Table 4. Relation of serum uric acid level to cardiovascular disease mortality.

	Uric Acid Level, mg/dl	No. of Deaths	Mortality Rate*	Age Adjusted Hazard Ratio	95% CI	Fully Adjusted† Hazard Ratio	95% CI
Cardiovascular disease mortality							
Men	< 5.0	266	10.3	1.0		1.0	
	5.0–5.9	201	7.7	0.89	0.74, 1.07	0.89	0.74, 1.07
	6.0–6.9	156	7.5	0.94	0.77, 1.14	0.83	0.67, 1.01
	7.0–7.9	65	7.0	0.94	0.71, 1.23	0.86	0.65, 1.13
	≥ 8.0	63	10.2	1.40	1.05, 1.83	1.08	0.81, 1.44
Women	< 4.0	457	5.6	1.0		1.0	
	4.0–4.9	382	6.5	1.06	0.92, 1.21	1.01	0.88, 1.15
	5.0–5.9	232	9.2	1.18	1.01, 1.38	1.08	0.91, 1.27
	6.0–6.9	111	14.9	1.91	1.54, 2.34	1.58	1.27, 1.96
	≥ 7.0	51	20.1	2.21	1.64, 2.93	1.79	1.31, 2.39
Coronary heart disease mortality							
Men	< 5.0	54	2.1	1.0		1.0	
	5.0–5.9	53	2.0	1.17	0.80, 1.71	1.14	0.78, 1.67
	6.0–6.9	33	1.6	0.99	0.63, 1.51	0.83	0.52, 1.28
	7.0–7.9	17	1.8	1.21	0.68, 2.04	1.02	0.56, 1.74
	≥ 8.0	20	3.2	2.14	1.25, 3.51	1.52	0.87, 2.58
Women	< 4.0	85	1.0	1.0		1.0	
	4.0–4.9	70	1.2	1.03	0.75, 1.42	0.96	0.69, 1.31
	5.0–5.9	49	1.9	1.33	0.93, 1.89	1.08	0.75, 1.55
	6.0–6.9	34	4.6	3.13	2.08, 4.62	2.28	1.47, 3.46
	≥ 7.0	12	4.7	2.67	1.38, 4.71	1.87	0.95, 3.38
Stroke mortality							
Men	< 5.0	139	5.4	1.0		1.0	
	5.0–5.9	96	3.7	0.83	0.64, 1.07	0.82	0.63, 1.07
	6.0–6.9	72	3.4	0.85	0.64, 1.13	0.76	0.56, 1.01
	7.0–7.9	30	3.2	0.85	0.56, 1.24	0.83	0.54, 1.22
	≥ 8.0	29	4.7	1.25	0.82, 1.84	0.95	0.61, 1.42
Women	< 4.0	216	2.7	1.0		1.0	
	4.0–4.9	175	3.0	1.01	0.83, 1.23	0.96	0.79, 1.18
	5.0–5.9	103	4.1	1.10	0.87, 1.39	1.01	0.79, 1.28
	6.0–6.9	48	6.4	1.71	1.23, 2.32	1.39	0.99, 1.91
	≥ 7.0	23	9.1	2.01	1.27, 3.03	1.67	1.05, 2.55

* Values are expressed per 1000 person-years. † In addition to age, adjusted for BMI, smoking status, alcohol consumption, systolic blood pressure, total cholesterol level, histories of hypertension, diabetes, coronary heart disease, kidney disease and malignant tumor, and estimated radiation dose from the atomic bombs.

subjects were divided into 3 groups depending on baseline age: < 45, 45–54, and ≥ 55 years. As shown in Table 5, in the age groups < 45 years (most subjects likely to be premenopausal) and ≥ 55 years (most subjects likely to be postmenopausal), a significant increase in hazard ratio for all-cause and cardiovascular mortality was observed with increasing uric acid levels. In the age group 45–54 years, which includes both menstrual and postmenopausal women, the association of uric acid level with mortality was not significant.

Since information about diuretic use was not available in our study, and since most users of diuretics are patients with hypertension, those individuals were excluded, and association of uric acid level with subsequent mortality was analyzed in women. As shown in Table 6, exclusion of hypertensive individuals (n = 1781) did not affect the association of uric acid level with all-cause and cardiovascular mortality in women. Similarly, when the subjects were restricted to those without baseline cardiovascular disease, non-diabetics, non-smokers, and those with low total cholesterol (< 200 mg/dl), association of uric acid level with mortality did not substantially change except for cardiovascular mortality for those without baseline cardiovascular disease in the uric acid category ≥ 7.0 mg/dl (Table 6).

DISCUSSION

This large prospective study found that serum uric acid concentration is independently associated with cardiovascular mortality in women and with all-cause mortality in both men and women. Association of serum uric acid level with cardiovascular disease or mortality has been described in women in several other cohort studies[2,6,7,11], whereas the results in men are more inconsistent[2-4,7-14]. Among 2 large prospective studies conducted recently in the United States,

Table 5. Relation of serum uric acid level to all-cause and cardiovascular mortality stratified by age among women (fully adjusted*).

	Baseline Age Category, yrs†					
	< 45		45–54		≥ 55	
Uric Acid Level, mg/dl	Hazard Ratio	95% CI	Hazard Ratio	95 % CI	Hazard Ratio	95% CI
All-cause mortality						
< 4.0	1.0		1.0		1.0	
4.0–4.9	1.15	0.92, 1.44	0.77	0.62, 0.95	1.13	1.02, 1.26
5.0–5.9	1.27	0.93, 1.70	0.96	0.74, 1.24	1.04	0.92, 1.19
6.0–6.9	2.11	1.32, 3.22	1.01	0.68, 1.47	1.45	1.21, 1.73
≥ 7.0	2.32	0.90, 4.86	1.28	0.67, 2.20	1.72	1.35, 2.16
Cardiovascular disease mortality						
< 4.0	1.0		1.0		1.0	
4.0–4.9	1.26	0.76, 2.07	0.78	0.54, 1.11	1.00	0.86, 1.17
5.0–5.9	1.55	0.80, 2.85	1.09	0.72, 1.63	1.00	0.82, 1.20
6.0–6.9	2.14	0.72, 5.11	1.23	0.66, 2.16	1.57	1.22, 1.99
≥ 7.0	5.88	1.36, 17.5	1.83	0.63, 4.27	1.74	1.23, 2.39

* In addition to age, adjusted for BMI, smoking status, alcohol consumption, systolic blood pressure, total cholesterol level, histories of hypertension, diabetes, coronary heart disease, kidney disease and malignant tumor, and estimated radiation dose from the atomic bombs. † The number of deaths due to all causes was 414, 509, and 2036 for the age categories < 45, 45–54, and ≥ 55 years, respectively. The number of deaths due to cardiovascular disease was 88, 193, and 952 for the same age categories, respectively.

Table 6. Relation of serum uric acid level to all-cause and cardiovascular mortality in women stratified by cardiovascular risk profiles (fully adjusted*).

		All-Cause		Cardiovascular	
	Uric Acid Level, mg/dl	Hazard Ratio	95% CI	Hazard Ratio	95 % CI
Non-hypertensives					
	6.0–6.9	1.68	1.33, 2.09	1.88	1.25, 2.72
	≥ 7.0	1.67	1.12, 2.38	1.99	1.00, 3.55
No cardiovascular disease					
	6.0–6.9	1.42	1.21, 1.66	1.76	1.13, 2.63
	≥ 7.0	1.62	1.28, 2.02	1.95	0.86, 3.81
Non-diabetics					
	6.0–6.9	1.43	1.21, 1.67	1.52	1.19, 1.91
	≥ 7.0	1.64	1.30, 2.06	1.79	1.28, 2.45
Non-smokers	6.0–6.9	1.51	1.27, 1.78	1.71	1.32, 2.17
	≥ 7.0	1.81	1.41, 2.29	2.02	1.41, 2.82
Low total cholesterol (< 200 mg/dl)					
	6.0–6.9	1.51	1.18, 1.89	1.72	1.21, 2.40
	≥ 7.0	1.80	1.28, 2.45	1.96	1.17, 3.11

* In addition to age, adjusted for BMI, smoking status, alcohol consumption, systolic blood pressure, total cholesterol level, histories of hypertension, diabetes, coronary heart disease, stroke, kidney disease and malignant tumor, and estimated radiation dose from the atomic bombs. † Hazard ratio for only 2 categories with high uric acid levels is presented.

the Framingham Heart Study showed no significant association of uric acid level with cardiovascular or all-cause mortality in either men or women[9]. The First National Health and Nutrition Examination Survey (NHANES I), on the other hand, showed a significant and independent association of uric acid level with cardiovascular and all-cause mortality in both sexes[11]. Since both studies are population-based and their adjusted confounders are similar, the source for the difference in the results is unclear. Our study utilized the largest cohort with the longest followup period among the cohorts so far analyzed, and adds further evidence for the association of uric acid level with cardiovascular mortality in women. Our population consisted entirely of Japanese subjects, and as shown in the baseline characteristics (Table 1), they are generally slimmer and have lower cholesterol levels compared with people in Western countries. Although such baseline factors were all adjusted in the analysis, ethnic differences existing in the study population might also have

played a role in the differences in results between our study and previous studies.

The strengths of our study are its large population size, long followup period, complete coverage of mortality during the followup period, and large number of subjects reaching the endpoint. Limitations include unavailability of information regarding diuretic use. Culleton, *et al* concluded that diuretic use was the major confounding factor in the apparent association of uric acid level with cardiovascular events among women in the Framingham Heart Study population[9]. On the other hand, several other studies including the NHANES I study have shown that the association of uric acid level with cardiovascular events or mortality remained significant even after adjustment for diuretic use[5,11,15-18]. We performed an analysis excluding hypertensive individuals, the major users of diuretics, and obtained nearly identical results. Therefore, it seems unlikely that diuretic use was the source for the association of uric acid level with cardiovascular mortality in our study. Unavailability of information on serum creatinine level is one more limitation of our study. It has also been reported in other studies, however, that adjustment for serum creatinine level did not render the association of serum uric acid level with cardiovascular or total mortality insignificant[5,11,15,16]. Other limitations may include misclassification of causes of death due to inaccuracy of diagnoses coded on death certificates.

