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Disclosures

None.

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Liver Enzymes as a Predictor for Incident Diabetes in a Japanese Population: The Hisayama Study

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Abstract

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Objective: We studied the relationship between liver enzymes and the development of diabetes in a general Japanese population.

Research Methods and Procedures: A total of 1804 nondiabetic subjects 40 to 79 years of age were followed-up prospectively for a mean of 9.0 years.

Results: During the follow-up, 135 subjects developed diabetes. In both sexes, the age-adjusted cumulative incidence of diabetes increased significantly with elevating quartiles of serum γ-glutamyltransferase (GGT) and alanine aminotransferase (ALT) levels. This pattern was also observed in aspartate aminotransferase (AST) quartiles for men but not for women. In multivariate analyses after adjusting for comprehensive risk factors and other liver enzymes, the risk of developing diabetes was significantly higher in the highest GGT quartile than in the lowest quartile [odds ratio (OR), 2.54; 95% confidence interval (CI), 1.03 to 6.26 for men; OR, 5.73; 95% CI, 1.62 to 20.19 for women]. Similar results were observed in ALT quartiles (OR, 2.32; 95% CI, 0.91 to 5.92 for men; OR, 4.40; 95% CI, 1.38 to 14.06 for women) but not in AST quartiles in either sex. Significant positive associations of GGT and ALT with diabetes were seen within each stratified category of risk factors, namely fasting insulin, BMI, waist-to-hip ratio, high-sensitivity C-reactive protein, and alcohol consumption. In receiver operating characteristic analyses, the areas under the receiver operating characteristic curve of GGT and ALT were significantly larger than that of AST, fasting insulin, waist-to-hip ratio, or C-reactive protein.

Discussion: Our findings suggest that serum GGT and ALT concentrations are strong predictors of diabetes in the general population, independent of known risk factors.

Key words: liver, longitudinal, C-reactive protein, diabetes, visceral obesity

Introduction

The liver, a major site of insulin clearance, plays an important role in maintaining normal glucose concentrations during fasting and postprandially (1). Recently, several cohort studies have shown that serum γ-glutamyltransferase (GGT)[1] (2–6), alanine aminotransferase (ALT) (7–9), and aspartate aminotransferase (AST) (10) levels are predictors of diabetes. In one of these reports, a study on Pima Indians (8) found that high serum ALT levels were a significant risk factor for diabetes, although no clear association between serum GGT and diabetes was seen. On the other hand, serum GGT levels, but not AST levels, have been identified as an independent predictor of incident diabetes in British men selected from lists of general practitioners (2). Moreover, the Mexico City Diabetes Study

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[1] Nonstandard abbreviations: GGT, γ-glutamyltransferase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HS-CRP, high-sensitivity C-reactive protein; HDL-C, high-density lipoprotein cholesterol; OR, odds ratio; CI, confidence interval; ROC, receiver operating characteristic.

found that serum AST is an independent risk factor for future diabetes in multivariable adjustment, whereas no association was observed between serum GGT or ALT and the development of diabetes (10). These reports suggest that the liver is associated with the development of diabetes; however, to the best of our knowledge, there have been no studies to date to determine which of these three enzymes is the best marker for incident diabetes. Furthermore, it also remains unknown whether liver enzyme markers are stronger predictors of future diabetes than well-known risk factors for diabetes, such as adiposity, insulin resistance, and inflammation. The purpose of this study is to examine the effects of serum liver enzymes, i.e., GGT, ALT, and AST, on the development of diabetes in a prospective study of a defined Japanese population, taking into account comprehensive risk factors, including BMI, waist-to-hip ratio, fasting insulin, and high-sensitivity C-reactive protein (HS-CRP) levels.

