assessed by abdominal CT are relatively good indicators of the risk of cardiovascular disease (*8–13*). Abdominal CT enables quantification of the visceral fat area (VFA) and therefore serves as the gold standard for visceral fat assessment. On the other hand, WC measurement is recommended as a simpler and easier screening method (*14*). However, abdominal CT has drawbacks, including exposure to radiation, lack of ease and simplicity, and high cost. WC includes subcutaneous fat, and WC measurement therefore has drawbacks such as an inability to account for an individual's height and a low level of reproducibility in the case of marked obesity.

Simple methods for assessing visceral fat accumulation using ultrasonography (US) have been studied in recent years (*15–20*). In addition, previous studies have indicated a relationship between hypertension and visceral fat assessed by abdominal CT and WC, but US was not used in any of those studies (*21–24*). Thus, in the present study, we assessed the usefulness of visceral fat assessment by US in outpatients. Then, based on the results of a cross-sectional study, we assessed the relationships between abdominal obesity determined by US and cardiovascular disease risk factors, particularly blood pressure levels.

Methods

Study 1

The subjects were 45 men and 61 women outpatients (mean ages: 55.4±19.4 years for men and 67.5±10.8 years for women). Individuals with cardiovascular disease, renal disease or a severe debilitating disease were excluded from participation. Height, body weight, WC, VFA and total fat area (TFA) were determined by abdominal CT, and visceral fat distance (VFD) was determined by US. The subcutaneous fat area (SFA) was calculated by subtracting VFA from TFA.

Informed consent was obtained from each outpatient, who completed a form consenting to testing. Height, body weight and visceral fat levels were measured on the same day, and BMI was calculated. Correlations between VFA, SFA, VFD, BMI and WC were investigated.

Measurement of Visceral Fat Levels

CT equipment from Toshiba Medical Systems (Tokyo, Japan) was used for abdominal CT. Imaging was done at the end of expiration at the umbilical level. Tracing in cross-sectional images was done using a trackball; the total cross-sectional area was determined by automatic calculation of portions with a CT number of −200 to 1,000 Hounsfield units (HU) using the method of Grauer *et al.* (*25*). In addition, portions with a CT number of −200 to −10 HU were separated as adipose tissue and their areas were automatically calculated.

WC was measured with non-stretchable measuring tape while subjects bared the circumference of the abdomen. The umbilical circumference was measured in increments of 0.1 cm during expiration while standing (*14*).

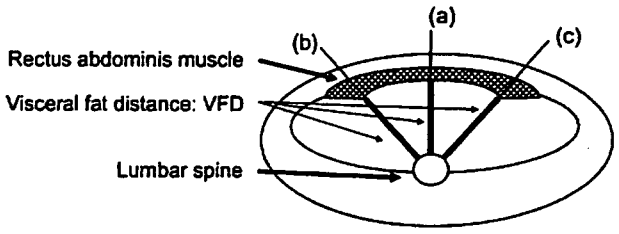

Fig. 1. *VFD was measured between the peritoneum and the lumbar spine, and which was taken as the average value. VFD = (a + b + c)/3. Each subject assumed a supine position, and at the end of expiration the distance from the peritoneum to the front of the vertebral body was measured perpendicularly three times with a 3.5 MHz linear probe while making the slightest contact possible, and the average value was used as the VFD.*

VFD was measured using VF-750XT portable ultrasonography equipment (Fukuda Electrical, Tokyo, Japan) by the method of Stolk *et al.* (*18, 19*). That is, each subject assumed a supine position, and at the end of expiration the distance from the peritoneum to the front of the vertebral body was measured perpendicularly three times with a 3.5 MHz linear probe while making the least possible amount of contact, and the average value was used as the VFD (Fig. 1). All measurements were performed by the same investigator.

Study 2

The subjects were 353 men and 457 women (mean ages: 62.8±12.2 years for men and 57.8±12.6 years for women) out of 1,455 individuals who underwent screening for local residents of a rural community; individuals being treated for hypertension, diabetes or hyperlipidemia were excluded. The study was approved by the Ethics Committee of Sapporo Medical University, and written informed consent was obtained from each subject.

For all subjects, height and body weight were measured after fasting for 8 h or longer since their last meal, blood pressure levels were measured and blood samples were taken. The blood samples were used to measure high-density lipoprotein (HDL)–cholesterol levels (HDL-c), triglyceride levels (TG), fasting plasma glucose levels (FPG) and serum insulin levels. Afterwards, WC and VFD were measured. Height and body weight were measured at intervals of 0.1 cm and 0.1 kg, respectively, with subjects lightly dressed and shoes removed. Blood pressure was measured twice consecutively on the upper arm using an automated sphygmomanometer (HEM-907, Omron Instruments, Tokyo, Japan) with subjects in a seated resting position, and the average was used for systolic blood pressure (SBP) and diastolic blood pressure (DBP).

Table 1. Characteristics of the Subjects for Study 1

	Men (n=45)	Women (n=61)	p-value
Age (years)	55.4±19.4	67.5±10.8	<0.001
Body weight (kg)	67.1±11.8	56.4±8.8	<0.001
BMI (kg/m^2)	24.2±3.2	24.7±3.9	0.462
Lean: BMI<22	11/45 (24%)	14/61 (23%)	
Overweight: 22≤BMI<25	17/45 (38%)	23/61 (38%)	
Obese: 25≤BMI	17/45 (38%)	24/61 (39%)	
WC (cm)	84.9±8.8	85.6±10.1	0.787
VFD (cm)	5.2±1.2	4.9±1.43	0.459
SFA (cm^2)	147.0±63.8	221.2±132.4	<0.001
VFA (cm^2)	137.0±62.6	128.9±51.8	0.606

All values are mean±SD. BMI, body mass index; WC, waist circumference; VFD, visceral fat distance; SFA, subcutaneous fat area; VFA, visceral fat area.

Table 2. Correlation between Adipose Tissue Measured by CT and Other Anthropometric Parameters

	Adipose tissue measured by CT	
	SFA	VFA
Men (n=45)		
BMI	0.763*	0.565*
WC	0.861*	0.646*
VFD	0.237	0.660*
Women (n=61)		
BMI	0.591*	0.571*
WC	0.595*	0.499*
VFD	0.289**	0.643*

Values are Pearson's correlation coefficients. *p<0.001, **p<0.05. SFA, subcutaneous fat area; VFA, visceral fat area; BMI, body mass index; WC, waist circumference; VFD, visceral fat distance.

Measurement Methods

HDL-c was measured by the enzymatic method (homogenous), TG was measured by the enzymatic colorimetric method (free glycerol elimination), FPG was measured by the GOD immobilized oxygen electrode maximum reaction acceleration method, and serum insulin level was measured by the enzyme immunoassay method. In addition, homeostasis model assessment index (HOMA-IR) was calculated on the basis of FPG and serum insulin levels (*26*).

Diagnostic Criteria for Cardiovascular Disease Risk Factors

Diagnostic criteria for cardiovascular disease risk factors followed the NCEP ATPIII criteria for MS (*6*). High blood pressure (HBP) was defined as SBP ≥130 mmHg and/or DBP ≥85 mmHg or higher, hypertriglyceridemia (HTG) was defined as TG ≥150 mg/dl, low HDL cholesterolemia (LHDL) was defined as HDL-c <40 mg/dl for men and <50 mg/dl for women, and high fasting plasma glucose (HFPG) was defined as FPG ≥110 mg/dl.

Statistical Analysis

Statistical analysis was done using Windows SPSS version 11.5J. Numerical values are shown as means (mean)±SD. The correlation between two variables was evaluated using Pearson's correlation coefficient. Comparison between two groups was done with an unpaired t-test. For logistic regression analysis, subjects were divided into tertiles based on VFD and WC, adjusted for age (model 1) and then adjusted for age and BMI (model 2); with the low VFD and low WC groups as a reference, odds ratios (OR) and individual cardiovascular disease risk factors were examined. Comparison of three groups was done by multiple comparisons after one-way ANOVA. For multiple regression analysis, blood pressure level served as a dependent variable, and the relationships between cardiovascular disease risk factors with VFD and WC were studied. In all instances, the level of significance was p<0.05.