Insulin resistance may be a plausible explanation for the association of uric acid level with cardiovascular disease risk since insulin resistance has been reported to be associated with both increased risk for cardiovascular events and increased serum uric acid levels[22,23]. Several other mechanisms have also been suggested, including activation of platelets and cytokine production[24-26]. Oxygen free radicals are generated when xanthine oxidase produces uric acid, and this xanthine oxidase activity in vascular endothelial cells may be associated with impaired endothelial cell function, which may in turn lead to the development of atherosclerosis[27-29]. It has also been suggested that elevated serum uric acid level may be a compensatory mechanism to counteract oxidative damage related to atherosclerosis[30,31]. In animal models, direct association of increased uric acid level with hypertension and uric acid-induced proliferation of vascular smooth muscle cells have been suggested[32,33].

The source for the difference in association of uric acid level with cardiovascular mortality between men and women in our study is unclear. A stronger association of uric acid level with cardiovascular disease in women than in men has also been reported in previous studies[2,7]. In men, serum uric acid level is generally higher than in women, a phenomenon also observed in our study. The sex difference in serum uric acid level is largely due to the difference in renal clearance rate of uric acid: men have a lower clearance rate than women[34]. Such physiological differences controlling serum uric acid level may be functioning in men in a way that obscures the association of serum uric acid level with cardiovascular risk. It may not be the case that female hormones alone contributed to the closer association of uric acid level with mortality risk in women, because the analysis stratified by age in our study suggested that the association is significant in both premenopausal and postmenopausal women.

Our study showed that serum uric acid concentration is associated with cardiovascular mortality risk in women. Although the causal mechanism for such an association remains unknown, it can be inferred that serum uric acid level may be used in both clinical and healthcare settings as a marker reflecting cardiovascular disease risk especially for women.

REFERENCES

1. Gertler MM, Garn SM, Levine SA. Serum uric acid in relation to age and physique in health and in coronary heart disease. Ann Intern Med 1951;34:1421-31.
2. Reunanen A, Takkunen H, Knekt P, Aromaa A. Hyperuricemia as a risk factor for cardiovascular mortality. Acta Med Scand 1982;668 Suppl:49-59.
3. Yano K, Reed DM, McGee DL. Ten-year incidence of coronary heart disease in the Honolulu Heart Program. Relationship to biologic and lifestyle characteristics. Am J Epidemiol 1984;119:653-66.
4. Brand FN, McGee DL, Kannel WB, Stokes J 3rd, Castelli WP. Hyperuricemia as a risk factor of coronary heart disease: The Framingham Study. Am J Epidemiol 1985;121:11-8.
5. Bengtsson C, Lapidus L, Stendahl C, Waldenstrom J. Hyperuricaemia and risk of cardiovascular disease and overall death. A 12-year follow-up of participants in the population study of women in Gothenburg, Sweden. Acta Med Scand 1988;224:549-55.
6. Levine W, Dyer AR, Shekelle RB, Schoenberger JA, Stamler J. Serum uric acid and 11.5-year mortality of middle-aged women: findings of the Chicago Heart Association Detection Project in Industry. J Clin Epidemiol 1989;42:257-67.
7. Freedman DS, Williamson DF, Gunter EW, Byers T. Relation of serum uric acid to mortality and ischemic heart disease. The NHANES I Epidemiologic Follow-up Study. Am J Epidemiol 1995;141:637-44.
8. Wannamethee SG, Shaper AG, Whincup PH. Serum urate and the risk of major coronary heart disease events. Heart 1997;78:147-53.
9. Culleton BF, Larson MG, Kannel WB, Levy D. Serum uric acid and risk for cardiovascular disease and death: the Framingham Heart Study. Ann Intern Med 1999;131:7-13.
10. Liese AD, Hense HW, Lowel H, Doring A, Tietze M, Keil U. Association of serum uric acid with all-cause and cardiovascular disease mortality and incident myocardial infarction in the MONICA Augsburg cohort. World Health Organization Monitoring Trends and Determinants in Cardiovascular Diseases. Epidemiology 1999;10:391-7.
11. Fang J, Alderman MH. Serum uric acid and cardiovascular mortality. The NHANES I epidemiologic follow-up study, 1971-1992. JAMA 2000;283:2404-10.
12. Moriarity JT, Folsom AR, Iribarren C, Nieto FJ, Rosamond WD. Serum uric acid and risk of coronary heart disease: Atherosclerosis Risk in Communities (ARIC) Study. Ann Epidemiol 2000;10:136-43.
13. Tomita M, Mizuno S, Yamanaka H, et al. Does hyperuricemia affect mortality? A prospective cohort study of Japanese male

workers. J Epidemiol 2000;10:403-9.
14. Sakata K, Hashimoto T, Ueshima H, Okayama A. Absence of an association between serum uric acid and mortality from cardiovascular disease: NIPPON DATA 80, 1980-1994. National Integrated Projects for Prospective Observation of Non-communicable Diseases and its Trend in the Aged. Eur J Epidemiol 2001;17:461-8.
15. Alderman MH, Cohen H, Madhavan S, Kivlighn S. Serum uric acid and cardiovascular events in successfully treated hypertensive patients. Hypertension 1999;34:144-50.
16. Verdecchia P, Schillaci G, Reboldi G, Santeusanio F, Porcellati C, Brunetti P. Relation between serum uric acid and risk of cardiovascular disease in essential hypertension. The PIUMA study. Hypertension 2000;36:1072-8.
17. Franse LV, Pahor M, Di Bari M, et al. Serum uric acid, diuretic treatment and risk of cardiovascular events in the Systolic Hypertension in the Elderly Program (SHEP). J Hypertens 2000;18:1149-54.
18. Bickel C, Rupprecht HJ, Blankenberg S, et al. Serum uric acid as an independent predictor of mortality in patients with angiographically proven coronary artery disease. Am J Cardiol 2002;89:12-7.
19. Lehto S, Niskanen L, Ronnemaa T, Laakso M. Serum uric acid is a strong predictor of stroke in patients with non-insulin-dependent diabetes mellitus. Stroke 1998;29:635-9.
20. Hollingsworth JW. Delayed radiation effects in survivors of the atomic bombings; review of the findings of the Atomic Bomb Casualty Commission, 1947-1959. New Engl J Med 1960;263:481-7.
21. Atomic Bomb Casualty Commission. Research plan for joint ABCC-JNIH Adult Health Study in Hiroshima and Nagasaki. ABCC Technical Report, Hiroshima, 1962;11-62.
22. Howard G, O'Leary DH, Zaccaro D, et al. Insulin sensitivity and atherosclerosis. The Insulin Resistance Atherosclerosis Study (IRAS) Investigators. Circulation 1996;93:1809-17.
23. Facchini F, Chen YD, Hollenbeck CB, Reaven GM. Relationship between resistance to insulin-mediated glucose uptake, urinary uric acid clearance, and plasma uric acid concentration. JAMA 1991;266:3008-11.
24. Ginsberg MH, Kozin F, O'Malley M, McCarty DJ. Release of platelet constituents by monosodium urate crystals. J Clin Invest 1977;60:999-1007.
25. Roberge CJ, de Medicis R, Dayer JM, Rola-Pleszczynski M, Naccache PH, Poubelle PE. Crystal-induced neutrophil activation. V. Differential production of biologically active IL-1 and IL-1 receptor antagonist. J Immunol 1994;152:5485-94.
26. Netea MG, Kullberg BJ, Blok WL, Netea RT, van der Meer JW. The role of hyperuricemia in the increased cytokine production after lipopolysaccharide challenge in neutropenic mice. Blood 1997;89:577-82.
27. Cardillo C, Kilcoyne CM, Cannon RO 3rd, Quyyumi AA, Panza JA. Xanthine oxidase inhibition with oxypurinol improves endothelial vasodilator function in hypercholesterolemic but not in hypertensive patients. Hypertension 1997;30:57-63.
28. Butler R, Morris AD, Belch JJ, Hill A, Struthers AD. Allopurinol normalizes endothelial dysfunction in type 2 diabetics with mild hypertension. Hypertension 2000;35:746-51.
29. Doehner W, Schoene N, Rauchhaus M, et al. Effects of xanthine oxidase inhibition with allopurinol on endothelial function and peripheral blood flow in hyperuricemic patients with chronic heart failure: results from 2 placebo-controlled studies. Circulation 2002;105:2619-24.
30. Nieto FJ, Iribarren C, Gross MD, Comstock GW, Cutler RG. Uric acid and serum antioxidant capacity: a reaction to atherosclerosis? Atherosclerosis 2000;148:131-9.
31. Kirschbaum B. Renal regulation of plasma total antioxidant capacity. Med Hypotheses 2001;56:625-9.
32. Mazzali M, Hughes J, Kim YG, et al. Elevated uric acid increases blood pressure in the rat by a novel crystal-independent mechanism. Hypertension 2001;38:1101-6.
33. Kanellis J, Watanabe S, Li JH, et al. Uric acid stimulates monocyte chemoattractant protein-1 production in vascular smooth muscle cells via mitogen-activated protein kinase and cyclooxygenase-2. Hypertension 2003;41:1287-93.
34. Adamopoulos D, Vlassopoulos C, Seitanides B, Contoyiannis P, Vassilopoulos P. The relationship of sex steroids to uric acid levels in plasma and urine. Acta Endocrinol 1977;85:198-208.

