, an index of IR (that is, ISI-M or HOMA-IR), age, sex, TG and SBP were used as independent variables. In model 2, BMI was added to independent parameters incorporated into model 1 (Table 4). In model 1, ISI-M was significantly associated with development of hypertension ($P = 0.029$, $\beta = -0.37$) as were TG and SBP, whereas a significant association of HOMA-IR with hypertension development could not be demonstrated. In model 2, significant association with hypertension was detected for age, TG, SBP and BMI but not for ISI-M or HOMA-IR.

As the regression dilution bias (that is, 'flattening' of the slope of the line describing the relation between an exposure variable and an outcome of interest by random measurement error in the exposure variable) might have underlain the lack of association between ISI-M and hypertension in model 2, we assessed the effects of IR on risk of hypertension development in different levels of BMI. Considering the effect of baseline age on hypertension development (Table 2), we first divided subjects into a group of <60 years old and a group of $\geqslant 60$ years old and then subjects in each age group were further divided by 3×2 factors (tertile of BMI and high or low IS) as shown in Figure 3. To divide subjects into insulin-sensitive and -insensitive subgroups, HOMA-IR of 1.73 and median value of ISI-M were used as cutoff values. The value of HOMA-IR (that is, 1.73) was based on our previous studies showing that HOMA-IR >1.73 predicts IR defined by the *M*-value determined by euglycemic glucose clamp ($M < 167.3$ mg m^{-2} per min) and that by insulin levels during 75-g OGTT.[35,36] As shown in Figure 3a, in subjects <60 years old, increase in OR of hypertension by IR was indicated in the first and third tertiles of BMI. However, such an effect of BMI

Table 3 Comparison of baseline parameters between study subjects who developed hypertension during the 10-year follow-up period and those who remained normotensive during the follow-up period

	Hypertension (+) (n = 241)	*Hypertension (−) (n = 366)*	P-*value*	P-*value after adjustment**
Sex (male/female)	101:140	153:213	0.9	—
Age, (years old)	59.4 ± 9.1	56.4 ± 10.9	0.0006	—
BMI, kg m^{-2}	23.6 ± 2.7	22.7 ± 2.6	<0.0001	<0.0001
SBP, mm Hg	123.7 ± 10.1	116.2 ± 10.5	<0.0001	<0.0001
DBP, mm Hg	74.5 ± 7.5	71.2 ± 7.2	<0.0001	<0.0001
TG, mg dl^{-1}	117.3 ± 56.6	111.2 ± 57.6	0.2	0.4
HDL-C, mg dl^{-1}	55.3 ± 13.2	56.4 ± 14.3	0.3	0.2
LDL-C, mg dl^{-1}	112.3 ± 28.8	108.6 ± 27.8	0.02	0.1
FPG, mmol l^{-1}	4.9 ± 10.3	5.3 ± 3.1	0.4	0.7
PG_{120}, mmol l^{-1}	5.8 ± 19.2	5.6 ± 17.5	0.04	0.08
FPI, mU l^{-1}	5.9 ± 3.4	5.3 ± 3.1	0.02	0.03
PI_{120}, mU l^{-1}	27.6 ± 16.5	26.1 ± 19.1	0.3	0.4
HOMA-IR	1.28 ± 0.78	1.14 ± 0.72	0.03	0.08
ISI-M	11.4 ± 6.4	13.0 ± 6.9	0.004	0.005
ΔSBP, mm Hg	24.6 ± 17.1	6.1 ± 12.2	<0.0001	<0.0001
ΔDBP, mm Hg	9.0 ± 9.0	0.8 ± 8.7	<0.0001	<0.0001
ΔBMI, kg m^{-2}	0.46 ± 1.6	0.32 ± 1.8	0.3	0.2
ΔTG, mg dl^{-1}	−13.0 ± 54.6	−10.6 ± 60.9	0.6	0.6

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; FPG, fasting plasma glucose; FPI, fasting plasma insulin; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment index of insulin resistance; ISI-M, Matsuda–DeFronzo insulin sensitivity index; LDL-C, low-density lipoprotein cholesterol; PG_{120}, plasma glucose at 120 min after 75-g glucose loading; PI_{120}, plasma insulin level at 120 min after 75-g glucose loading; SBP, systolic blood pressure; TG, serum triglyceride.
All values are shown as mean ± s.d.
**P*-values adjusted for age and sex by multiple regression are presented in addition to unadjusted *P*-values.