Results

Study 1

Table 1 shows characteristics of the 45 male and 61 female outpatient subjects whose visceral fat levels were measured by abdominal CT. No significant difference between the male and female subjects was found in BMI, WC, VFD or VFA. SFA was significantly larger for women than for men.

The correlations between SFA and VFA determined by abdominal CT and BMI, VFD and WC are shown in Table 2. The correlation coefficients between VFA and VFD were r=0.660 (p<0.001) for men and r=0.643 (p<0.001) for women. In addition, VFA had a stronger correlation to VFD than to BMI or WC. Moreover, BMI and WC had stronger

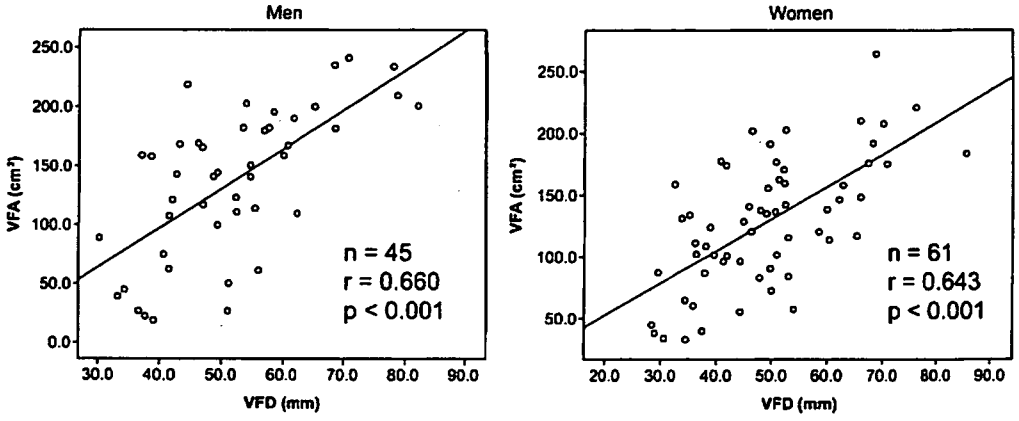

Fig. 2. *Scattergrams of relationship between VFD and VFA for men and women. VFD, visceral fat distance assessed by ultrasonography; VFA, visceral fat area assessed by CT. There were significant positive correlations between VFD and VFA in both men and women.*

Table 3. Characteristics of the Study Subjects of Residents of a Rural Community

	Men (n=353)	Women (n=457)	p-value
Age (years)	62.8±12.2	57.8±12.6	<0.001
Body weight (kg)	63.9±10.1	53.7±7.6	<0.001
BMI (kg/m²)	23.7±3.2	23.0±3.2	0.002
Lean: BMI<22	107/353 (30%)	177/457 (39%)	
Overweight: 22≤BMI<25	143/353 (41%)	171/457 (37%)	
Obese: 25≤BMI	103/353 (29%)	109/457 (24%)	
WC (cm)	84.7±9.1	82.6±9.9	0.002
VFD (cm)	5.5±1.7	4.7±1.3	<0.001
SBP (mmHg)	131.9±20.1	127.0±21.2	0.001
DBP (mmHg)	75.5±11.6	71.9±10.6	<0.001
HDL-c (mg/dl)	51.3±11.7	59.3±14.5	<0.001
TG (mg/dl)	115.1±75.2	88.3±49.2	<0.001
FPG (mg/dl)	96.8±15.7	94.4±17.7	0.041
Serum insulin levels (μU/ml)	4.5±4.7	4.4±2.9	n.s.
HOMA-IR	1.13±1.38	1.04±0.72	n.s.

All values are mean±SD. BMI, body mass index; WC, waist circumference; VFD, visceral fat distance; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL-c, high-density lipoprotein-cholesterol; TG, triglyceride; FPG, fasting plasma glucose; HOMA-IR, homeostasis model assessment index; n.s., not significant.

correlations to SFA than to VFA (Table 2).

Figure 2 shows scattergrams of the relationships between VFD and VFA for men and women. There were significant positive correlations between VFD and VFA in both sexes.

Study 2

Table 3 shows the characteristics of the subjects in Study 2. Average VFDs were 5.5±1.7 cm for men and 4.7±1.3 cm for women, and average WCs were 84.7±9.1 cm for men and 82.6±9.9 cm for women.

The subjects were divided into tertiles based on VFD and WC; OR for cardiovascular disease risk factors with individual low-tertile groups as a reference are shown in Table 4. Adjusted only for age (model 1), OR increased significantly for the male VFD group in comparison to that for the low VFD group in HBP (OR: 3.45 [95% CI: 1.83–5.77]; p<0.001) and HTG (OR: 3.74 [1.72–8.12]; p<0.05), and it increased significantly for the female group in HBP (OR: 2.31 [1.37–3.92]; p<0.05), HTG (OR: 13.3 [3.02–58.5]; p<0.05) and LHDL (OR: 4.62 [2.47–8.62]; p<0.001). Similarly, OR increased significantly for the male WC group in comparison to that for the low WC group in HBP (OR: 2.00 [1.15–3.45]; p<0.05), HTG (OR: 3.09 [1.41–6.75]; p<0.05) and LHDL (OR: 8.82 [1.98–39.3]; p<0.05), and it increased significantly for the female group in HBP (OR: 1.95 [1.18–3.23];

Table 4. Odds Ratios and 95% CIs of CAD Risk Factors by Tertile of VFD and WC

	HBP	HTG	HFPG	LHDL
Men (n=353)				
Model 1				
VFD				
Lower tertile	1.00	1.00	1.00	1.00
Middle tertile	1.79 (1.04–3.09)*	2.31 (1.04–5.16)*	1.04 (0.4–2.44)	1.95 (0.83–4.59)
Upper tertile	3.45 (1.83–5.77)†	3.74 (1.72–8.12)*	0.80 (0.32–2.00)	2.02 (0.85–4.77)
WC				
Lower tertile	1.00	1.00	1.00	1.00
Middle tertile	2.10 (1.22–3.59)*	3.41 (1.56–7.44)*	0.79 (0.32–1.99)	16.4 (3.79–71.1)†
Upper tertile	2.00 (1.15–3.45)*	3.09 (1.41–6.75)*	1.26 (0.54–2.96)	8.82 (1.98–39.3)*
Model 2				
VFD				
Lower tertile	1.00	1.00	1.00	1.00
Middle tertile	1.67 (0.95–2.95)	2.21 (0.97–5.04)	0.88 (0.36–2.13)	1.71 (0.71–4.14)
Upper tertile	2.75 (1.37–5.50)*	3.35 (1.35–8.32)*	0.52 (0.17–1.62)	1.44 (0.52–4.04)
WC				
Lower tertile	1.00	1.00	1.00	1.00
Middle tertile	1.60 (0.86–2.96)	3.09 (1.31–7.31)*	0.71 (0.25–1.96)	17.6 (3.77–82.2)†
Upper tertile	1.15 (0.51–2.59)	2.54 (0.87–7.41)	1.00 (0.29–3.46)	10.1 (1.75–58.1)*
Women (n=457)				
Model 1				
VFD				
Lower tertile	1.00	1.00	1.00	1.00
Middle tertile	1.76 (1.04–2.98)*	6.28 (1.38–28.6)*	0.52 (0.16–1.72)	2.32 (1.23–4.38)*
Upper tertile	2.31 (1.37–3.92)*	13.3 (3.02–58.5)*	1.82 (0.71–4.69)	4.62 (2.47–8.62)†
WC				
Lower tertile	1.00	1.00	1.00	1.00
Middle tertile	1.05 (0.63–1.76)	3.79 (1.21–11.8)*	1.10 (0.43–2.82)	2.72 (1.52–4.86)*
Upper tertile	1.95 (1.18–3.23)*	5.79 (1.93–17.4)*	0.93 (0.37–2.34)	2.46 (1.36–4.43)*
Model 2				
VFD				
Lower tertile	1.00	1.00	1.00	1.00
Middle tertile	1.27 (0.73–2.22)	4.59 (0.99–21.3)	0.56 (0.16–1.92)	1.91 (0.99–3.70)
Upper tertile	1.06 (0.55–2.04)	6.36 (1.30–31.3)*	2.16 (0.67–6.92)	2.94 (1.40–6.17)*
WC				
Lower tertile	1.00	1.00	1.00	1.00
Middle tertile	0.65 (0.37–1.15)	2.37 (0.73–7.73)	0.90 (0.32–2.47)	1.78 (0.95–3.33)
Upper tertile	0.74 (0.37–1.45)	2.06 (0.56–7.57)	0.60 (0.17–2.05)	0.97 (0.45–2.09)