(3)今後の研究計画

統合コホートデータベースには健診項目数が拡大された1986年以降に広島放影研で健診を受けた約4600人のデータを提出した。データの提出に際して所内の倫理委員会(人権擁護委員会)ならびに研究担当理事の承認を受けている。ベースライン時にはHDL ｺﾚｽﾃﾛｰﾙ、ﾍﾓｸﾞﾛﾋﾞﾝ A1c、CRPの測定は実施されていない。今後、これら3項目に関する統合データの解析が必要な場合は、再度所内委員会の承認を得た後、データ提出が可能である。

現在このコホートの平均年齢は約75歳であり、2006年度からの1健診サイクルで年齢60-100歳の約2400人の健診が見込まれる。健診対象者の同意を得て、ABI、PWV、頚動脈IMTの測定を追加測定することにより、動脈硬化の進展の程度を総合的に評価し、リスク因子の関与について検討したい。

7．端野・壮瞥町研究

分担研究者　斎藤 重幸　札幌医科大学医学部第二内科・講師

1）端野・壮瞥町研究の概要

札医大第二内科では1977年に、北海道の２つの町において循環器疾患の病態解明を目的とした疫学調査を開始した。両町の自然環境の差違は大きく２月の室外平均気温はそれぞれ－14℃、－6℃である。当初の目論見は、この気温差をふくめた環境の差違が高血圧や循環器疾患の発症に影響を与えるか否かを検討することであった。

検診は毎年続けられ、今日までの30年間にわたりこの疫学研究は継続されている。この間、高血圧の長期生命予後、寒冷と高血圧進展の関連、耐糖能異常や肥満の長期生命予後、耐糖能異常と高血圧の成因論的関連、冠危険因子とインスリン抵抗性・高インスリン血症の関連などを報告してきた。

対象地域は人口規模、経済背景が類似した２つの地域、北海道常呂郡端野町と有珠郡壮瞥町で、調査開始時人口は1975年の国勢調査では端野町5,568名、壮瞥町4,447名であった。両町とも農業従事者が多く端野町は畑作、壮瞥町は果樹栽培が主体である。コホートは40～64歳の住民から、端野町996名（男性475名、女性521名、平均年齢51±6歳）、壮瞥町1,000名（男性469名、女性531名、平均年齢51±6歳）の計1,996人を住民台帳から無作為抽出した。両町で対象者の性別、平均年齢、年齢構成に差異はない。身体測定、問診、血圧測定、血液生化学検査、心電図などの調査を端野町では1977年から、壮瞥町は1978年から開始しデータを集積した。基本的調査項目は既往歴、嗜好、家族歴、栄養調査、血圧、肥満度、血清脂質値、尿酸値、ブドウ糖負荷試験などである。検診は毎年夏と冬に行っている。検診結果は医師、保健師による個別指導を行い個人に還元し、必要と判断された者には二次検査の紹介状を発行している。検査諸量は初年度の検査値を採用したが、他に疾患発症以前の検査値の加算平均を用いた検討も行なった。血圧値は計測に慣れた医師が水銀血圧計により測定していたが、平成13年度からは自動血圧測定器を導入、水銀血圧測定値と自動血圧計測定値の差違が有意でないことを確認し、その後、自動血圧計測定に変更した。また、ABPMや家庭血圧計を用いたプロトコールも実施した。疾患の発症および死亡については、本人、家族、地域保健師により情報を得、各主治医に発症状況、病歴、検査成績などの調査票を送付の上、確認し診断を確定している。

また1991年と1992年に検診受診者約2,100名に悉皆的の75g経口ブドウ糖負荷試験を実施、これらの対象の追跡研究から耐糖能異常と他の動脈硬化危険因子の関連を解析し、インスリン抵抗性、メタボリックシンドロームをkey wordsに解析を進めている。

2）最新の研究成果

動脈硬化性疾患は高血圧、糖尿病、高脂血症、肥満などの生活習慣病を基盤として発症すると考えられている。これらの危険因子は多くの基礎的、臨床的、疫学的研究によってそれぞれが独立して動脈硬化の成因に関与していることが明らかにされ、その意義が確立されている。一方で、高血圧、糖尿病、高脂血症が同一個人に複合して存在していることはよく知られている。これはインスリン抵抗性を基盤とする multiple risk factor clustering として認識されてきたが、最近、メタボリックシンドロームの名称で内臓脂肪蓄積型肥満を発症基盤とする病態の知識が整理されてきた。しかしながら、その疫学や動脈硬化性疾患発症における病態的意義は解明の途中にある。また、内臓脂肪蓄積型肥満ではインスリン抵抗性の成因として脂肪細胞から分泌される液性因子の意義が解明されつつある。特にアディポネクチンは主要な役割を担うことが明らかとなった。最近の端野・壮瞥町研究では住民検診成績から、インスリン抵抗性、メタボリックシンドローム、アディポネクチンの役割の循環器疾患の疫学を検討している。本稿では最近のこれらの研究成果から主なものを紹介する。

研究報告 1：*Hyperens Res 2005; 28 : 665-670*

インスリン抵抗性は高血圧、糖尿病、脂質代謝異常など危険因子の背景因子として重要であるが、インスリン抵抗自体も心血管疾患の危険因子である可能性が指摘されている。本研究では端野・壮瞥町の男女 1,227 名を対象として、インスリン抵抗と心血管疾患の関連を縦断成績から解析した。糖負荷後 2 時間のインスリン値（64 μU/mL 以上）をインスリン抵抗ありと定義した。8 年間の追跡中インスリン抵抗のあるのもでは非インスリン抵抗に比較して虚血性心疾患が 5.6 倍、脳卒中が 2.8 倍増加した。コレステロール、喫煙など他の危険因子で調整してもインスリン抵抗ありは虚血性心疾患発症を規定する因子となった（odds 比 3.2）。以上から、日本人の心血管疾患の発症・死亡にインスリン抵抗性が直接関与する可能性を示唆した。

研究報告 2 ：*Hyperens Res 2005; 28: 203-208*

2001 年の米国 National Cholesterol Education Program(NCEP)の Adult Treatment Panel III(ATP III)では Metabolic syndrome(MS)の診断基準を公開し、その管理の重要性を強調した。今回は端野・壮瞥町住民検診の縦断成績より日本人男性における MS の予後を解析した。男性 808 名（平均年齢 60.3±11.2 歳）で高 TG 血症群、低 HDL 血症群、高血圧群、高 FPG 血症群、腹部肥満群を分類し、これらを 3 個以上集積する MS を判定した。危険因子の集積に伴いインスリン抵抗性指標は有意に増加した。全体中 MS は 25.3%であった。この集団を 8 年間追跡すると、心疾患発症は、MS では non-MS に比較して 2.23 倍の odds 比で上昇した。日本人男性でもインスリン抵抗性症候群の判定に NCEP-ATPIII の MS の概念は有用であり、MS は心血管疾患の危険因子として捉えられる可能性が示唆された。

研究報告３：*European Journal of Endocrinology 2005; 153: 91-98*

アディポネクチンの血中レベルは性・年齢で異なるが、この相違の原因を、性ホルモンと腎機能の変化から検討した。端野・壮瞥町住民検診より、空腹時の一般採血に加えて、アディポネクチン、各種性ホルモンを測定した。これにより年齢、性、腎機能など多因子の解析を行うと、高齢者でのアディポネクチンレベルの上昇は腎でのアディポネクチンのクリアランスの低下が主に作用する可能性が示唆され、性ホルモンの影響は少ないと考えられた。今後、代謝異常のマーカーや動脈硬化性疾患の危険因子としてアディポネクチンを検討する場合に、年齢、性に加え、腎機能も考慮にいれる必要があることが示唆された。ま地域住民の断面成績より、危険因子の集積であるＭＳと非ＭＳでのアディポネクチンの血中レベルを検討した。ＭＳではアディポネクチンが低下し、これを介する軽症リスクの集積が動脈性疾患発症に関与する可能性が示された。

３）今後の研究計画

端野・壮瞥町研究は約 30 年前に日本人の循環器疾患、高血圧、糖尿病の病態生理を理解するために企画された前向き疫学研究である。これまでに、耐糖能異常、糖尿病、インスリン抵抗性、メタボリックシンドロームなど過栄養や肥満を基盤とする状態が日本人一般住民でも心血管疾患発症に重要であることを示してきた。これらの知見は肥満者が増加し糖尿病が急増している日本の現状下では重要であると考えられる。今後も、現代の日本人の心血管疾患発症病態を解明すべく検討を進めるが、この際 key word となるのがメタボリックシンドローム、内臓脂肪蓄積型肥満である。

メタボリックシンドロームは 2005 年に日本人の診断基準が公開され、この新基準を用いた解析が行われつつあるが、端野・壮瞥町研究でも新基準の妥当性と意義の解析を進める。一方、メタボリックシンドロームは軽症リスクの集積を表現するものとも捉えることができるが、どのリスクの組あわせが予後を規定する上で有用であるかを一般住民レベルのリスク集積状態から解析する。

内臓脂肪蓄積型肥満は種々のアジポサイトカインと関連し、直接動脈硬化を進展させる可能性が示唆される。現在内臓脂肪蓄積型肥満の評価方法として汎用されるのは腹囲径測定だが、その診断基準も含めて検討が必要とされており、その評価を多方面から行う。現在、端野・壮瞥町研究では、住民における腹部超音波法やインピーダンス法を用いた方法により、より簡便かつ正確に内臓脂肪蓄積を評価すべく検討を開始したところである。今後これらの新しい測定法の妥当性を証明し臨床応用を図るべく研究を継続する。またアディポネクチンなどの血中アジポサイトカイレベルンの測定を行い、これらによる内臓脂肪蓄積型肥満の病態解明はもとより、動脈硬化の進展のマーカーとしての臨床応用の可能性を追求する。以上の検討は過栄養、運動不足、肥満を背景とした現代日本人の循環器疾患の予防に極めて重要であると考えられ、各地の疫学研究と比較、協調して研究成果が応用できるように考慮する。

Original Article

Development and Progression of Atherosclerotic Disease in Relation to Insulin Resistance and Hyperinsulinemia

Tadashi FUJIWARA, Shigeyuki SAITOH, Satoru TAKAGI, Hiroshi TAKEUCHI, Takeshi ISOBE, Yu CHIBA, Tetsuji MIURA, and Kazuaki SHIMAMOTO

It is unclear whether the role of insulin resistance in the development of atherosclerotic cardiovascular disease is similar in populations in which the incidence of atherosclerotic diseases significantly differs from that in Western countries. The aim of this study was to determine the relationship between insulin resistance and the development of cardiovascular disease in the Japanese population. We conducted 75 g-oral glucose tolerance tests (OGTTs) on 1,928 inhabitants of two towns in Hokkaido, Japan. Subjects using antihypertensive agents and known diabetic patients were excluded from the study. Data from the remaining 1,227 subjects (540 males and 687 females; mean age 56.0±10.8 years) were used for the analysis, and 1,051 subjects were seen in a follow-up care setting for a period of 8 years. The presence of insulin resistance was defined according to the guidelines reported our previous study: insulin levels of 64.0 mU/l or higher 2 h after the 75 g-OGTT. The insulin-resistant (IR) group had several risk factors such as hypertension, diabetes, treated or untreated hypercholesterolemia, hypertriglyceridemia, low high-density-lipoprotein (HDL) cholesterol levels, and obesity. During the follow-up period of 8 years, the incidence of coronary artery disease, which was adjusted for age, body mass index, sex, systolic blood pressure, fasting plasma glucose, total cholesterol, triglyceride, and HDL cholesterol was significantly (3.2 times) higher in the IR group than in the insulin non-resistant group. The results suggested that insulin resistance is an independent risk factor for coronary artery disease in Japanese subjects, as has also been demonstrated in the case of individuals in Europe and USA. (*Hypertens Res* 2005; 28: 665–670)