Research Methods and Procedures

Study Population and Follow-up Survey

A population-based prospective study of cardiovascular disease has been underway since 1961 in the town of Hisayama, a suburb in the Fukuoka metropolitan area on Kyushu Island in Japan. The age and occupational distributions of the town population were almost identical to those of Japan as a whole from 1961 to the present based on data from the national census. A screening survey for this study was performed in 1988. A detailed description of this survey has been published previously (11,12). Briefly, of all 3227 residents 40 to 79 years of age listed in the town registry, 2587 (80.2%) consented to take part in a comprehensive assessment, including an interview covering medical history (including diabetes, hypertension, and other chronic diseases) and current medical treatment with insulin and oral anti-diabetic agents. The baseline classification of subjects as either having or not having diabetes was based on the fasting criteria of the American Diabetes Association (13): subjects with a fasting plasma glucose level of ≥7.0 mM or those who were taking anti-diabetic medications were defined as having diabetes. A total of 2274 subjects (963 men and 1311 women) were enrolled in the baseline examination after the exclusion of 1 subject for whom no blood sample was obtained, 75 subjects who had already taken breakfast before the examination, 233 subjects with diabetes, and 4 subjects who had died before starting our follow-up.

After the initial screening in 1988, fasting glucose levels were again measured between 1993 and 1998. Of the 2274 subjects, 1804 (719 men and 1085 women) underwent a follow-up examination (follow-up rate, 79.3%). We considered a subject to have developed diabetes when his/her fasting glucose level met the above-mentioned American Diabetes Association criteria or if the subject started taking anti-diabetic medication during the follow-up period. During this period, 135 subjects (71 men and 64 women) developed diabetes.

Clinical Evaluation and Laboratory Measurements

Blood samples were collected after at least 12 hours of fasting for the determination of serum liver enzymes, plasma glucose, and other parameters. Serum GGT concentrations were measured using a modified version of the method of Orlowski and Meister (14). Both serum ALT and AST concentrations were determined by a kinetic ultraviolet ray method based on the rate of reduced nicotinamide adenine dinucleotide oxidation. Plasma glucose levels were determined by a glucose-oxidase method, and serum insulin levels were measured by double-antibody, solid-phase radioimmunoassay. Hemoglobin A_{1c} levels were measured by high-pressure liquid chromatography. Total cholesterol, high-density lipoprotein cholesterol (HDL-C) and triglycerides were determined enzymatically. HS-CRP concentrations were analyzed using a modified latex-enhanced HS-CRP assay (Behring Diagnostics, Westwood, MA). Serum hepatitis B surface antigen was detected by an immunoprecipitation method (Shino-test, Tokyo, Japan), and presence of hepatitis C virus antibody was assessed by both particle agglutination assay (Serodia-HCV; Fujirebio, Tokyo, Japan) and recombinant immunoblot assay (RIBA 2.0; Ortho Diagnostic Systems, Raritan, NJ).

Blood pressure was obtained three times using a mercury sphygmomanometer with the subject in a sitting position; the averages of the three values were used in this analysis. Hypertension was defined as a systolic blood pressure of ≥140 mm Hg and/or a diastolic blood pressure of ≥90 mm Hg and/or current treatment with anti-hypertensive agents. The height and weight of each subject were recorded with the subject wearing light clothes but no shoes, and BMI (kg/m^2) was calculated. Abdominal girth at the umbilical level and hip circumference at 5 cm below the spina iliaca anterior superior were measured and used to calculate the waist-to-hip ratio.

On baseline examination, each participant completed a self-administered questionnaire covering medical history, anti-hypertensive treatment, alcohol intake, and smoking habits, and the questionnaire was checked by trained interviewers at the screening. Diabetes in first- or second-degree relatives was taken to indicate a family history of diabetes. Subjects engaging in sports at least three times per week during their leisure time were defined as the regular exercise group. Alcohol intake and smoking habits were used to classify subjects as having current habits or not.

Statistical Analysis

Because the distributions of GGT, ALT, AST, fasting insulin, HS-CRP, and triglycerides were skewed, these variables were natural log-transformed for statistical analyses.