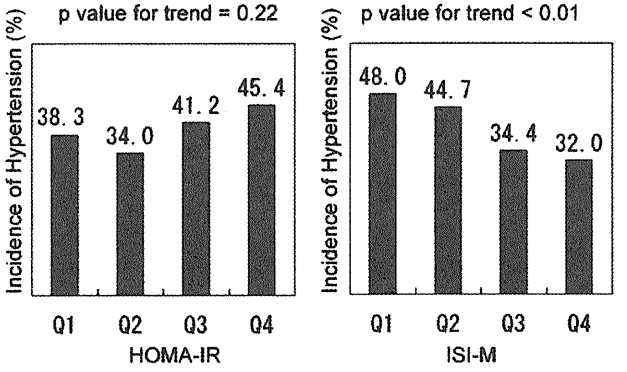

Figure 2 Incident rates of hypertension during the 10-year follow-up period in subjects with different levels of insulin sensitivity at the start of follow-up. Incidence of hypertension is shown for each quartile of ISI-M and HOMA-IR levels. HOMA-IR quartiles: Q1 –0.59, Q2 0.60–1.05, Q3 1.06–1.67, Q4 1.68–. ISI-M quartiles: Q1 –6.9, Q2 7.0–10.2, Q3 10.3–15.5, Q4 15.6–.

on OR of hypertension was not detected in subjects ⩾60 years old (Figure 3b). Interestingly, increased OR of hypertension in low ISI-M groups <60 years old was consistently observed for any level of BMI tertiles (Figure 3c). In subjects ⩾60 years old, influence of IR on OR of hypertension was not shown by ISI-M, regardless of BMI level (Figure 3d).

Discussion

The contribution of IR to development of hypertension has been assessed in several cross-sectional and longitudinal studies in the past two decades. However, significant association of IR with development of hypertension has not been consistently demonstrated either by cross-sectional studies or by longitudinal studies.[16–25] Use of different indices for assessment of IS is one of the possible reasons for the inconsistent results of earlier studies. Currently, several indices are used for determination of IR in human subjects: *M*-values determined by various types of glucose clamp, HOMA-IR, ISI-M, quantitative IS check index, K_{ITT} (an index determined by intravenous insulin tolerance test), FPI, ΣIRI (that is, sum of plasma insulin levels during 75-g OGTT), Belfiore index and Cederholm index.[42–44]

Table 4 Multiple logistic regression analysis of factors contributing to new-onset hypertension during the 10-year follow-up period

	Model 1		*Model 2*	
	β-*value*	P-*value*	β-*value*	P-*value*
Age (y.o.)	0.026	0.003	0.027	0.003
Sex (female)	−0.0080	0.930	0.0059	0.950
TG (mg dl^{-1})	0.0023	0.044	0.0029	0.016
SBP (mm Hg)	0.070	<0.0001	0.0068	<0.0001
HOMA-IR	0.24	0.094	0.095	0.540
BMI			0.099	0.008
Age (y.o.)	0.026	0.004	0.027	0.0030
Sex (female)	0.0051	0.960	0.0038	0.970
TG (mg dl^{-1})	0.0026	0.004	0.0030	0.014
SBP (mm Hg)	0.069	<0.0001	0.068	<0.0001
ISI-M	−0.37	0.029	−0.19	0.320
BMI			0.092	0.017

Abbreviations: BMI, body mass index; HOMA-IR, homeostasis model assessment index of insulin resistance; ISI-M, Matsuda–DeFronzo insulin sensitivity index; SBP, systolic blood pressure; TG, serum triglyceride.