Key Words: insulin resistance, cardiovascular disease, risk factors

Introduction

The incidence of cardiovascular disease is high in patients with multiple risk factor syndrome (or metabolic syndrome). Although the criteria for the diagnosis of multiple risk factor syndrome have not been standardized, there is a consensus that insulin resistance is an important factor underlying the association of this syndrome with atherosclerotic cardiovascular diseases. Insulin resistance is known to cause multiple pro-atherosclerotic effects on the hemostatic system as well as on vascular endothelial function (*1*, *2*). Furthermore, several studies using meta-analysis have indicated that hyperinsulinemia is associated with various atherosclerotic cardiovascular diseases, including the coronary artery disease (*3–7*). However, the incidence of atherosclerotic vascular diseases differs among different races; epidemiological studies conducted to date have revealed racial differences in the relationship between insulin resistance and atherosclerotic diseases (*8*, *9*). No study has yet been conducted to clarify the impact of insulin resistance on the development and progress of atherosclerotic cardiovascular disease in the general Japa-

From the Second Department of Internal Medicine, Sapporo Medical University School of Medicine, Sapporo, Japan.
Address for Reprints: Tadashi Fujiwara, M.D., Second Department of Internal Medicine, Sapporo Medical University School of Medicine, S-1, W-16, Chuo-ku, Sapporo 060–8543, Japan. E-mail: tfujiwar@sapmed.ac.jp
Received October 29, 2004; Accepted in revised form July 24, 2005.

Table 1. Baseline Characteristics

	Male	Female
Age (year)	57.2±11.3	55.1±10.3
BMI (kg/m^2)	23.2±3.0	23.3±2.9
SBP (mmHg)	125.2±15.8	123.3±16.5
DBP (mmHg)	75.4±9.0	73.4±9.0
FPG (mg/dl)	89.9±12.0	87.3±10.9
TC (mg/dl)	184.3±30.2	196.3±34.6
TG (mg/dl)	148.0±110.4	111.1±62.9
HDL-C (mg/dl)	52.6±14.0	57.7±13.2

Values are expressed as means±SD. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; TC, total cholesterol; TG, triglyceride; HDL-C, high-density-lipoprotein cholesterol.

nese population.

In the present study, we aimed to determine the relationship of insulin resistance with established risk factors and with the incidence of cardiovascular events in the general Japanese population. We performed mass screening examinations, including a 75 g-oral glucose tolerance test (OGTT), for the inhabitants of two towns in Hokkaido, Japan, and followed these individuals for 8 years for cardiovascular events and mortality. Insulin resistance was diagnosed on the basis of blood insulin levels 2 h after administration of the 75 g-OGTT, according to the methods described in our previous study (*10*).

The present results support the hypothesis that insulin resistance is an important independent risk factor in coronary artery disease and its occurrence in the Japanese population.

Methods

Study Subjects

The subjects of this study were 2,138 inhabitants of two towns in Hokkaido, who participated in a health examination program in 1991 and 1992 (*9*). The subjects inhabited a largely agricultural area. Subjects using anti-hypertensive agents and those undergoing medical treatment for diabetics were excluded from the analysis, because these morbid states exert an effect on insulin resistance. Data obtained from the remaining 1,227 subjects (540 males and 687 females; mean age 56.0±10.8 years) were used for analysis.

Parameters

Blood samples were obtained from the subjects in the early morning after an overnight fast, and the following factors were measured: fasting plasma glucose (FPG), total cholesterol (TC), triglyceride (TG) and high-density-lipoprotein (HDL) cholesterol levels, and blood pressure (systolic and diastolic blood pressure [*i.e.*, SBP and DBP]), which was measured twice with the subject in a sitting position after a 5-min rest to calculate the mean blood pressure. A 75 g-OGTT was then performed on each subject to determine the blood insulin level 2 h after administration of the test (120 IRI). The cutoff point of 120 IRI≥64.0 mU/l was used to determine insulin resistance according to the report by Oimatsu *et al.* (*10*).

The following definitions of risk factors and cardiovascular diseases were employed: obesity was defined as a body mass index (BMI) of 25 kg/m^2 or higher (*11*) and according to the criteria of JNC-VI of the International Hypertension Society, hypertension was defined as a SBP of 140 mmHg or higher, or a DBP of 90 mmHg or higher (*12*). The 1997 criteria of the American Diabetes Society was used for the diagnosis of diabetes mellitus, namely, a FPG level of 126 mg/dl or higher, or a plasma glucose level 2 h after the administration of the 75 g-OGTT of 200 mg/dl or higher (*13*). Hypercholesterolemia was defined as a plasma cholesterol level of 220 mg/dl or higher. Hypertriglyceridemia was defined as plasma TG levels of 150 mg/dl or higher, and low HDL cholesterol was defined as blood HDL cholesterol levels of less than 40 mg/dl (*14*). Coronary artery disease was defined as myocardial infarction or angina pectoris. Cerebral vascular disease was defined as cerebral infarction or cerebral hemorrhage. We excluded subjects with subarachnoid hemorrhage and unclassified stroke from the analysis. Public health nurses, who were continuously engaged in local public health services, performed the follow-up examinations. The diagnosis of cases involving morbidity was confirmed by answers to questionnaires mailed to the doctors in charge of the cases in hospitals or in outpatient clinics, and electrocardiographies and brain CT scans were also reviewed in as many cases as possible. The nurses checked the death certificates in cases of mortality.

The present study was carried out in accordance with the Declaration of Helsinki (1981) of the World Medical Association, and the study protocol was approved by the Research Committee of Sapporo Medical University, Sapporo. Informed, written consent was obtained from all subjects after they had been provided with a complete explanation of the purpose, nature, and risks of all procedures used.

The data are shown as mean±SD. An unpaired *t*-test was used to test the differences between mean values in the two groups, and a p value of less than 0.05 was considered statistically significant. TG values were logarithmically transformed before the analysis. A simple correlation analysis was applied to test the relationship between the onset of disease and insulin resistance using a significance level of $p<0.05$. The χ^2 test was used to examine the relationship between insulin resistance and risk factors for atherosclerosis. Because there were significant differences in age between the insulin non-resistant (NR) group and the insulin-resistant (IR) group, we used the Mantel-Haenszel test to assess differences in the onset of cardiovascular disease and insulin resistance. Multiple logistic regression analysis was used to test the relation-

Table 2. Baseline Characteristics in the NR Group and the IR Group

	Male			Female		
	NR group	IR group	*p*-value	NR group	IR group	*p*-value
Age (year)	57.1±11.4	58.8±10.1	0.381	54.9±10.3	58.5±9.4	0.041
BMI (kg/m^2)	23.0±2.8	26.7±2.8	<0.001	23.1±2.8	26.4±2.6	<0.001
SBP (mmHg)	125±15.7	128.4±17.0	<0.001	122.6±16.2	137.7±15.6	<0.001
DBP (mmHg)	75.2±9.2	78.4±6.4	0.008	73.1±8.9	79.1±9.1	<0.001
FPG (mg/dl)	89.6±11.9	94.8±12.9	0.011	87.1±11.0	91.8±7.0	<0.001
TC (mg/dl)	183.4±29.3	196.5±38.6	0.049	195.3±34.2	214.3±37.3	0.002
log TG (mg/dl)	4.788±0.528	5.056±0.528	0.659	4.578±0.428	5.008±0.537	<0.001
HDL-C (mg/dl)	52.9±13.9	48.4±14.6	0.074	58.0±13.2	51.4±13.2	0.004

Values are means±SD. NR, insulin non-resistant; IR, insulin-resistant; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; TC, total cholesterol; TG, triglyceride; HDL-C, high-density-lipoprotein cholesterol.

Table 3. Frequency of Each Risk Factor in the IR Group and the NR Group

	NR group	IR group	*p*-value
Number	1,155	72	
Obesity (%)	24.1	74.6	<0.001
Hypertension (%)	18.0	33.8	0.002
Diabetes mellitus (%)	1.0	5.6	0.012
High total cholesterol (%)	19.0	36.1	0.001
High triglyceride (%)	22.8	44.4	<0.001
Low high-density-lipoprotein cholesterol (%)	12.9	29.6	<0.001

Values are expressed as %. NR, insulin non-resistant; IR, insulin-resistant.

ship between the onset of cardiovascular disease and insulin resistance and/or other risk factors. The commercially available statistical package SPSS Version 12.0J was used for the statistical analyses.

Results

A cross-sectional investigation was conducted in the first year of the current study. The baseline characteristics of subjects of each gender are shown in Table 1. As regards risk factors, the levels of the following factors were higher in men than in women: age, FPG, DBP, and TG. On the other hand, TC and HDL cholesterol levels were higher in women. There were no significant gender-related differences in SBP. The subjects were divided into an NR group (control group) and an IR group. In the IR group, 6.5% of the subjects were males and 4.4% were females. Among males; the IR group had significantly higher BMI, SBP, DBP, FPG, and TC values than the NR group. However, no significant difference was observed in terms of age, log TG, or HDL cholesterol between the two groups. Among females, the IR group had significantly higher age, BMI, SBP, DBP, FPG, TC, and log TG values than the NR group. Moreover, females in the IR group had lower HDL cholesterol levels than the NR group (Table 2). The prevalence of female or male subjects with obesity, hypertension, diabetes, or abnormalities in plasma lipid levels were significantly higher in the IR group than in the NR group (Table 3).