Model 1: adjusted for age; Model 2: adjusted for age and BMI. Significantly different from the Lower tertile: *p<0.05, †p<0.001. CI, confidence interval; CAD, cardiovascular disease; HBP, high blood pressure; HTG, hypertriglyceridemia; HFPG, high fasting plasma glucose; LHDL, low high-density lipoprotein cholesterolemia; VFD, visceral fat distance; WC, waist circumference.

p<0.05), HTG (OR: 5.79 [1.93–17.4]; p<0.05) and LHDL (OR: 2.46 [1.36–4.43]; p<0.05).

When additionally adjusted for BMI (model 2), OR increased significantly for the male VFD group in comparison to that for the low VFD group in HBP (OR: 2.75 [1.37–5.50]; p<0.05) and HTG (OR: 3.35 [1.35–8.32]; p<0.05). However, no significant association was found between WC and HBP or between WC and HTG. In addition, OR increased significantly for the female high VFD group in comparison to that for the low VFD group in HTG (OR: 6.36 [1.30–31.3]; p<0.05) and LHDL (OR: 2.94 [1.40–6.17]; p<0.05). However, no significant association was found between WC and any of the factors.

Table 5 shows the results of multiple regression analysis with SBP and DBP as dependent variables. For men, VFD was selected as a significant independent variable for both SBP and DBP. However, there was no significant association between WC and SBP or between WC and DBP.

Table 5. Results of Multiple-Regression Analysis Related to SBP and DBP

	Independent	Dependent			
		SBP		DBP	
		β	p-value	β	p-value
Men (n=353)	VFD	2.093	0.015	1.049	0.047
	WC	0.287	0.226	0.163	0.265
Women (n=457)	VFD	1.422	0.118	0.739	0.154
	WC	0.110	0.425	−0.057	0.466

Dependent variables: systolic blood pressure (SBP) or diastolic blood pressure (DBP). Independent variables: visceral fat distance (VFD) or waist circumference (WC) and additionally adjusted for age, triglyceride (TG), high-density lipoprotein-cholesterol (HDL-c), fasting plasma glucose (FPG), body mass index (BMI). β: standardized regression coefficient.

Although the data are not shown, when VFD was divided into tertiles, HOMA-IR increased significantly in the higher tertiles. Moreover, in multiple regression analysis using HOMA-IR as a dependent variable and using age, SBP, TG and VFD as independent variables, VFD was found to be a significant independent variable of HOMA-IR for both men and women.

Discussion

The significance of visceral obesity has been noted in recent years, and the accumulation of visceral fat must be accurately assessed. However, abdominal CT is not a simple technique, and WC also has the drawback of leading to an assessment that includes subcutaneous fat. In contrast, US involves no radiation exposure, the technique can be quickly learned, it is typically completed in less than 5 min, and it has been reported to have a good level of reproducibility (*15–20*). In the present study we therefore investigated whether US can be used as an easy screening method for the accurate estimation of the accumulation of visceral fat in Japanese as well.

When the correlations between VFA, SFA, BMI, VFD and WC were examined, VFD was found to have a stronger positive correlation with VFA than with SFA for both men and women. Additionally, BMI and WC each had a stronger positive correlation with SFA than with VFA. This is because measurements of BMI and WC are assessment methods that include elements of subcutaneous fat. The present study indicated that VFD measurement is a simple method for assessing visceral fat that does not include elements of subcutaneous fat and that VFD measurement is a useful means of assessing visceral fat in a large number of subjects.

The relationships between visceral fat and cardiovascular disease risk factors were then assessed in a study using US performed on inhabitants of a rural community who were not being treated for hypertension, diabetes or hyperlipidemia. The data presented in Table 4, obtained after adjustment for age and BMI (model 2), showed that VFD was significantly correlated with HBP, HTG and LHDL in men and with HTG and LHDL in women. On the other hand, WC was correlated with LHDL in men but showed only weak correlations with risk factors in women.

What eliminated the relationship between WC and cardiovascular disease risk factors in women subjects in particular was the effect of subcutaneous fat. Subcutaneous fat has less of an effect on arteriosclerosis than visceral fat and instead has antiarteriosclerotic action (*27*). In general, visceral obesity, a condition in which visceral fat readily accumulates, affects men more than women; women are affected by female sex hormones and exhibit body types that feature subcutaneous obesity (*28, 29*). Thus, in assessment by BMI and WC, the effects of subcutaneous fat are more intensely reflected in women than in men. This fact is supported by the stronger correlation of BMI and WC to SFA than to VFA in the study of outpatient cases (Study 1).

We could not find a significant association between FPG and a rise in VFD or WC for either men or women. The reasons are threefold. First, individuals on medication for type 2 diabetes were excluded in this study and, second, the study was conducted in a homogenous population with a relatively low FPG. Third, we could not find participants with impaired glucose tolerance (IGT) because we did not conduct oral glucose tolerance test (OGTT) in this study. Thus, there was a small number of participants with high FPG and there was no significant relationship between FPG and VFD for either men or women.

The results of multiple regression analysis showed that VFD was an independent explanatory variable of blood pressure in men. No significant relationship was found between WC and blood pressure in men or women. VFD may be a good indicator of blood pressure in men. Moreover, VFD may also be a useful index for the management of blood pressure in men with metabolic syndrome.

In a state of visceral fat accumulation, it is thought that free fatty acid produced by the decomposition of TG flows into the liver and induces insulin resistance. Moreover, substances that induce insulin resistance such as tumor necrosis factor (TNF)-α are produced from visceral fat. Studies have indicated the possibility that elevation of blood pressure is induced in a state of insulin resistance by various mechanisms *via* adipocytokines (*30*). It has also been reported that compensatory hyperinsulinemia, which occurs in a state of insulin

resistance, plays a role in blood pressure elevation *via* renal mechanisms (*31*).

In multiple regression analysis, no relationship was found between VFD and blood pressure in women. Possible reasons for this are the influence of an autocorrelation due to the addition of BMI to the adjusted items and both the small mean value and the low distribution of VFD in female subjects.

WC measurement is a very useful screening method for assessing visceral fat because it is simple and cheap. It does, however, have drawbacks, such as an inability to assess tall individuals differently than short ones and a low level of reproducibility in the case of marked obesity, since WC includes subcutaneous fat. Therefore, the Japanese criteria of MS recommend assessing real visceral fat accumulation by CT when we find individuals with WC ≥85 cm in men and ≥90 cm in women. Although abdominal CT is the gold standard for visceral fat assessment, it entails exposure to radiation, lack of ease and simplicity, and high cost. General practitioners may have a good deal of opportunity to assess individuals with MS, but very few physicians have CT equipment in their clinics. Assessment by US is a simpler technique than abdominal CT and allows general practitioners to assess visceral fat accumulation in their clinics. When we find high-risk individuals with an accumulation of risk factors and without abdominal obesity (WC <85 cm in men, WC <90 cm in women), it is important to confirm their fat distribution by other methods than WC. In such cases, the US method may be useful simply assessing the accumulation of visceral fat.