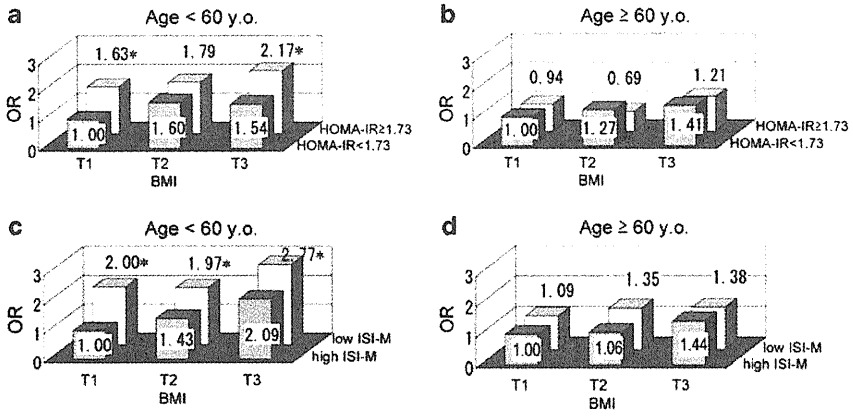

Figure 3 Odds ratio (OR) of new-onset hypertension during the 10-year follow-up period. OR was calculated for subgroups divided by an index of insulin sensitivity (ISI-M or HOMA-IR) and tertiles of BMI. Results are shown for subjects <60 years old (panels **a** and **c**) and for those ⩾60 years old (panels **b** and **d**). Low ISI-M and high ISI-M were classified by the median value of ISI-M (that is, 10.7). *$P<0.05$ *vs* OR in the same BMI tertile. BMI tertiles: T1 –21.8, T2 21.9–24.1, T3 24.2–.

Quantitative IS check index is, such as HOMA-IR, an index determined by fasting plasma glucose and insulin, which primarily indicates hepatic IS. Belfiore index is based on the product of mean plasma glucose concentration and mean insulin concentration during OGTT. Cederholm index incorporates mean plasma glucose concentration, mean insulin concentration G_0 and G_{120} to reflect peripheral IS. The correlation coefficient between *M*-value by euglycemic glucose clamp and ISI-M is reportedly larger than the coefficient between the *M*-value and Belfiore or Cederholm index (0.732 *vs* 0.534, 0.623).[33]

In the present study, we found that ISI-M correlates more significantly with BP than does HOMA-IR in cross-sectional analysis (Figure 1), and cumulative incidence of hypertension was higher in subjects with lower ISI-M (Figure 2). Furthermore, multiple logistic regression analysis indicated that ISI-M, but not HOMA-IR, was contributory to the development of hypertension during the 10-year follow-up period. HOMA-IR represents primarily IS of the liver, as the liver is responsible for >75% of endogenous glucose production. On the other hand, ISI-M represents IS of the whole body (that is, liver and skeletal muscles) and it more closely correlates with the *M*-value than does HOMA-IR.[33,45] Taken together, the present findings suggest that extra hepatic IR has a significant role in the development of hypertension. We did not selectively assess contribution of skeletal muscle IS to development of hypertension in the present study. However, this issue may be examined in future projects by use of the Cederholm index and/or a recently devised index of skeletal muscle IS (that is, the rate of plasma glucose concentration decay from its peak to its nadir during the OGTT divided by the mean plasma insulin concentration).[46]

Difference in characteristics of subjects (that is, race and proportions of females and/or obesity) recruited to the studies is also a possible reason for inconsistent association of IR with hypertension in the literature. We performed a *post hoc* analysis to examine gender difference in the correlation of ISI-M or HOMA-IR with BP and in the relationship between level of ISI-M or HOMA-IR and incidence of new-onset hypertension. However, a significant difference was not detected between male and female subjects in any of the relationships. This lack of gender difference might be attributable to the relatively advanced age of female subjects at entry to the present follow-up study. The mean age of female subjects was 56.8 ± 10.2 years and the majority of them were post-menopausal at entry. Thus, effects of estrogens on IS and BP might not have been predominant and detectable in the present female cohort.