Table 1. Characteristics of subjects by sex

	Men (n = 719)	Women (n = 1085)
Age (yrs)	58 ± 10	58 ± 10
GGT (units/L)	22 (11 to 95)	13 (8 to 35)
ALT (units/L)	14 (7 to 38)	11 (6 to 24)
AST (units/L)	22 (14 to 45)	19 (12 to 33)
Fasting plasma glucose (mM)	5.6 ± 0.5	5.5 ± 0.5
Hemoglobin A_{1c} (%)	5.5 ± 0.5	5.4 ± 0.5
Family history of diabetes (%)	9.2	7.2
Fasting insulin (pM)	30.0 (18.0 to 72.0)	36.0 (18.0 to 72.0)
BMI (kg/m^2)	22.9 ± 2.9	23.0 ± 3.1
Waist-to-hip ratio	0.92 ± 0.05	0.91 ± 0.07
Total cholesterol (mM)	5.07 ± 1.03	5.54 ± 1.04
HDL-cholesterol (mM)	1.25 ± 0.30	1.34 ± 0.29
Triglycerides (mM)	1.24 (0.57 to 3.49)	1.02 (0.49 to 2.32)
HS-CRP (mg/L)	0.49 (0.07 to 7.14)	0.36 (0.06 to 3.22)
Systolic blood pressure (mm Hg)	131 ± 17	130 ± 20
Diastolic blood pressure (mm Hg)	82 ± 11	76 ± 11
Hypertension (%)	42.8	33.2
Current drinking (%)	60.8	8.6
Current smoking (%)	47.3	5.5
Regular exercise (%)	15.9	4.9

HDL, high-density lipoprotein; HS-CRP, high-sensitivity C-reactive protein; GGT, γ-glutamyltransferase; AST, aspartate aminotransferase; ALT, alanine aminotransferase. Variables of GGT, AST, ALT, fasting insulin, triglycerides, and CRP are median values (95% confidence intervals). All other values are given as mean ± standard deviation or as a percentage.

To analyze liver enzyme levels as categorical variables, these levels were divided into four groups on the basis of quartiles by sex: GGT, men, 6 to 16, 17 to 22, 23 to 37, and 38 to 529 U/L; GGT, women, 6 to 10, 11 to 13, 14 to 17, and 18 to 261 U/L; ALT, men, 5 to 10, 11 to 13, 14 to 18, and 19 to 354 U/L; ALT, women, 5 to 8, 9 to 11, 12 to 14, and 15 to 153 U/L; AST, men, 8 to 17, 18 to 21, 22 to 27, and 28 to 424 U/L; AST, women, 7 to 16, 17 to 18, 19 to 22, and 23 to 273 U/L. The age-adjusted cumulative incidences of diabetes were calculated by the direct method using all subjects, and the results were compared by the Mantel-Haenszel χ^2 test using 10-year age-groupings. Age- and multivariate-adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were calculated by logistic regression analysis. The sensitivity of cut-off points was defined as their ability to correctly identify individuals who later developed diabetes, and their specificity was defined as their ability to correctly identify individuals who did not develop diabetes. To compare the prognostic abilities of risk factors including liver enzymes and to detect the presence or absence of future diabetes across a range of the values for each risk factor, we plotted receiver operating characteristic (ROC) curves and compared the areas under them (15,16). The diagnostic properties of specific cut-off levels of each risk factor were defined by maximizing the sensitivity and specificity to identify future diabetes. A value of $p < 0.05$ was considered statistically significant in all analyses.

This study was conducted with the approval of the Ethics Committee of the Faculty of Medicine, Kyushu University, and written informed consent was obtained from all participants.

Results

The clinical characteristics of all subjects by sex are shown in Table 1. The mean age was 58 years for both sexes. The mean values of GGT, ALT, AST, fasting plasma glucose, hemoglobin A_{1c}, waist-to-hip ratio, triglycerides, HS-CRP, systolic and diastolic blood pressures, frequency of hypertension, alcohol intake, smoking habits, and regular exercise were higher in men than in women, whereas women had higher concentrations of fasting insulin, total cholesterol, and HDL-C. The frequency of family history of diabetes and mean BMI levels did not differ between the sexes.

The age-adjusted cumulative incidence of diabetes was 9.6% for men and 5.9% for women, giving a statistically significant difference ($p = 0.002$). Figure 1 shows the age-adjusted cumulative incidence of diabetes according to quartiles of each liver enzyme level by sex. The cumulative incidence in the third and forth GGT quartiles was significantly higher compared with that of the first quartile in both sexes. A similar tendency was observed for ALT quartiles: there were significant differences between the first and fourth quartiles in both sexes. This pattern was also found in AST quartiles for men but not for women.