One limitation of the present study is that all of the subjects were Japanese; thus the results may not apply to Westerners or individuals of certain ethnic groups. The female body type in particular differs between Westerners and Japanese. Nevertheless, diagnostic criteria for WC that take into account ethnicity have been incorporated in the International Diabetes Federation (IDF)'s diagnostic criteria for MS. While there are differences in extent, the relationship between visceral fat accumulation and cardiovascular disease risk factors is universal (*32*, *33*).

No statistical analysis was performed to evaluate the differences in the measured parameters between premenopausal and postmenopausal women in our study group. In general, postmenopausal women tend toward obesity more than premenopausal women, and their blood pressure levels and visceral fat levels are known to increase (*34*, *35*). A study taking this into account is needed in the future. Additionally, the present study involved cross-sectional studies, and additional prospective studies on the relationship between abdominal obesity and elevated blood pressure are needed.

In conclusion, US is a simpler technique than abdominal CT, and its usefulness in visceral fat assessment was demonstrated in the screening of residents of a rural community. VFD is thought to be a good index for assessing not only visceral fat accumulation but also cardiovascular risk factors. Moreover, in men VFD showed a significant correlation with blood pressure. Visceral fat assessment by US may be useful for epidemiological studies and for clinics with no abdominal CT equipment to identify high-risk individuals such as those with metabolic syndrome.

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論文題名	Influence of Hypertension on the Incidence of Cardiovascular Disease in Two Rural Communities in Japan: The Tanno-Sobetsu Study.
著者名	Fumio Obara, Shigeyuki Saitoh, Satoru Takagi, Kazuaki Shimamoto.
書誌情報	Hypertension Research. 2007; 30: 677-682.

目的	これまでに我々はWHO/ISH基準の血圧階層で血圧レベルが増すごとに全死亡、心血管疾患死亡が増加することを報告した。しかし死亡をエンドポイントとした場合には、重症例の把握のみで真の心血管疾患発症と高血圧の関連を過小評価している可能性が残る。そこで地域住民を対象に、WHO/ISH基準の血圧階層別に心血管疾患発症について追跡調査を行い、各血圧階層別の心血管疾患発症率を比較検討し、日本人一における高血圧の循環器疾患発症への影響を明らかにすることを目的とした。
研究デザイン	前向きコホート研究。1991年、1992年にベースライン調査、その後1999年8月まで追跡。
セッティング	北海道端野町、北海道壮瞥町
対象者	1991年と1992年の住民検診受診者2,136名のうち、降圧薬服用者338名を除外し血圧階層分類が可能であった1,798名（男性806名、平均年齢59.5±11.2歳、女性992名57.8±12.1歳）を対象とした。循環器疾患の既往者は解析対象から除外した。
エンドポイント	心血管疾患の発症とした。新規発症の脳卒中または虚血性心疾患、狭心症・心筋梗塞および心臓突然死は検診時のアンケート調査と心電図の経年変化から判定し、また医師の診断を受け通院中のものは主治医に確認した。初年度調査以来検診を受診していない例については家族への訪問およびアンケートにより発症の情報を得て、通院中のものは主治医にその詳細を確認した。
統計解析	群間の比較は一元配置分散分析を用い、交絡因子を補正した心血管疾患発症の相対危険度の解析はCox比例ハザードモデルを用いた。
主な結果	対象1,798名の平均追跡期間は5.74年で、追跡率は84.2%。追跡期間中の心血管疾患発症例は94例(脳卒中発症は64名、虚血性心疾患発症は30名)、死亡は17例を認めた。心血管疾患粗発症率、(対千人・年）は、至適血圧＋正常血圧群で6.24、正常高値血圧群で11.26、グレード1～3高血圧群で15.83と血圧階層が上がるに従い高率となり、グレード1～3高血圧群と至適血圧＋正常血圧群との間に有意差あり。Cox比例ハザードモデルにより性、年齢、BMI、血糖、コレステロールで補正した心血管疾患発症の相対危険度は、グレード1～3高血圧群で1.46倍となり至適血圧＋正常血圧群に対して有意(95%信頼区間1.00-1.68)であった。
結論	血圧のレベルが上がるにつれて心血管疾患発症のリスクが増大するという結果が得られた。これは、他の危険因子の影響を除外しても認められることから、地域一般住民で高血圧はいまだに心血管疾患発症の独立した危険因子として重要であることが明らかとなった。
CQ	1. 血圧と心血管疾患の間にJカーブ現象は観察されたか？ 2. 脈圧が大きいことは心血管疾患発症のリスクか？ 3. 喫煙、飲酒の影響は明らかになったか？ 4. 心血管疾患に対して、高血圧に加えて年齢、性別はリスクとなっているか？
Answer	1. No. 観察対象、観察人年も少ないが、本研究ではJカーブ現象は認められなかった。 2. No. 本研究では収縮期血圧、拡張期血圧ともにリスクであり、脈圧の関与は小さいと考えられた。 3. No. 今回の調査において喫煙、飲酒は調べていない。 4. Yes. 至適血圧群に対しグレード1～3高血圧それぞれの群で発症率の違いに差を認めたが、性、年齢を調整するとグレード1と2の相対危険度の差は消失した。

Original Article

Influence of Hypertension on the Incidence of Cardiovascular Disease in Two Rural Communities in Japan: The Tanno-Soubetsu Study

Fumio OBARA[1)], Shigeyuki SAITOH[1)], Satoru TAKAGI[1)], and Kazuaki SHIMAMOTO[1)]

The purpose of this study was to determine the relationship between hypertension and onset of cardiovascular disease in Japan. As part of an ongoing epidemiological survey of cardiovascular diseases in Hokkaido, Japan, 1,798 subjects (806 males and 992 females; mean age in the initial year of the survey, 58.6±11.8 years) were selected, after excluding subjects who had been taking antihypertensive drugs, from a total of 2,136 subjects who had undergone medical examinations in 1991 in the town of Tanno and in 1992 in the town of Sobetsu, two rural communities in Hokkaido. Height, weight, casual systolic and diastolic blood pressures in the sitting position and blood biochemical values of all subjects were measured, and the subjects were divided into blood pressure level groups according to the 1999 World Health Organization/International Society of Hypertension (WHO/ISH) criteria. The follow-up survey was concluded at the end of August in 1999. The endpoints in this study were onset of circulatory disease or death due to circulatory disease. During the follow-up period, circulatory diseases (ischemic heart disease or stroke) occurred in 94 of the subjects. The incidence rates of cardiovascular disease (per 1,000 persons/year) for subjects divided into blood pressure groups according to the 1999 WHO/ISH blood pressure classification were 6.24 for the optimal+normal blood pressure level group, 11.26 for the normal high blood pressure level group, and 15.83 for the grade 1–3 hypertension group. Thus, the incidence rate of circulatory disease increased as the blood pressure level increased, and there was a significant difference between the incidence rate in subjects in the grade 1–3 hypertension group and the incidence rate in subjects in the optimal+normal blood pressure level group ($p<0.05$). In a Cox's proportional hazards model with onset of circulatory disease as the endpoint, diastolic blood pressure was shown to be an independent risk factor with a relative risk of 1.01. The results suggest that hypertension is an independent risk factor for onset of circulatory disease. (*Hypertens Res* 2007; 30: 677–682)