The association between insulin resistance and the aggregation of risk factors is shown in Fig. 1. The prevalence of insulin resistance (0.7, 4.4, 10.6, and 19.2%: $p<0.001$) was found to increase with the number of risk factors present (0, 1, 2, and 3 or more). In addition, 70.2% of the subjects in the IR group had two or more risk factors, whereas 70.6% of the subjects in the NR group had none or only one risk factor (data not shown).

During the follow-up period, coronary artery diseases developed in 43 subjects (acute myocardial infarction in 15 subjects and angina pectoris in 28 subjects), and cerebral vascular accidents occurred in 15 subjects (cerebral infarction in 11 subjects and cerebral hemorrhage in four subjects). The incidence of coronary artery disease in the IR group (16.1%) was significantly higher than that in the NR group (3.4%), but no significant difference was found between these two groups in terms of the incidence of cerebral vascular disease (3.6 *vs.* 1.3%, $p=0.188$) (Table 4).

Table 5 shows the results of the multiple logistic analyses of the determinants of coronary artery disease-associated morbidity during an 8-year follow-up period. The IR group had a 3.2-fold higher incidence of coronary artery disease than the NR group, even after corrections were made for age, gender, BMI, SBP, FPG, and TC. SBP, age, and sex were also shown to be significant risk factors in the present dataset.

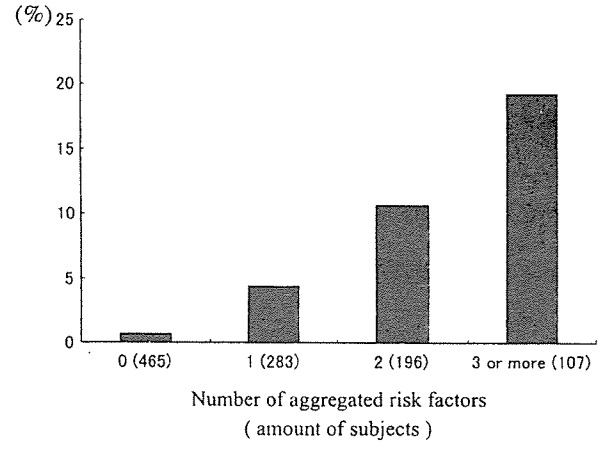

Fig. 1. *Percentages of IR and NR subjects according to the aggregation of risk factors. The percentage of IR subjects tended to be higher than that of NR subjects with respect to an increasing number of risk factors. Risk factors: obesity, hypertension, diabetes mellitus, high total cholesterol, high triglyceride, low high-density-lipoprotein cholesterol.*

Discussion

It is known that the following are potential markers of insulin resistance: the product of insulin levels and plasma glucose levels, as determined by the 75 g-OGTT (Σ BS/IRI, sum of the 0–120 min values), and the fasting insulin and FPG levels (HOMA values; 104/Ip×Gp, where Gp and Ip are maximum blood glucose level and maximum insulin level, respectively). A cutoff point of IRI≥64.0 mU/l at 120 min after the administration of the 75 g-OGTT was used as a marker of insulin resistance in the present study. This cutoff point has been demonstrated as a valid marker of insulin resistance, as the insulin level observed 120 min after glucose loading in the context of the 75 g-OGTT is known to correlate negatively with the *M* value obtained by the glucose clamp method, thus indicating that insulin secretion has been maintained (*10*). Age, gender, and medication potentially exert effects on insulin sensitivity, and diuretic agents, α and β blockers, calcium channel blockers, and angiotensin converting enzyme inhibitors have been shown to affect insulin resistance. However, since the subjects of the present study were primarily inhabitants of rural communities (excluding those subjects administered anti-hypertensive agents and diabetes medications), it is expected that the above factors had only limited effects on the results. The findings of the above mentioned meta-analysis revealed that the fasting insulin level or a cutoff value in the 80th percentile could be used for the determination of insulin resistance. According to the criteria for diagnosis used in the present study, 5.3% of the subjects suffered from insulin resistance. However, the criteria used in our study were stricter than those used in the studies conducted in Western countries, and it is therefore difficult to draw conclusions regarding differences in the effects of insulin resistance on the development of coronary artery disease in the Western samples.

Zavaroni *et al.* examined subjects living in a workers' community; in that study, a glucose intolerant non-obese group suffering from hyperinsulinemia was compared to a group with normal insulin levels, and the results showed that before the onset of diabetes, the former group had higher levels of TG, low-density-lipoprotein (LDL) cholesterol, and blood pressure, as well as a higher incidence of coronary artery disease, than the latter group (*15*). Moreover, on the basis of the results of a follow-up study carried out over a period of 8 years, the San Antonio Heart Study revealed associations between fasting hyperinsulinemia and the onset of diabetes, low HDL cholesterol, and hypertension (*16*). It has also been reported that subjects with multiple risk factors had significantly higher fasting insulin levels than did those presenting with only a single risk factor. The results of the cross-sectional investigation in the first year of the present study showed that in the IR group, the incidence of hypertension, diabetes, and abnormal lipid metabolism was significantly higher than that in the NR group. The present results also suggested that insulin resistance is associated with atherosclerotic risk factors and also with the accumulation of these risk factors. These results are thus consistent with the findings of recent studies conducted in Western countries.

Several studies have been conducted to investigate the relationship between insulin resistance and the onset of coronary artery disease; differences between such studies were considered in terms of baseline characteristics such as age, male-to-female ratio, drug usage, and length of follow-up period, as well as in terms of the criteria used for the diagnosis of insulin resistance by determination of the insulin level. Ruige *et al.* carried out a meta-analysis of 17 past major epidemiological studies in Western countries, and they showed that insulin resistance and hyperinsulinemia are independent risk factors in ischemic heart disease, and that race influences the relationship between the onset of coronary artery disease and insulin resistance (*7*). Racial differences have been shown to exist in the relationship between insulin resistance and atherosclerotic diseases. The IRAS study showed that the progression of atherosclerosis differs among races (*17*). Pima Indians, who have high insulin resistance, have a low incidence of coronary artery disease (*8*). A comparison of Japanese and Western samples revealed that the latter group had the capacity to secrete more insulin, and most of the Japanese diabetes patients studied did not have hyperinsulinemia (*18*). In Westerners, pancreatic insulin secretion function is maintained after the onset of type II diabetes. The condition of diabetes associated with hyperinsulinemia and insulin resistance differs greatly from that observed among Japanese. The results of our follow-up study of Japanese subjects showed that a significant relationship existed between insulin resistance and the incidence of coronary artery disease, even after the correction of risk factors for atherosclerosis, such as age,

Table 4. Cardiovascular Event in the IR Group and the NR Group

	NR group	IR group	Odds ratio	*p*-value
Follow up	995	56		
Coronary artery disease	34	9	5.4 (4.6*)	<0.001 (<0.001*)
(Morbidity (%))	(3.4)	(16.1)		
Stroke	13	2	2.8 (2.1*)	0.188 (0.348*)
(Morbidity (%))	(1.3)	(3.6)		

Values are expressed as % or number. NR, insulin non-resistant; IR, insulin-resistant. *Adjusted for age.

Table 5. Multiple Logistic Analysis for Coronary Artery Disease Morbidity

	Odds ratio	95.0% CI	*p*-value
IR/NR	3.203	1.260–8.142	0.014
SBP	1.023	1.004–1.042	0.020
Age	1.040	1.003–1.077	0.033
Sex (male)	1.976	0.995–3.925	0.052
TC	1.006	0.966–1.016	0.234
HDL-C	0.991	0.996–1.016	0.458
TG	0.999	0.995–1.003	0.611
FPG	0.994	0.963–1.026	0.709
BMI	1.015	0.903–1.141	0.801

Independent variables: coronary artery disease morbidity. Dependent variables: insulin resistance (IR/NR), age, sex, BMI, SBP, FPG, TC, TG, HDL-C. Odds ratios for continuous risk factors expressed for single value higher. NR, insulin non-resistant; IR, insulin-resistant; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; TC, total cholesterol; TG, triglyceride; HDL-C, high-density-lipoprotein cholesterol.

gender, blood pressure, blood glucose, and total cholesterol. Insulin resistance causes atherosclerosis by giving rise to risk factors for atherosclerosis. Moreover, insulin itself directly promotes atherosclerosis. Insulin resistance is classified as decreased tissue sensitivity to insulin or compensatory hyperinsulinemia. The pathological states caused by low insulin sensitivity include glucose intolerance and lipid metabolism disorders, such as hypertriglyceridemia, elevated very low-density-lipoprotein cholesterol, and low HDL cholesterol. Hyperinsulinemia can cause hypertension *via* an increase in sympathetic nerve activity, increased renin-angiotensin activity, sodium retention in the kidneys, increased Na^+/H^+ pump activity, activation of insulin-like growth factor (IGF) receptors, and impaired endothelium-dependent vasodilation. We believe that insulin resistance is a marked risk factor for the development of coronary artery disease, even after subtraction of the influence of other risk factors, because increased Na^+/H^+ pump activity, IGF receptor activation, and impaired endothelium-dependent vasodilation can be direct causes of atherosclerotic disease, and because plasminogen-activator-inhibitor-1 (PAI-1) can increase blood coagulability to accelerate atherosclerosis. PAI-1 levels are known to be elevated in patients in an insulin-resistant state. However, these pathways are known to differ among races. Nonetheless, the results of the present study indicated that insulin resistance in Japanese, as well as in Westerners, is involved in the development of coronary artery disease, independent of the other risk factors for atherosclerosis.

Our results did not show a significant correlation between insulin resistance and the incidence of stroke. However, the Helsinki Policemen Study showed that insulin resistance is a predictor not only of coronary artery disease, but also of stroke (*19*). In our study, only a small number of subjects experienced cerebrovascular disorders. The following potential reasons for this were considered: the mean age of the subjects included in the analysis was 56, which is otherwise associated with a relatively low prevalence of cerebrovascular disorder; patients who were under treatment for hypertension and diabetes were excluded from the study, resulting in a sample with only a low risk of cerebrovascular disorder; and mild transient ischemic attack might have been missed in the present study. Moreover, in a previous study of Japanese subjects, it was found that the percentage of subjects with insulin resistance was significantly high but only in the atherothrombotic infarction group, and not in groups with other types of cerebrovascular disorder (*20*).