The age-adjusted OR for the development of diabetes increased significantly with elevating quartiles of each liver enzyme concentrations in both sexes (Table 2, Model 1). In the multivariate analyses after adjustment for age, family history of diabetes, fasting insulin, BMI, waist-to-hip ratio, total cholesterol, HDL-C, triglycerides, HS-CRP, hypertension, current drinking, current smoking, and physical activity, the ORs of future diabetes increased significantly with elevating quartiles of serum GGT and ALT (Model 2). These trends were also observed in AST quartiles for men but not for women. As shown in Model 3 of Table 2, after additional adjustment for the other liver enzymes, these relationships remained substantially unchanged in both GGT and ALT quartiles but not in AST in either sex.

To examine the influence of insulin resistance-related factors, inflammation and alcohol intake on the development of diabetes, we estimated the age- and sex-adjusted ORs and 95% CIs of diabetes by increments of 1 log in each liver enzyme in men and women together in accordance with other risk factor levels (Table 3). Analyses were performed dividing the subjects into three groups according to tertiles of fasting insulin, BMI, waist-to-hip ratio, and HS-CRP or to alcohol intake levels (0, 1 to 30, and ≥30 g/d). Significant positive associations of GGT and ALT with diabetes were observed in all stratified categories of each risk factor; however, we found no significant associations between AST and diabetes in the third tertile of BMI, in the third tertile of waist-to-hip ratio, or in the second level of alcohol intake.

To compare the ability of each risk factor to predict future diabetes over a mean of 9 years of follow-up, we plotted ROC curves and calculated optimal cut-off points, sensitivities, specificities, and the area under the ROC curves (Table 4). Both maximum sensitivity and specificity exceeded 60% only for GGT and ALT, and the areas under the ROC curve of GGT and ALT were significantly larger than that of AST, fasting insulin, waist-to-hip ratio, or HS-CRP and were slightly but not significantly larger than that of BMI. The difference in the area under the ROC curve between GGT and ALT was not significant.

Viral hepatitis infection can increase liver enzyme levels without liver fat accumulation. Thus, hepatitis B and C virus markers were examined in 1583 of the 1804 subjects in 1998. We found 13 viral hepatitis subjects (3 subjects with hepatitis B virus and 10 with C virus; 10.7%) in 122 subjects of the group developing diabetes and 104 viral hepatitis subjects (25 subjects with hepatitis B virus and 79 with C virus; 7.1%) in 1461 subjects of the group that did not develop diabetes: the difference was not significant ($\chi^2 = 2.1$; $p = 0.15$).

Discussion

We have shown, in a prospective study of a general Japanese population, that elevated levels of GGT and ALT, but not AST, are independent predictors of diabetes for both sexes after adjustment for age, family history of diabetes, fasting insulin, BMI, waist-to-hip ratio, total cholesterol, HDL-C, triglycerides, HS-CRP, hypertension, current drinking, current smoking, physical activity, and the other liver enzymes. In our stratified analyses, associations of both GGT and ALT with the development of diabetes were observed in all layers of other risk factors, such as fasting insulin, BMI, waist-to-hip ratio, HS-CRP, and alcohol intake. ROC analyses showed that the predictive power of GGT and ALT was similar to that of BMI but stronger than that of AST, fasting insulin, waist-to-hip ratio, and HS-CRP. To the best of our knowledge, this study is the first report to indicate that liver enzymes are independent risk factors for developing diabetes in a general Japanese population in either sex, taking into account comprehensive risk factors for diabetes. Several prospective studies have found that high levels of hepatic enzymes, including GGT (2–6), ALT (7–9), and AST levels (10), are associated with later development of diabetes. These findings, together with these results, strongly suggest that the liver plays an important role in the development of diabetes in relatively lean Asian populations who may have smaller fat content in the liver, as it does in Western populations.