***Key Words*: prospective study, population-based, hypertension, onset of cardiovascular disease**

Introduction

Hypertension has long been considered the most potent risk factor for cardiovascular diseases (*1*, *2*). The diagnostic criteria for hypertension were recently revised, and the necessity of blood pressure management in order to prevent other concurrent diseases has been emphasized (*3*). Hypertension was found to be a significant risk factor for cerebrovascular and ischemic heart diseases in the Framingham Heart Study in the United States (*4*). On the other hand, no significant correlation was found between the incidence of ischemic heart diseases and hypertension in the Hisayama study, although the incidence of cerebral infarction was found to increase with increase in blood pressure (*5*). Many studies have shown that the incidence of cardiovascular diseases increases with increase in blood pressure in the elderly (*6–9*). However, both the rate of death from cardiovascular diseases and the inci-

From the [1)]Second Department of Internal Medicine, Sapporo Medical University School of Medicine, Sapporo, Japan.
Address for Reprints: Fumio Obara, M.D., Hakodate Goryokaku Hospital, 38-3, Goryokaku-cho, Hakodate 040-8611, Japan. E-mail: obara_f@d6.dion.ne.jp
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dence of cardiovascular diseases were found to be not significantly correlated with systolic blood pressure (SBP) or diastolic blood pressure (DBP) in the elderly without a previous history of such diseases, as shown by Tervahauta *et al.* (*10*) and the Zutphen Elderly Study (*11*). Thus, there is no consensus among researchers as to the relationship between blood pressure and cardiovascular diseases in populations that include elderly individuals. It is possible that the influence of blood pressure on occurrence of ischemic and cerebrovascular diseases is different between Japanese and people in the United States and European countries.

In a previous study, we divided subjects into several categories based on blood pressure according to the guidelines of the World Health Organization/International Society of Hypertension (WHO/ISH) (*12*) and found that individuals who belonged to higher blood pressure categories had higher all-cause death rates and higher rates of death from cardiovascular diseases (*13*). Since death was considered to be the endpoint in our previous study, however, there remains the possibility that only patients with severe diseases were examined, and consequently the relationship between blood pressure and cardiovascular diseases was not duly evaluated.

In this study, we followed up the occurrence of cardiovascular diseases in a general population that included elderly individuals. For this purpose, we divided subjects into categories on the basis of their blood pressure according to the WHO/ISH guidelines and compared the incidences of cardiovascular diseases in the different categories. We thereby attempted to clarify the influence of blood pressure on cardiovascular diseases in Japanese subjects.

Methods

We have been carrying out a prospective epidemiological investigation of cardiovascular diseases in the towns of Tanno and Sobetsu in Hokkaido since 1976 (*14*). In this study, subjects who had cardiovascular diseases were excluded at baseline. Of the 2,136 inhabitants who underwent health examinations in 1991 and 1992, 338 receiving antihypertensive medication were also excluded. The reason for the exclusion of subjects treated with antihypertensive drugs was that most of them had cardiovascular diseases. The remaining 1,798, who could be divided into categories based on their blood pressure, were subjects of this study. The 1,798 subjects included 806 men who were 59.5±11.2 years old on average in the first study year and 992 women who were 57.8±12.1 years old on average in the first study year. In the first study year, there were 277 men and 304 women who were 65 years of age or older. Health examinations were carried out in fasting subjects early in the morning. Nurses interviewed the subjects, measured their height and weight, and calculated their body mass index (BMI). Three readings of blood pressure were taken for each subject with a mercury sphygmomanometer after resting in a seated position for at least 5 min. Thereafter, blood samples for analysis were collected from a brachial vein. Items for analysis were age, BMI, casual SBP and casual DBP in the seated position, fasting plasma glucose concentration (FPG), and plasma concentrations of total cholesterol (TC), triglyceride (TG), and high-density lipoprotein-cholesterol (HDL-C). Blood concentrations of these substances were determined by the following methods: FPG, by the glucose oxidase-electrode method; TC, by the cholesterol oxidase/dimethoxy-anilline hydroxy-3-sulfopropyl (DAOS) method; TG, by the glycerol-3-phosphate oxidase/DAOS method; HDL-C, by the dextran sulfate magnesium chloride precipitation method.

The subjects were divided into 6 categories based on their casual blood pressure in the seated position according to the WHO/ISH guidelines. Those with SBP below 120 mmHg and DBP below 80 mmHg were classified into a category with optimal blood pressure. Those with SBP between 120 and 130 mmHg and DBP between 80 and 85 mmHg were classified into a normal blood pressure category. Those with SBP between 130 and 140 mmHg or DBP between 85 and 90 mmHg were classified into a normal high blood pressure category. Those with SBP between 140 and 160 mmHg or DBP between 90 and 100 mmHg were classified into a grade 1 hypertension category. Those with SBP between 160 and 180 mmHg or DBP between 100 and 110 mmHg were classified into a grade 2 hypertension category. Those with SBP over 180 mmHg or DBP over 110 mmHg were classified into a grade 3 hypertension category. In this study, analysis was done in three groups: an optimal+normal blood pressure level group, a normal high blood pressure level group and a grade 1–3 hypertension group.

Follow-up was commenced on August 31, 1992 and terminated on August 31, 1999. The endpoints were onset of cardiovascular disease or death due to cardiovascular disease. Occurrence of strokes and ischemic heart diseases, *i.e.*, angina pectoris/cardiac infarction, and sudden cardiac deaths was detected by interview, at the health examinations, or by monitoring yearly changes in the ECG. The occurrence of the above diseases and deaths of the subjects who did not undergo the health examinations were detected by sending questionnaires to the subjects or the family members. For subjects who received medical treatment, we tried to obtain as much information as possible from the chief physicians about their diseases, particularly about clinical symptoms and findings in ECGs, CT scans and MRIs. We visited surviving family members or sent them questionnaires to confirm the deaths, and we obtained detailed information about the diseases of the decedents from chief physicians. We obeyed the law protecting individual information, and data of the subjects were treated very carefully.

Based on the data collected, the incidence of cardiovascular diseases was calculated for each blood pressure–based category. In principle, we conducted posthumous investigations or investigations after the occurrence of diseases only when the involved subjects or surviving family members gave their consent. Fortunately, we were not refused in any of these cases.

Table 1. Results of Examinations on the Subjects in Different Categories Formed on the Basis of Their Blood Pressure in the First Study Year

	Optimal blood pressure	Normal blood pressure	Normal high blood pressure	Grade 1 hypertension	Grade 2 hypertension	Grade 3 hypertension
Number of subjects	628	403	323	334	98	12
Sex (male:female)	260:368	188:215	151:172	154:180	47:51	6:6
Age (years)	55.7±12.8	57.1±11.4	60.2±10.2*,†	62.3±10.1*,†,‡	64.0±10.0*,†,‡	63.3±9.5*
Body mass index (kg/m^2)	22.7±2.8	23.3±3.1*	24.0±3.0*	23.9±3.1*,†	24.4±3.5*,†	24.9±4.0*
Systolic blood pressure (mmHg)	109.4±8.0	123.9±3.4*	133.6±3.6*,†	146.7±6.6*,†,‡	166.8±10.2*,†,‡	180.2±30.3*,†,‡
Diastolic blood pressure (mmHg)	67.7±6.8	74.7±5.9*	78.4±6.5*,†	88.3±8.0*,†,‡	90.7±11.1*,†,‡	93.7±12.4*,†,‡
Fasting plasma glucose (mg/dL)	87.4±26.2	85.0±38.6	89.0±33.9	95.7±27.4*,†,‡	100.9±22.1*,†,‡	103.9±18.0*
Total cholesterol (mg/dL)	183.3±43.6	184.6±56.8	191.2±49.3*	195.1±30.9*,†	194.4±30.9*	215.3±33.8*
Triglyceride (mg/dL)	109.2±78.2	128.1±103.5*	134.2±106.3*	149.5±114.1*,†	150.4±86.2*,†	191.9±99.9*,†
HDL-C (mg/dL)	50.7±29.6	51.8±27.9	52.7±19.9	53.9±16.4	53.7±13.8	53.4±18.8

*$p<0.05$ *vs.* optimal blood pressure; †$p<0.05$ *vs.* normal blood pressure; ‡$p<0.05$ *vs.* normal high blood pressure. Atherogenic factors, such as age, body mass index, fasting plasma glucose, and lipids other than HDL-C increased with blood pressure. HDL-C, high-density lipoprotein-cholesterol.