Studies performed in Western countries have reported that insulin resistance leads to the development of hypertension, diabetes, and abnormal lipid metabolism, all of which are known to lead to the progression of atherosclerosis and the development of cardiovascular diseases. As has been noted in these reports, insulin resistance leads to hypertension in Japanese subjects (*21*). In the present study, we investigated the relationship between insulin resistance and the development of cardiovascular disease in Japanese subjects who had undergone a number of screening examinations. Our results demonstrated that insulin resistance is associated with the development of coronary artery disease; this finding is similar to those of studies conducted in Europe and in USA. According to the present study, the expected frequency of patients suffering from cerebral vascular disease while also having insulin resistance was low, *i.e.*, 0.8, and therefore it was impossible to arrive at a conclusion regarding the relationship between insulin resistance and the onset of cerebral vascular disease (*22*). In our study, the stroke incidence was 1.4%, which was also low compared with that expected for Japanese

people in general. It is thought that the reason for this relatively low value was that we analyzed a group from which patients with a previous history of hypertension or diabetes were excluded.

The number of Japanese with risk factors for atherosclerosis (*e.g.*, hypertension, diabetes, hyperlipidemia, and obesity) has been increasing in recent years due to changes in diet and habitual exercise. The incidence of either hyperinsulinemia or insulin resistance is also believed to be increasing in Japan. Therefore, the evaluation of insulin resistance will be important in the future for the prevention of atherosclerotic disease. An investigation of changes in insulin resistance should enable the determination of the risk for atherosclerotic disease in the Japanese population, and would contribute to the elucidation of racial differences in the relationship between insulin resistance and the development of atherosclerotic disease.

References

1. Juhan-Vague I, Thompson SG, Jespersen J: Involvement of the hemostatic system in the insulin resistance syndrome. A study of 1500 patients with angina pectoris. The ECAT Angina Pectoris Study Group. *Arterioscler Thromb* 1993; **13**: 1865–1873.
2. Suzuki M, Shinozaki K, Harano Y, *et al*: Insulin resistance as an independent risk factor for carotid wall thickening. *Hypertension* 1996; **28**: 593–598.
3. Wingard DL, Barrett-Connor EL, Ferrara A: Is insulin really a heart disease risk factor. *Diabetes Care* 1995; **18**: 1299–1304.
4. Jarrett RJ: Is insulin atherogenic? *Diabetologia* 1988; **31**: 71–75.
5. Stout RW: Insulin and atheroma. 20-yr perspective. *Diabetes Care* 1990; **13**: 631–654.
6. Reaven GM, Laws A: Insulin resistance, compensatory hyperinsulinaemia, and coronary heart disease. *Diabetologia* 1994; **37**: 948–952.
7. Ruige JB, Assendelft WJ, Dekker JM, Kostense PJ, Heine RJ, Bouter LM: Insulin and risk of cardiovascular disease: a meta-analysis. *Circulation* 1998; **97**: 996–1001.
8. Nelson RG, Sievers ML, Bennett PH, *et al*: Low incidence of fatal coronary heart disease in Pima Indians despite high prevalence of non-insulin-dependent diabetes. *Circulation* 1990; **81**: 987–995.
9. Saitoh S, Tanaka S, Iimura O, *et al*: Glucose tolerance, obesity, and hypertension: epidemiological study in Hokkaido, Japan. *Ann N Y Acad Sci* 1993; **676**: 342–344.
10. Oimatsu H, Saitoh S, Ura N, Shimamoto K: A practical index for evaluation of insulin resistance. *J Jpn Diabetes Soc* 2000; **43**: 205–213.
11. Matsuzawa Y: The new diagnostic criteria of obesity. *J Jpn Soc Study Obesity* 2000; **6**: 18–28.
12. The sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Arch Intern Med* 1997; **157**: 2413–2446.
13. American Diabetes Association: Clinical practice recommendations 1997. *Diabetes Care* 1997; **20** (Suppl 1): S1–S70.
14. Investigating Committee of Guideline for Diagnosis and Treatment of Hyperlipidemias, Japan Atherosclerosis Society: Guideline for Diagnosis and Treatment of Hyperlipidemias in Adults. Tokyo, Japan Atherosclerosis Society, 1997.
15. Zavaroni I, Bonora E, Passeri M, *et al*: Risk factors for coronary artery disease in healthy persons with hyperinsulinemia and normal glucose tolerance. *N Engl J Med* 1989; **320**: 702–706.
16. Haffner SM, Valdez RA, Hazuda HP, Mitchell BD, Morales PA, Stern MP: Prospective analysis of the insulin-resistance syndrome (syndrome X). *Diabetes* 1992; **41**: 715–722.
17. Howard G, O'Leary DH, Bergman R, *et al*: Insulin sensitivity and atherosclerosis. *Circulation* 1996; **93**: 1809–1817.
18. Tanaka Y, Atsumi Y, Kawamori R, *et al*: Usefulness of revised fasting plasma glucose criterion and characteristics of the insulin response to an oral glucose load in newly diagnosed Japanese diabetic subjects. *Diabetes Care* 1998; **21**: 1133–1137.
19. Pyorala M, Miettinen H, Halonen P, Laakso M, Pyorala K: Insulin resistance syndrome predicts the risk of coronary heart disease and stroke in healthy middle-aged men: the 22-year follow-up results of the Helsinki Policemen Study. *Arterioscler Thromb Vasc Biol* 2000; **20**: 538–544.
20. Shinozaki K, Naritomi H, Harano Y, *et al*: Role of insulin resistance associated with compensatory hyperinsulinemia in ischemic stroke. *Stroke* 1996; **27**: 37–43.
21. Hirose H, Saito I, Kawabe H, Saruta T: Insulin resistance and hypertension: seven-year follow-up study in middle-aged Japanese men (the KEIO study). *Hypertens Res* 2003; **26**: 795–800.
22. Sugaya T, Yasu T, Saito M, *et al*: Effect of atrial septal aneurysm on risk of cerebrovascular events in Japanese patients. *Int J Cardiol* 2004; **93**: 253–256.

Original Article

Metabolic Syndrome and Cardiac Disease in Japanese Men: Applicability of the Concept of Metabolic Syndrome Defined by the National Cholesterol Education Program–Adult Treatment Panel III to Japanese Men—The Tanno and Sobetsu Study

Hiroshi TAKEUCHI, Shigeyuki SAITOH, Satoru TAKAGI, Hirofumi OHNISHI, Junichi OHHATA, Takeshi ISOBE, and Kazuaki SHIMAMOTO

Results of a 6-year follow-up study were used to determine whether the concept of and the criteria for metabolic syndrome as defined by the National Cholesterol Education Program–Adult Treatment Panel III (NCEP-ATP III) can be applied to Japanese men for prediction of the occurrence of cardiac disease. The subjects were 808 men who underwent mass health check-ups in 1993 and who were not on medication for hypertension, diabetes or hyperlipidemia. Individuals who had hypertriglyceridemia, hypo-high density lipoprotein (HDL) cholesterolemia, high blood pressure, and/or high fasting plasma glucose levels were identified on the basis of the NCEP-ATP III criteria. Not in conformity with the NCEP-ATP III, however, a cut-off value of 85 cm was used for waist girth as an indicator of abdominal obesity. The subjects who had 3 or more risk factors were judged as having metabolic syndrome. The proportion of subjects having metabolic syndrome was 25.3%. In the 6-year follow-up study, cardiac disease occurred in 11.7% of the subjects in the metabolic syndrome group and in 6.7% of the subjects in the non-metabolic syndrome group. Results of regression analysis using Cox's proportional hazards model showed that subjects in the metabolic syndrome group had a 2.2-times greater risk of developing cardiac disease than did subjects in the non-metabolic syndrome group. The concept of metabolic syndrome as defined in the NCEP-ATP III was therefore considered to be useful for predicting the occurrence of cardiac disease in Japanese men. (*Hypertens Res* 2005; 28: 203–208)

Key Words: **metabolic syndrome, National Cholesterol Education Program–Adult Treatment Panel III, insulin resistance, prognosis**

Introduction

The third revision of the Adult Treatment Panel (ATP III) (*1*) is a guideline for cholesterol testing and management in the United States published by the National Cholesterol Education Program (NCEP) in 2001. The NCEP-ATP III emphasizes, in addition to the importance of cholesterol control, the importance of other risk factors for development of cardiovascular diseases, especially coronary heart disease, and proposes that concurrence of risk factors in individuals be designated as metabolic syndrome. This indicates that rigid control of the serum cholesterol level alone cannot completely prevent the occurrence of coronary heart diseases and

From the Second Department of Internal Medicine, Sapporo Medical University School of Medicine, Sapporo, Japan.
Address for Reprints: Hiroshi Takeuchi, M.D., Second Department of Internal Medicine, Sapporo Medical University School of Medicine, South-1, West-16, Chuo-ku, Sapporo 060–8543, Japan. E-mail: takeuchi@sapmed.ac.jp
Recieved August 23, 2004; Accepted in revised form November 26, 2004.

Table 1. Characteristics of Subjects with and without Metabolic Syndrome at Baseline (1993)

	Subjects with metabolic syndrome (n=197)	Subjects without metabolic syndrome (n=583)	p
Age (years)	61.8±11.2	59.8±12.1	0.050
BMI (kg/m^2)	25.2±2.9	22.5±2.8	<0.001
Waist (cm)	89.9±6.8	80.5±8.6	<0.001
SBP (mmHg)	140.6±14.4	131.3±18.5	<0.001
DBP (mmHg)	84.8±8.2	80.0±9.1	<0.001
T-cho (mg/dl)	192.8±34.1	184.8±30.4	0.004
HDL (mg/dl)	45.4±13.6	57.2±13.3	<0.001
TG (mg/dl)	211.1±99.2	124.3±64.3	<0.001
FPG (mg/dl)	103.5±25.7	90.7±15.2	<0.001

BMI, body mass index; Waist, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; T-cho, total cholesterol level; HDL, high density lipoprotein-cholesterol level; LDL, low density lipoprotein-cholesterol level; TG, triglyceride level; FPG, fasting plasma glucose. Values are means±SDs.

that risk factors other than low density lipoprotein (LDL)-cholesterol and their concurrence in individuals are crucial to the development of coronary heart diseases.