A recent study using a fatless mouse model has shown that ectopic fat accumulation in the liver is associated with severe insulin resistance (17). In normal weight and moderately overweight subjects, directly determined liver fat content has also been shown to correlate with several features of insulin resistance, independent of BMI and intra-abdominal or overall obesity (18). These findings indicate that hepatic fat accumulation is a critical manifestation of insulin resistance. However, direct measurement of liver fat requires ultrasound, computed tomography, or proton spectroscopy, and such techniques are unlikely to be recommended in routine clinical practice. Some circulating variables, including serum ALT, GGT, and AST, provide insight into the extent of liver fat accumulation. Among these, ALT is found primarily in the liver, whereas AST and GGT are also found in other tissues and are, therefore, less specific markers of liver function. Therefore, ALT is the most specific marker of liver pathology and seems to be the best marker for liver fat accumulation: serum ALT is cor-

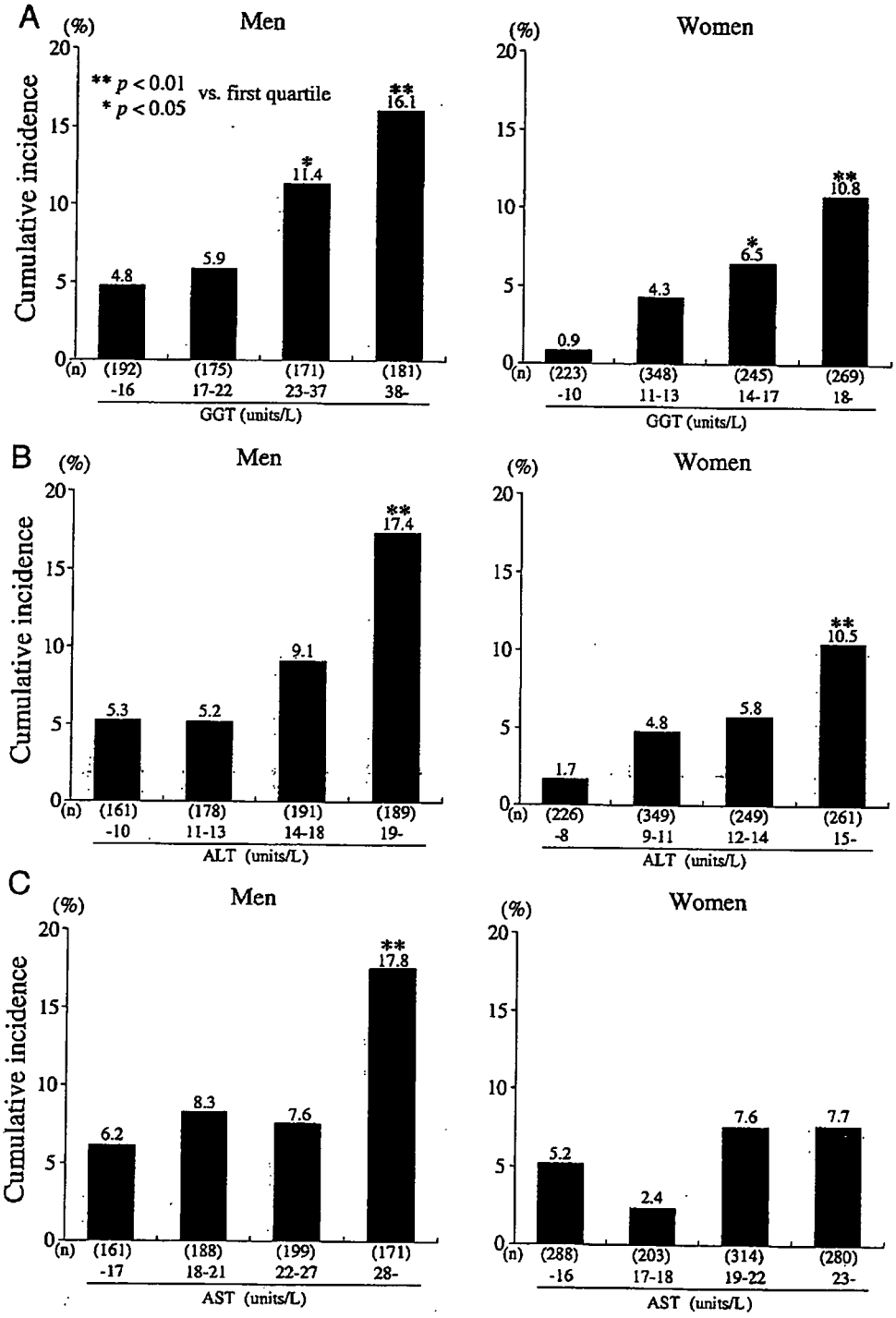

Figure 1: The age-adjusted cumulative incidences of diabetes according to quartiles of serum liver enzymes. (A) GGT, γ-glutamyltransferase; (B) ALT, alanine aminotransferase; (C) AST, aspartate aminotransferase.