Table 2. The Incidence of Cardiovascular Diseases per 1,000 Persons/Year in Each Category

	Optimal+normal blood pressure	Normal high blood pressure	Grade 1–3 hypertension
Sex (male:female)	448:583	151:172	207:237
Age (years)	56.3±12.3	60.2±10.2	62.7±10.0
Number of incidence	38	27	29
Observed persons/year	6,093.2	2,397.6	1,831.4
Crude incidence rate (per 1,000 persons/year)	6.24	11.26	15.83*

*$p<0.05$ *vs.* optimal+normal blood pressure. The incidence of cardiovascular diseases per 1,000 persons/year was higher in higher blood pressure categories. Significant differences were noted in the incidence between the optimal+normal blood pressure group and the grade 1–3 hypertension group.

All numerical values are expressed as the means±SD. Differences between two groups were examined using Student's *t*-test. Relative risk of occurrence of cardiovascular diseases in individual categories was obtained as a value relative to that in the optimal+normal blood pressure group after adjusting for sex, age, and other parameters. For this purpose, a Cox's proportional hazards model was used. For statistical analysis, Statview Ver. 5.0 (Macintosh) was used. To compare frequencies, χ^2-tests were performed. The significance level was set at $p<0.05$.

Results

Table 1 summarizes the results of examinations for the subjects in different categories based on blood pressure in the first study year. Atherogenic factors, including age, BMI, FPG, and lipids other than HDL-C, increased with increase in blood pressure category.

The 1,798 subjects in the follow-up study included 806 men (mean age, 59.5±11.2 years) and 992 women (mean age, 57.8±12.1 years). Cardiovascular diseases occurred during the follow-up period in 94 subjects (55 men and 39 women). Seventeen subjects died as a result of newly occurring cardiovascular diseases. Strokes occurred in 37 men and 27 women, and ischemic heart diseases occurred in 18 men and 12 women.

The incidence rate of cardiovascular disease per 1,000 persons/year was higher in the higher blood pressure categories: The incidence rates were 6.24 for the optimal+normal blood pressure level group, 11.26 for the normal high blood pressure level group, and 15.83 for the grade 1–3 hypertension group. There was a significant difference between the incidences in the optimal+normal blood pressure level group and the grade 1–3 hypertension group (Table 2).

The relative risk of occurrence of cardiovascular diseases in the individual groups, expressed as a multiple of that in the optimal+normal blood pressure level group, was calculated after adjusting for sex, age, FPG, TC and BMI using Cox's proportional hazards model. The relative risk increased in the higher blood pressure groups and there was a significant difference between the risk in the optimal+normal blood pressure level group and the grade 1–3 hypertension group (Table 3).

Table 3. The Relative Risk of Cardiovascular Diseases Adjusting for Sex, Age, Fasting Plasma Glucose, Total Cholesterol and Body Mass Index Using a Cox's Proportional Hazards Model

	Relative risk	*p* value	95% confidence interval
Optimal+normal blood pressure	1.00	—	—
Normal high blood pressure	1.19	0.3	0.89–1.20
Grade 1–3 hypertension	1.46	0.011	1.00–1.17

The relative risk increased in higher blood pressure categories, and there was a significant difference in the risk between the optimal+normal blood pressure group and the grade 1–3 hypertension group.

With regard to DBP, the relative risk of occurrence of cardiovascular diseases was 1.01, a significant value, in a Cox's proportional hazards model in which occurrence of cardiovascular diseases was taken as the endpoint and variables such as sex and age were included. This result indicates that DBP is an independent risk factor. In the groups having a DBP above 90 mmHg, the relative risk was 1.3-fold that in the optimal+normal blood pressure level group.

Discussion

The results of this study showed that in a relatively old cohort with a mean age of about 60 years, the risk for occurrence of cardiovascular diseases increased in the higher blood pressure groups. In the first stage of this study, we carried out analysis separately for occurrence of stroke and occurrence of heart diseases. However, we failed to reveal significant differences among the blood pressure categories for either the incidence or risk of stroke or heart disease. Since a tendency suggesting a close relationship between blood pressure and the incidence and risk of these diseases was noted in such analyses, we combined the two disease groups into one and studied the relationship between the blood pressure categories and occurrence of disease in this combined disease group.

The reason for the exclusion of subjects treated with antihypertensive medication was that many of them had cardiovascular diseases and that some antihypertensive drugs might not only have an inhibitory effect on but might also promote the onset of cardiovascular diseases *via* their effects on the metabolic and endocrine systems. However, we did not know the types of antihypertensive drugs the subjects were being treated with, and we therefore decided to exclude subjects taking antihypertensive drugs in order to eliminate the possible effect of blood pressure on the onset of cardiovascular diseases in those subjects.

The results of previous studies regarding the relationship between blood pressure and occurrence of cardiovascular diseases have been inconsistent. SBP (*6*, *9*) and DBP (*6*) were found to have close positive correlations with the risk of cardiac infarction in men and women in the Framingham heart study (*6*), which included subjects aged 65–94 years, and also in a study by the Chicago Heart Association (*9*) with subjects aged 60–74 years. On the other hand, two other studies reported that there was no close correlation between DBP or SBP and the incidence of cardiovascular diseases or the rate of death resulting from cardiovascular diseases (*10*, *11*). The incidence of cardiac infarction has been reported to increase with decreases in SBP (*15*, *16*) and DBP (*11*, *15*, *16*) in the aged.

Several possible reasons for the absence of an overt correlation between blood pressure and risk of cardiac infarction in the aged have been proposed. For instance, at the time of entry into a prospective study program, many elderly subjects might already have cardiac infarction (*17*), or they might have high blood pressure, thus obscuring the effect of blood pressure (*18*). Previous studies (*10*, *11*, *15*, *16*) have shown a U- or J-shaped relation between blood pressure and the incidence of cardiovascular diseases (*11*, *19–21*).

Diastolic blood pressure has been shown to decrease with advance of age because of increased arterial stiffness due to arteriosclerosis (*22*, *23*). Since many old people have a combination of several diseases, they might have reduced diastolic blood pressure and as a result have a high death rate (*18*, *24*). In addition, mechanisms are conceivable by which a reduction in blood pressure increases the incidence of cardiovascular diseases. Decrease in DBP, for instance, results in reduced blood flow in the coronal artery in patients with severe coronal stenosis and thereby increases the risk of death from ischemic cardiac diseases (*18*, *24*).

The results of studies in Japan are inconsistent with those in other countries. The incidence of cerebral infarction increased with a rise in blood pressure in the first group in the Hisayama-cho study, whereas antihypertensive medication failed to reduce the risk of occurrence of ischemic cardiovascular diseases in the third group. Hypertension was reported to be a less potent risk factor for ischemic heart diseases than for strokes in Japan (*5*). In the present study, cardiovascular diseases, including strokes and ischemic heart diseases, occurred in 94 subjects during the follow-up period. The incidence of cardiovascular diseases increased in the higher blood pressure–based groups, and the incidence in the optimal+normal blood pressure group was significantly smaller than that in the grade 1–3 hypertension group. This study therefore indicates that hypertension increases the risk of cardiovascular diseases in the general population in Japan. Analysis of data for the 30 subjects in whom heart diseases occurred and for the 64 subjects in whom stroke occurred showed similar correlations between blood pressure and these diseases. The

findings described above indicate that the incidence of cardiovascular diseases has a positive correlation with blood pressure in the general population in Japan and that blood pressure is an age- and sex-independent risk factor for cardiovascular diseases, including stroke and ischemic heart diseases.