In the NCEP-ATP III, metabolic syndrome in men is defined as the coexistence in an individual of at least three of the following: 1) waist girth over 102 cm, 2) serum triglyceride level over 150 mg/dl, 3) serum high density lipoprotein (HDL)-cholesterol level below 40 mg/dl, 4) systolic blood pressure (SBP) over 130 mmHg and/or diastolic blood pressure (DBP) over 85 mmHg, and 5) fasting plasma glucose level over 110 mg/dl. The existence of insulin resistance seems to underlie metabolic syndrome. We previously reported that the existence of insulin resistance contributes to the development of metabolic syndrome in Japanese men (*2–4*). In Japanese people with a genetic predisposition to low mean serum cholesterol levels, insulin resistance is relatively more influential than the other risk factors for cardiovascular diseases, including coronary heart disease (*4, 5*). The designation of metabolic syndrome in the NCEP-ATP III appears to be useful for prevention of arteriosclerotic diseases in Japanese people as in the United States. However, to our knowledge, there has been no report on the association between metabolic syndrome and cardiac diseases in Japanese people.

The aim of this study was to determine whether the concept of and the criteria for metabolic syndrome proposed by the NCEP-ATP III can be applied to Japanese men to predict onset of cardiac diseases and whether the criterion of three or more risk factors for the diagnosis of metabolic syndrome is a reasonable one on the basis of the results of a 6-year follow-up study.

Methods

The subjects were 808 men who underwent health examinations in the towns of Tanno and Sobetsu in Hokkaido, Japan (*6*) and who were not receiving treatment for hypertension, diabetes or hyperlipidemia. The mean age of the subjects was 60.3±11.9 years. Information on medication being taken by the subjects was obtained through questionnaires distributed by a health nurse. Informed consent for inclusion in this study was obtained from all subjects. Blood samples were collected early in the morning from subjects more than 10 h after the last dietary intake. The plasma level of glucose (determined by the glucose-oxidize electrode method), and the serum total cholesterol (cholesterol-oxidize–dimethoxy-anilinehydroxy-3-sulfopropyl [DAOS] method), serum HDL-cholesterol (dextran-sulfate magnesium-hydrochloride precipitation method) and serum triglyceride levels (glycerol-3-phosphate-oxidize–DAOS method) were measured. Waist girth was measured (*7*) after expiration at the level of the navel by the same technician. Blood pressure was measured twice in the sitting position using a mercury sphygmomanometer (the first phase of Korotkoff's sound was taken as the SBP and the fifth phase was taken as the DBP). The average of the two measurements was used for analysis.

Subjects having one or more of the following criteria for metabolic syndrome in the NCEP-ATP III were identified: serum triglyceride level over 150 mg/dl (hypertriglyceridemia [HTG]), serum HDL-cholesterol level below 40 mg/dl (low-HDL cholesterolemia [LHDL]), SBP over 130 mmHg and/or DBP over 85 mmHg (high blood pressure [HBP]), fasting plasma glucose level over 110 mg/dl (high fasting plasma glucose level [HFPG]), and waist girth over 85 cm (abdominal obesity [AO]). The criterion for abdominal obesity defined by the NCEP-ATP III is waist girth over 102 cm. Of the 808 subjects in the present study, only 17 (2.7%) fulfilled this criterion (waist girth over 102 cm). We therefore used waist girth over 85 cm, which is the criterion for obesity of visceral fat type of the Japan Society for the Study of Obesity (*7, 8*), as the criterion for AO. Subjects who had 3 or more of the risk factors were judged as having metabolic syndrome (MS group), and subjects who had 2 or less risk factors were judged as not having metabolic syndrome (non-MS group). Twenty-eight men for whom data on waist circumference or

Table 2. Characteristics of Subjects with and Subjects without Cardiac Disease at Baseline (1993)

	Subjects with cardiac disease (n=49)	Subjects without cardiac disease (n=566)	p
Age (years)	64.6±7.4	61.6±10.6	0.014
BMI (kg/m^2)	23.3±3.2	23.2±4.2	0.727
Waist (cm)	85.0±9.8	82.6±9.3	0.104
SBP (mmHg)	136.5±17.6	134.3±18.1	0.399
DBP (mmHg)	81.6±8.1	81.7±9.3	0.944
T-cho (mg/dl)	181.4±31.9	187.0±31.1	0.240
HDL (mg/dl)	53.6±14.9	54.6±14.4	0.676
TG (mg/dl)	139.0±62.2	144.3±85.2	0.584
FPG (mg/dl)	95.8±20.9	93.5±17.9	0.446

Abbreviations are the same as in Table 1. Cardiac diseases are angina pectoris, myocardial infarction, heart failure and death from such cardiac diseases. Values are means±SDs.

on biochemical measures included in the definition of MS were missing were excluded, leaving 780 men for analysis.

The subjects were followed up for 6 years. The end-point was the occurrence of cardiac diseases, including angina pectoris, myocardial infarction, and heart failure, or death from such cardiac diseases. Occurrence of cardiac diseases was determined by interviews with the subjects and their families, notification from district health nurses, and distribution of questionnaires to family doctors who had treated subjects with cardiac disease. Diagnosis of cardiac disease was made from clinical symptoms and results of laboratory examinations such as ECG, chest X-ray photograph (XP) and blood tests. Diagnosis of coronary heart disease was made on the basis of the criteria of the MONICA project (available from: http://www.ktl.fi/publications/monica/manual/index.htm). The incidence of cardiac diseases during the 6-year period was compared between the MS group and the non-MS group. Moreover, the incidences of cardiac diseases in subjects who had 2 or more risk factors (2, 3, 4 or 5 risk factors) and in subjects who had 4 or more risk factors (4 or 5 risk factors) in the first year were compared with the incidences in subjects who had less than 2 risk factors (0 or 1 risk factor) and in subjects who had less than 4 risk factors (1, 2 or 3 risk factors), respectively. Follow-up was started in August 1993 and completed in August 1999.

The Japanese Windows Edition of the Statistical Package for Social Science (SPSS) Ver. 11 was used for statistical analysis. All numerical values are expressed as the means±SD. The unpaired t-test was used for examination of intergroup differences. For analysis of factors determining prognosis, Cox's proportional hazards model was used. A p-value less than 0.05 was considered statistically significant.

Results

The mean age of all subjects was 60.3±11.9 years, the mean body weight was 61.3±9.8 kg, the mean body mass index (BMI) was 23.1±3.0 kg/m^2 and the mean waist girth was 82.8±9.2 cm. The mean SBP and DBP were 133.7±18.0 mmHg and 81.2±9.1 mmHg, respectively, and the mean plasma levels of total cholesterol, HDL-cholesterol, triglyceride and fasting blood glucose were 186.8±31.6 mg/dl, 54.3±14.4 mg/dl, 146.2±83.6 mg/dl and 94.1±19.3 mg/dl, respectively.

The proportions of subjects with AO, HTG, LHDL, HBP and HFPG were 43.1%, 35.7%, 16.5%, 59.4% and 13.8%, respectively. The proportions of subjects without risk factors was 18.1%, and the proportions of subjects with 1, 2, 3, 4 and 5 risk factors were 29.7%, 26.9%, 17.5%, 6.8% and 1.0%, respectively. The proportionsof subjects with 2 or more, 3 or more and 4 or more risk factors were 52.2%, 25.3% and 7.8%, respectively. Subjects who had 3 or more risk factors were assigned to the MS group.

Table 1 compares the profiles of subjects in the MS group with those of subjects in the non-MS group (*i.e.*, subjects with two or less risk factors). There were no significant differences between the two groups in age. The values of BMI, waist girth and blood pressure and the levels of total cholesterol, triglycerides and fasting plasma glucose were significantly higher in the MS group. The HDL-cholesterol level was significantly lower in the MS group.

During the follow-up study, from 1993 to 1999, 193 subjects dropped out. There was no significant difference between the subjects who dropped out and the remaining subjects in terms of the proportion of subjects with metabolic syndrome. The remaining 615 subjects were followed for a mean period of 4.8 years. Cardiac disease occurred in 49 subjects (angina pectoris occurred in 30 subjects, myocardial infarction in 15 subjects and heart failure in 4 subjects), or 31 subjects in the non-MS group and 18 subjects in the MS group.Thirty-two of the subjects with 2 or more risk factors and four of the subjects with 4 or more risk factors developed cardiac disease. Table 2 shows a comparison of clinical characteristics at baseline between subjects with and those without cardiac disease. There were no significant differences between the two groups in the values of BMI, waist girth or

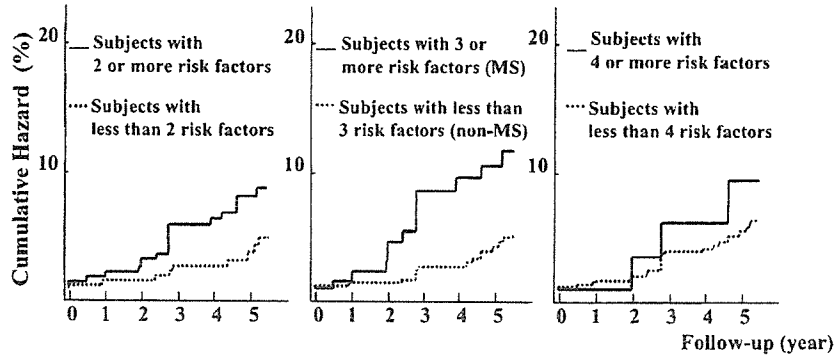

Fig. 1. *Kaplan-Meier hazard curves for onset of cardiac disease. The relative risk in the MS group was 2.23 (95% CI: 1.14–4.34, p = 0.019)-times higher than that in the non-MS group. The risk in the subjects with 2 or more risk factors relative to the risk in the subjects with less than 2 risk factors was 1.43 (0.73–2.81, p = 0.301). The risk in the subjects with 4 or more risk factors relative to the risk in the subjects with less than 4 risk factors was 1.74 (0.61–4.93, p = 0.299). Relative risk was determined by Cox's proportional hazards model adjusted for age, smoking and total cholesterol.*

blood pressure or in the levels of total cholesterol, triglycerides, fasting plasma glucose and HDL-cholesterol. The Kaplan-Meier hazard curve showed that the incidence of cardiac diseases was significantly higher in the MS group than in the non-MS group during the follow-up study (Fig. 1). The relative risk of occurrence of cardiac diseases in the MS group was 2.23 (95% confidence interval [CI]: 1.14–4.34; p=0.019)-times higher than that in the non-MS group according to the results of analysis using Cox's proportional hazards model adjusted for age, smoking and total cholesterol. The risks of occurrence of cardiac diseases in the subjects with 2 or more risk factors and in those with 4 or more risk factors relative to the risks in the subjects with less than 2 risk factors and in those with less than 4 risk factors were 1.43 (0.73–2.81, p=0.301) and 1.74 (0.61–4.93, p=0.299), respectively (Table 3).