The contribution of obesity and that of IR to hypertension are very difficult to assess separately as obesity is a major factor leading to the development of IR and obesity *per se* activates multiple mechanisms of BP elevation, including stimulation of the central sympathetic nervous system.[5,47–49] Thus, the finding that association of ISI-M with new-onset hypertension in the multiple logistic regression analysis was lost by incorporating BMI as a dependent variable (Table 4) does not necessarily exclude the possibility that IR *per se* contributes to the development of hypertension. In fact, OR of hypertension was higher in a subgroup with lower ISI-M than in a subgroup with higher ISI-M for each tertile of BMI in subjects <60 years old (Figure 3), whereas higher BMI was associated with higher OR of hypertension. Recently, Bonora *et al.*[25] reported that the *M*-value determined by hyperinsulinemic–euglycemic clamp was significantly associated with BP level after adjustment of age, sex, FPI and BMI in a cross-sectional analysis of 1093 subjects. On the other hand, such a BMI-independent association of IR with BP was not found in a similar cross-sectional analysis by Ferrannini *et al.*[24] In those cross-

sectional studies, mean BP levels were within normal ranges, and the impact of IR on BP might be difficult to detect in subjects with normal ranges of BP. Nevertheless, the observations in a study by Bonora *et al.*[25] and our results presented in Figure 3 suggest obesity-independent contribution of IR to hypertension.

Increased renal sodium retention, enhanced activation of sympathetic nerve activity and renin–angiotensin system, endothelial dysfunction and microvascular remodeling have been proposed as possible mechanisms of elevation of BP by IR.[5,13–15,47–50] However, the contribution of any of these mechanisms has not yet been unequivocally demonstrated in human subjects. Acute hyperinsulinemia, induced by insulin infusion, has been shown to reduce urinary sodium excretion and to increase plasma norpeinephrine and renin activity, but it does not consistently elevate BP.[51–54] In canine models, with and without obesity or renal insufficiency, not only acute but also chronic infusion of insulin failed to elevate BP, though it induced transient renal sodium retention.[51,52] In contrast, insulin infusion in salt-sensitive rats reportedly induced hypertension with augmented sodium retention, whereas BP was not changed by insulin in salt-resistant controls.[54] Interestingly, a recent clinical study showed that sodium reabsorption in proximal renal tubules was significantly elevated in subjects with IR and obesity.[55] Furthermore, Bonora *et al.*[25] showed that IR, but not hyperinsulinemia, was associated with elevation of BP in non-diabetic subjects. Taken together, these observations support the notion that reduced IS in the kidney, which modifies a set point of pressure natriuresis, has a more predominant role in BP elevation by IR than does hyperinsulinemia. This notion is consistent with the present findings that ISI-M was a better predictor than HOMA-IR and plasma insulin levels (Table 3).

As a limitation in this study, we cannot totally exclude the possibility of bias in results because of exclusion of subjects from data analyses. We excluded 47% of subjects in the Tanno–Sobetsu cohort based on exclusion criteria, and 18% of the subjects initially included in the cross-sectional analysis dropped out during the 10-year follow-up period. However, it is unlikely that such bias, if any, is substantial for two reasons. First, baseline characteristics of subjects used for the analyses (Table 1) are comparable to those reported for apparently healthy populations in Japan.[50,55] Second, baseline parameters in subjects used for the longitudinal analysis were similar to those for the cross-sectional analysis.

In conclusion, ISI-M is a better index of IR relevant to BP elevation than is HOMA-IR, and lower ISI-M in non-elderly subjects is associated with higher risk of hypertension, regardless of BMI level. These findings support the notion that IR in skeletal muscle has a significant role in the development of hypertension.

What is known about this topic

- Results regarding the association of insulin resistance with hypertension in previous population studies are inconsistent.[16–25]

What this study adds

- The Matsuda–DeFronzo insulin sensitivity index was found to be a better predictor of hypertension than in HOMA-IR, supporting the notion that insulin resistance in skeletal muscle has a significant role in the development of hypertension.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgements

The present study was supported by a Program for Developing the Supporting System for Upgrading the Education and Research of the Ministry of Education, Culture, Sports, Science and Technology, Tokyo, Japan, a grant for scientific research from the Ministry of Health, Labor and Welfare, Tokyo Japan (H19-cardiovascular-common-021) and Japanese Society for the Promotion of Science Grants-in-Aid for Scientific Research (no. 19590639), Tokyo, Japan.

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