In studies in the United States and Europe, such as the Framingham heart study, on the other hand, the incidence of ischemic heart diseases had positive correlations with SBP and pulse pressure and had a negative correlation with DBP (*25*). Pulse pressure had a close positive correlation with ischemic heart diseases (*26*). In the present study, there was no consistent correlation between pulse pressure and occurrence of cardiovascular diseases. Diastolic blood pressure was a risk factor for cardiovascular diseases even in the subjects aged over 60 years when they had diastolic blood pressure above 90 mmHg.

As to subtypes of strokes, cerebral infarction, cerebral hemorrhage and subarachnoid hemorrhage (SAH) accounted for about 66%, 23% and 11%, respectively, of the strokes that occurred in the 64 subjects during the follow-up period. These percentages of subtypes are similar to those reported recently in Japan (*27*). It has been reported that smoking status was an independent determinant of multiple silent cerebral infarction in a high-risk community-dwelling population in Japan (*28*). The relationships between blood pressure and subtypes of stroke should be studied further.

No differences were found in the incidences of cardiovascular diseases among the 3 hypertension categories in the grade 1–3 hypertension group. When the risk of occurrence of cardiovascular diseases in the individual categories relative to that in the optimal blood pressure category was analyzed using a Cox's proportional hazards model, which enabled us to adjust for sex and age, relative risk showed a tendency to increase in the higher blood pressure categories. However, a significant difference from the optimal blood pressure category was revealed only in the grade 3 hypertension category. One possible explanation for this finding is that subjects in the grade 2 and grade 3 hypertension categories in the first study year received antihypertensive medication during the subsequent follow-up period and their blood pressure and other risk factors were controlled. It is possible that the reason for the lack of a statistically significant difference in relative risk between the grade 1 and grade 2 hypertension groups was not there was no relationship, but rather that the power of detection was too small. It was thought that age and sex were strong risk factors for the incidence of cardiovascular diseases, and that these factors attenuated the risk of hypertension as a byproduct of cardiovascular disease. In this study, analysis was therefore done in three groups: an optimal+normal blood pressure level group, a normal high blood pressure level group and a grade 1–3 hypertension group. It is therefore possible that the influence of blood pressure in the first study year on the incidence of cardiovascular diseases was unduly low. It is also possible that the number of subjects in whom cardiovascular diseases occurred was not large enough to reveal statistically significant differences. Annual follow-up of these subjects should be continued hereafter.

The occurrence of cardiovascular diseases was confirmed by interviewing subjects or their family members, or by sending them questionnaires. The registered cases were those with newly occurring stroke, cardiac infarction or sudden death, which were confirmed by interviews with chief physicians and clinical records such as ECGs. There was a limitation with respect to determining the underlying cause of death, in that autopsies were not conducted.

In summary, a U- or J-shaped relation was not found between SBP or DBP and incidence of cardiovascular disease. Instead, the risk of occurrence of cardiovascular diseases increased with increase in blood pressure.

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メタボリックシンドロームにおける高尿酸血症の意義

札幌医科大学医学部第2内科
東浦　勝浩・斎藤　重幸・竹内　宏
高木　覚・浦　信行・島本　和明

I. 目　的

肥満と高尿酸血症（以下，HU）の関連については多くの報告があるが，HUがメタボリックシンドローム（以下，MetS）といかに関連するのかについては明らかではない。そこで本稿では端野・壮瞥町の住民健診受診者を対象に，地域一般住民男性におけるMetSの頻度と危険因子集積におけるHUの意義についての検討結果を報告する。

II. 方　法

対象は2002年に北海道端野町，壮瞥町の住民健診を受診した，薬剤治療者を除く男性588名（平均年齢63±13歳）。安静座位にて血圧を測定し，早朝空腹時に採血を施行して血糖，血清尿酸値，脂質パラメーター，血清インスリン値を測定した。HOMA-IR（homeostasis model assessment for insulin resistance）は空腹時血糖×血清インスリン濃度/405にて計算した。また，腹囲径は立位，軽呼気時，臍周囲にて計測した。全米コレステロール教育プログラム（NCEP-ATP-III）のMetSの診断基準[1]を一部改変，つまり肥満（腹囲≧85 cm），血圧高値（≧130/85 mmHg），高中性脂肪血症（≧150 mg/dl），低HDL血症（<40 mg/dl），空腹時血糖高値（≧110 mg/dl）の中で，三つ以上を有する者をMetSとして，非MetSの2群に分けて検討した。また，血清尿酸値>7.0 mg/dlをHUと定義した。なお，本検討は全対象から筆式にてインフォームドコンセントを得て施行した。

III. 結　果

対象の平均body mass index（BMI）は23.6±3.0 kg/m^2，平均腹囲径は84.8±8.6 cmであった。住民健診受診者全体の15.9%にHUを認め，また25.3%がMetSの診断基準を満たした。血清尿酸値はインスリン抵抗性の指標であるHOMA-IRと有意に正に相関した。MetSの中でHUを有するのは約20%であり，血清尿酸値はMetSで非MetSと比して有意に高かった（図1）。MetSの各危険因子と血清尿酸値の関係においては，腹部肥満，高中性脂肪血症，低HDL血症，血圧高値を有する群で，有さ

Significance of hyperuricemia for metabolic syndrome
Katsuhiro Higashiura, Shigeyuki Saitoh, Hiroshi Takeuchi, Satoru Takagi, Nobuyuki Ura, Kazuaki Shimamoto　*Second Department of Internal Medicine, Sapporo Medical University*
Key words：metabolic syndrome, hyperuricemia, insulin resistance

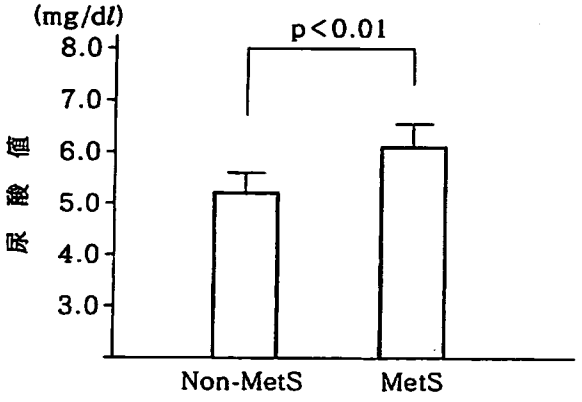

図 1　メタボリックシンドローム (MetS) の有無と血清尿酸値

表 1　重回帰分析（目的変数：危険因子の集積）

	β	t	p
AGE	0.23	5.04	<0.01
BMI	0.38	7.47	<0.01
HOMA-IR	0.27	5.44	<0.01
UA	0.10	2.19	<0.05

調整済み R^2値：0.33

危険因子の集積を従属変数とした重回帰分析では，年齢，BMI，HOMA-IR とともに尿酸(UA)も有意な説明因子として採択された。

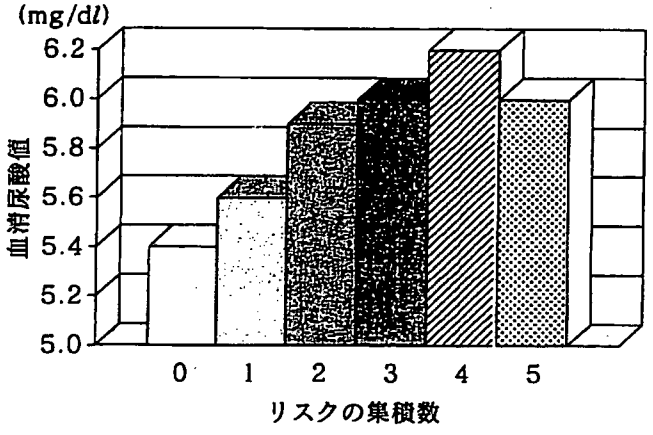

図 2　リスクの集積と血清尿酸値

ない群に比べ血清尿酸値は有意に高かった。

また，各危険因子の集積個数が多いほど血清尿酸値は段階的に上昇（図 2）し，高尿酸血症を有する群では有さない群に比べて危険因子の集積個数が有意に多かった。バリマックス因子分析を施行すると，HU は肥満，高中性脂肪血症，低 HDL 血症とともにインスリン抵抗性に関連する因子として選択された。一方で，危険因子の集積を目的変数として重回帰分析を施行すると，年齢，BMI，HOMA-IR に加えて，血清尿酸値も危険因子集積に有意に関連する因子であることが明らかになった（表 1）。