Discussion

Hyperlipidemia, hypertension, disorders in glucose tolerance, and obesity are well-known risk factors for cardiovascular diseases. It was clarified by epidemiological studies in the 1990s that even if the risks of individual factors were not serious, the probability of the occurrence of ischemic cardiac diseases would increase when many risk factors coexisted in an individual (*9–16*). The clinical findings for metabolic syndrome as defined by the NCEP-ATP III reflect this state. The definition of metabolic syndrome by NCEP-ATP III emphasizes the importance of abdominal obesity and includes in the diagnostic criteria mild risk factors such as blood pressure at high levels within the normal range and hyperglycemia under a fasting condition. The diagnostic criteria for individual risk factors are shown more clearly in the criteria of metabolic syndrome as defined by NCEP-ATP III. High blood pressure and hyperglycemia are defined as risk factors in MS, even though in general they are less severe conditions than hypertension or diabetes as defined in the Sixth Report of the Joint National Committee (JNC VI) (*17*), or by the criteria of the World Health Organization-International Society of Hypertension (WHO/ISH) (*18*), the World Health Organization (WHO) (*19*), or the American Diabetes Association (ADA) (*20*). This indicates that the concurrence of mild risk factors is crucial for the development of arteriosclerosis in the concept of metabolic syndrome.

In the present study, the criteria for metabolic syndrome in the NCEP-ATP III were applied to Japanese men with the modification that 85 cm instead of 102 cm was used for the cut-off value of waist girth for AO. Using the original NCEP-ATP III criteria, only 2.7% of the present subjects fulfilled the criterion of waist girth over 102 cm, and the prevalence of the metabolic syndrome was 12%. We therefore used as the criterion for AO waist girth over 85 cm, which is the criterion of the Japan Society for the Study of Obesity (*7, 8*) for obesity of visceral fat type. Waist girth of 85 cm in Japanese men is known to correspond to an area occupied by visceral fat of 100 cm^2 in transverse CT images at the level of the navel (*8*). The incidences of hypertension, diabetes, hyperlipidemia and diseases of the circulatory organs are high in men in whom the area of visceral fat exceeds 100 cm^2 in transverse CT images (*8, 21*). An increase in the amount of visceral fat, which causes abdominal obesity, tends to induce insulin resistance and is associated with arteriosclerosis (*8, 21, 22*). Measurement of waist girth is a simple but apparently useful method for diagnosing abdominal obesity. In Asians, decreasing the criterion of waist circumference increased the prevalence of the metabolic syndrome. When the criterion of waist

Table 3. Hazard Ratio for Occurrence of Cardiac Diseases According to the Results of Cox's Proportional Hazards Model Adjusted for Age, Smoking and Total Cholesterol

Subjects	Hazard ratio (95% confidence interval)
With 2 or more risk factors†	1.43 (0.73–2.81)
With 3 or more risk factors (MS)††	2.23 (1.14–4.34)*
With 4 or more risk factors†††	1.74 (0.61–4.93)

*$p<0.05$. †The risk of occurrence of cardiac diseases in the subjects with 2 or more risk factors relative to the risk in those with less than 2 risk factors. ††The risk in the MS group relative to the risk in the non-MS group. †††The risk in the subjects with 4 or more risk factors relative to the risk in those with less than 4 risk factors.

circumference was decreased from 102 cm to 90 cm, the prevalence of the metabolic syndrome increased 13% to 21% in the Singapore male population (*23*), and 16% to 29% in the Korean male population (*24*). This suggests that NCEP-ATP III criteria may underestimate the population at risk in the Asian population. There is thus need of a new abdominal obesity criterion for metabolic syndrome that is suitable for the Japanese population.

Lakka *et al.* (*25*) reported in 2002 that the risk of mortality from coronary heart diseases was higher in individuals with metabolic syndrome in the ordinary Finnish male population that included subjects who were receiving treatment for hypertension or hyperlipidemia, and they emphasized the importance of prevention of development of metabolic syndrome and the importance of its diagnosis and therapy in an early stage. In the present study, in the subjects who were not receiving treatment for hypertension, diabetes or hyperlipidemia, the relative risk of mortality and morbidity from cardiac disease in the metabolic syndrome group, even after adjusting for age, smoking and total cholesterol, was 2.2-times greater than that in the non-metabolic syndrome group.

On the other hand, there were no significant differences between cardiac disease mortality/morbidity in the subjects with 2 or more risk factors and those with less than 2 risk factors or between cardiac disease mortality/morbidity in the subjects with 4 or more risk factors and those with less than 4 risk factors. This indicates that the NCEP-ATP III criterion for metabolic syndrome, *i.e.*, the presence of 3 or more risk factors, is reasonable for predicting cardiac disease in the Japanese population.

Our results indicate that the concept of metabolic syndrome defined by the NCEP-ATP III is useful for prediction of onset of cardiac disease in Japanese men.

The concept of metabolic syndrome seems to be strategically important for prevention of arteriosclerotic diseases in Japan as well as in the United States, Finland or other countries, because individuals with metabolic syndrome can be easily identified according to the criteria. It is important to control risk factors for cardiovascular diseases, such as lipid metabolic disorders, high blood pressure, disorders in glucose tolerance, and obesity, in persons with metabolic syndrome (*i.e.*, in persons having three or more of these risk factors), even if the risk of each factor is not serious. A strategy for the control of these risk factors is therefore needed.

References

1. National Cholesterol Education Program: Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 2001; **285**: 2486–2497.
2. Ohnishi H, Saitoh S, Ura N, *et al*: Relationship between insulin resistance and accumulation of coronary risk factors. *Diabetes, Obes Metab* 2002; **4**: 388–393.
3. Takeuchi H, Saitoh S, Takagi S, *et al*: Metabolic syndrome and insulin resistance in Japanese males—Tanno-Soubestu study. *J Jpn Diab Soc* 2003; **46**: 739–744.
4. Murakami H, Ura N, Furuhashi M, Higashiura K, Miura T, Shimamoto K: Role of adiponectin in insulin-resistant hypertension and atherosclerosis. *Hypertens Res* 2003; **26**: 705–710.
5. Hirose H, Saito I, Kawabe H, Saruta T: Insulin resistance and hypertension: seven-year follow-up study in middle-aged Japanese men (the KEIO Study). *Hypertens Res* 2003; **26**: 795–800
6. Takagi S, Saitoh S, Nakano M, *et al*: Relationship between blood pressure level and mortality rate: an 18-year study conducted in two rural communities in Japan. *J Hypertens* 2000; **18**: 143–148.
7. Matsuzawa Y: The new diagnostic criteria of obesity. *J Jpn Soc Stud Obes* 2000; **6**: 18–28.
8. Examination Committee of Criteria for 'Obesity Disease' in Japan; Japan Society for the Study of Obesity: New criteria for 'obesity disease' in Japan. *Circ J* 2002; **66**: 987–992.
9. Ruige JB, Assendelft WJJ, Dekker JM, Kostense PJ, Heine RJ, Bouter LM: Insulin and risk of cardiovascular disease. A meta-analysis. *Circulation* 1998; **97**: 996–1001.
10. Lempiainen P, Mykkanen L, Pyorala K, Laakso M, Kuusisto J: Insulin resistance syndrome predicts coronary heart disease events in elderly nondiabetic men. *Circulation* 1999; **100**: 123–128.
11. Nakamura T, Tsubono Y, Kameda K, *et al*: Magnitude of sustained multiple risk factors for ischemic heart disease in Japanese employees: a case-control study. *Jpn Circ J* 2001; **65**: 11–17.
12. Reaven GM: Role of insulin resistance in human disease. *Diabetes* 1988; **37**:1595–1607.
13. Kaplan NM: The deadly quartet: Upper-body obesity, glucose intolerance, hypertriglyceridemia, and hypertension. *Arch Intern Med* 1989; **149**: 1514–1520.
14. DeFronzo RA, Ferranni E: Insulin resistance: a multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. *Diabetes Care* 1991; **14**: 173–194.
15. Zimmet P, Alberti KGMM, Shaw J: Global and societal

implications of the diabetes epidemic. *Nature* 2001; **414**: 782–787.
16. Tozawa M, Iseki K, Iseki C, *et al*: Impact of multiple risk factor clustering on the elevation of blood pressure. *Hypertens Res* 2002; **25**: 811–816.
17. Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Arch Intern Med* 1997; **157**: 2413–2446.
18. Guidelines Subcommittee: 1999 World Health Organization–International Society of Hypertension Guidelines for the Management of Hypertension. *J Hypertens* 1999; **17**: 151–183.
19. Alberti KG, Zimmet PZ: Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med* 1998; **15**: 539–553.
20. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 1997; **20**: 1183–1197.
21. Nakamura T, Tokunaga K, Shimomura I, *et al*: Contribution of visceral fat accumulation to the development of coronary artery disease in non-obese men. *Atherosclerosis* 1994; **107**: 239–246.
22. Nishina M, Kikuchi T, Yamazaki H, Kameda K, Hiura M, Uchiyama M: Relationship among systolic blood pressure, serum insulin and leptin, and visceral fat accumulation in obese children. *Hypertens Res* 2003; **26**: 281–288.
23. Tan CE, Ma S, Wai D, Chew SK, Tai ES: Can we apply the National Cholesterol Education Program adult treatment panel definition of the metabolic syndrome to Asians? *Diabetes Care* 2004; **27**: 1182–1186.
24. Oh JY, Hong YS, Sung YA, Barrett-Connor E: Prevalence and factor analysis of metabolic syndrome in an urban Korean population. *Diabetes Care* 2004; **27**: 2027–2032.
25. Lakka HM, Laaksonen DE, Lakka TA, *et al*: The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. *JAMA* 2002; **288**: 2709–2716.