IV. 考　察

今回の地域住民健診の男性における検討により，HU はインスリ抵抗性を背景因子として MetS に関連していることが明らかとなった。

MetS における HU の機序については腹部内臓脂肪の増加に伴う肝臓での中性脂肪合成亢進と連動した尿酸の *de novo* 合成増大[2]と，インスリン抵抗性/高インスリン血症に伴う腎臓での，Na の再吸収亢進に伴う尿酸の排泄低下[3]が関連していると考えられており，今回の検討結果はこれらの仮説に矛盾しないと考えられた。

一方で，血清尿酸値は BMI，HOMA-IR 等で補正した後も危険因子集積の有意な因子として選択されており，HU はインスリン抵抗性を介さない機序で危険因子集積に関わっている可能性が示唆された。この点については HU がレニン-アンジオテンシン系の賦活化に関わるとの報告[4]や炎症性マーカー[5]との関連についての指摘もあり，これらの機序を介して HU が MetS 発症に関わる可能性も考慮されるが，詳細については今後の検討課題と考える。

近年，高血圧[6]あるいは糖尿病患者[7]等のハイリスクグループにおいて，HU が心血管疾患の独立した危険因子であるとの報告が散見されている。これらのこともインスリン抵抗性に関連して生じた HU が，他の機転を介して危険因子集積に関わる可能性を示した本検討の結果を支持するものと考えられる。

ま と め

インスリン抵抗性は MetS の背景因子であると同時に HU の発症因子であり，HU 自体も MetS の病態形成に関わっている可能性が示唆

された。

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平成19年度厚生労働科学研究費補助金（循環器疾患等生活習慣病対策総合研究事業）
「疾病予防サービスに係わるエビデンス構築のための大規模コホート共同研究」
分担研究報告書

8. 大崎国民健康保険加入者コホート研究平成19年度研究成果および大崎市民コホート研究ベースライン調査結果の概要

分担研究者　辻　一郎 東北大学大学院医学系研究科公衆衛生学分野・教授

A．大崎国民健康保険加入者コホート研究の現況

1．はじめに

本コホートの対象は宮城県大崎保健所管内の1市13町に居住し、平成6年8月31日時点で40～79歳であった国民健康保険加入者全員54,996人である。平成6年10月から12月にかけてベースライン調査を行い（健診データは平成7年6月～9月）、52,029人（94.6%）から回答を得た。このうち平成6年12月までに死亡、または転出した774人を除いた51,255人について、平成7年1月から入院・入院外別の医療機関受診回数・入院日数と医療費に関するデータ、および死因・転出・がん罹患データを収集し続けている。

2．フォローアップ状況

平成7年1月1日より観察開始し、現在のところ表1に示すようなフォローアップ状況である。

表1．フォローアップ状況

医療費データ	平成18年12月31日まで完了（12年分）
死亡・転出データ	平成18年12月31日まで完了（12年分）
死因データ	平成18年12月31日まで完了（12年分）
がん罹患データ	平成15年12月31日まで完了（ 9年分）

医療費データには入院・入院外別の医療機関受診回数・入院日数と医療費が含まれている。宮城県国民健康保険団体連合会から医療費データおよび死亡・転出データの提供を受けている。

B．大崎国民健康保険加入者コホート研究平成19年度研究成果

大崎国民健康保険加入者コホート研究の平成19年度研究成果は、以下の通りである。

	著者	Title	Publish
1	Ohmori-Matsuda K, et al.	The joint impact of cardiovascular risk factors upon medical costs.	Prev Med 2007; 44: 349-355.
2	Shimazu T, et al.	Dietary patterns and cardiovascular mortality in Japan: a prospective cohort study.	Int J Epidemiol 2007; 36: 600-609.
3	Nakaya N, et al.	Alcohol consumption and suicide mortality among Japanese men: the Ohsaki Study.	Alcohol 2007; 41: 503-510.
4	佐藤文美、他.	日本における魚摂取と前立腺癌罹患リスクに関する前向きコホート研究.	日本泌尿器科学会雑誌, 2008; 99: 14-21.
5	柿崎真沙子、他.	睡眠時間と前立腺がん罹患リスクに関する前向きコホート研究：大崎国保コホート研究.	第18回日本疫学会学術総会.
6	酒井太一、他.	初産年齢と長期的死亡リスクに関する前向きコホート研究：大崎国保コホート研究.	第18回日本疫学会学術総会.
7	渡邊生恵、他.	緑茶摂取と肺炎死亡リスクに関する前向きコホート研究：大崎国保コホート研究.	第18回日本疫学会学術総会.

１．動脈硬化危険因子と医療費：大崎国保コホート研究

【目的】我が国の地域住民の基本健康診査（基本健診）における動脈硬化危険因子（高血圧、脂質代謝異常、高血糖、肥満）とその集積が医療費に及ぼす影響を検討すること。

【方法】大崎国保コホート研究では、宮城県大崎保健所管内 40～79 歳の国民健康保険（国保）加入者を対象にベースライン調査を平成 6 年に実施し、医療費の追跡を行っている。同研究参加者のうち平成 7 年の基本健診で採血、血圧測定、身体測定を受け、脳卒中・心筋梗塞・がんの既往のない 12,340 名を解析対象者とした。

対象者について、国保レセプトとのリンケージにより平成 8 年 1 月から平成 14 年 12 月の医療費を算出し、国保異動記録より生存死亡を確認した。

基本健診結果から、高血圧、脂質代謝異常、高血糖、過体重を以下の条件で定義した。①高血圧：血圧値 140/90mmHg 以上又は高血圧既往歴あり、②脂質代謝異常：随時血清コレステロール値 220 mg/dl 以上、又は HDL40mg/dl 未満、③高血糖：随時血糖値 150mg/dl 以上又は糖尿病既往歴あり、④過体重：Body Mass Index　25 以上。

性別、年齢、喫煙、飲酒について補正した共分散分析から、動脈硬化危険因子の有無別の医療費を検討した。次に、医療費と関連のあった３つの主要な動脈硬化危険因子（高血圧・高血糖・過体重）の保有状況（なし、各１つ×３、２つの組合せ×３、３つすべて）によって８つのグループに分け、その後６年間の医療費を性別、年齢、喫煙、飲酒について補正して共分散分析を用いて検討した。

【結果】高血圧・高血糖・過体重は医療費の増加と関連したが、高脂血症は医療費と統計学的に有意な関連は認められなかった。危険因子がないグループに比べ、危険因子の数が２つ、３つと増えるにつれて、医療費は高くなった。１か月当たりの平均医療費増加の割合は、危険因子が１つの場合、過体重または肥満のグループでは 5.1%、高血圧のグループでは 33.0%、高血糖のグループでは 48.3%であった。危険因子が２つになった場合、肥満と高血圧では 45.4%、肥満と高血糖では 44.2%、高血圧と高血糖では 85.2%であった。さらに、肥満、高血圧、高血糖の３つの危険因子がすべて揃ったグループでは、91.0%で、１人当たり１か月に２万円近く高くなった。これら３つの危険因子に関連した医療費は、対象者全体の健診後６年間の医療費のうち、17.2%を占めていた。