Table 2. Age- and multivariate-adjusted ORs and 95% CIs for the development of diabetes according to quartiles of each liver enzyme by sex during mean 9 years of follow-up

	Range	Population at risk (*n*)	Number of events (*n*)	Model 1: OR (95% CI)	*p* for trend	Model 2: OR (95% CI)	*p* for trend	Model 3: OR (95% CI)	*p* for trend
GGT (U/L)									
Men	0 to 16	192	10	1 (referent)		1 (referent)		1 (referent)	
	17 to 22	175	10	1.10 (0.45 to 2.71)		0.85 (0.32 to 2.28)		0.85 (0.31 to 2.27)	
	23 to 37	171	20	2.39 (1.09 to 5.28)		2.02 (0.84 to 4.88)		1.99 (0.82 to 4.80)	
	38 to	181	31	3.71 (1.75 to 7.87)	0.0001	2.71 (1.13 to 6.52)	0.0040	2.54 (1.03 to 6.26)	0.0088
Women	0 to 10	223	3	1 (referent)		1 (referent)		1 (referent)	
	11 to 13	348	15	3.29 (0.94 to 11.48)		2.65 (0.74 to 9.47)		2.64 (0.74 to 9.42)	
	14 to 17	245	16	5.10 (1.46 to 17.74)		3.72 (1.04 to 13.29)		3.66 (1.02 to 13.09)	
	18 to	269	30	8.98 (2.70 to 29.87)	0.0001	5.80 (1.67 to 20.12)	0.0011	5.73 (1.62 to 20.19)	0.0017
ALT (U/L)									
Men	0 to 10	161	9	1 (referent)		1 (referent)		1 (referent)	
	11 to 13	178	9	0.90 (0.35 to 2.33)		0.71 (0.25 to 1.98)		0.68 (0.24 to 1.92)	
	14 to 18	191	17	1.65 (0.71 to 3.83)		1.31 (0.52 to 3.32)		1.18 (0.46 to 3.03)	
	19 to	189	36	3.98 (1.83 to 8.64)	0.0001	2.85 (1.17 to 6.92)	0.0017	2.32 (0.91 to 5.92)	0.016
Women	0 to 8	226	5	1 (referent)		1 (referent)		1 (referent)	
	9 to 11	349	17	2.18 (0.79 to 6.00)		2.28 (0.74 to 7.02)		2.26 (0.73 to 6.99)	
	12 to 14	249	14	2.60 (0.92 to 7.34)		2.83 (0.90 to 8.92)		2.86 (0.90 to 9.07)	
	15 to	261	28	5.15 (1.95 to 13.59)	0.0001	4.53 (1.50 to 13.64)	0.0027	4.40 (1.38 to 14.06)	0.0077
AST (U/L)									
Men	0 to 17	161	10	1 (referent)		1 (referent)		1 (referent)	
	18 to 21	188	16	1.43 (0.63 to 3.24)		0.96 (0.40 to 2.31)		0.91 (0.38 to 2.19)	
	22 to 27	199	15	1.26 (0.55 to 2.89)		0.88 (0.37 to 2.10)		0.81 (0.33 to 1.95)	
	28 to	171	30	3.27 (1.54 to 6.94)	0.0016	2.30 (1.01 to 5.21)	0.030	1.87 (0.77 to 4.53)	0.17
Women	0 to 16	288	12	1 (referent)		1 (referent)		1 (referent)	
	17 to 18	203	5	0.56 (0.19 to 1.62)		0.40 (0.12 to 1.29)		0.40 (0.12 to 1.28)	
	19 to 22	314	24	1.79 (0.86 to 3.73)		1.69 (0.80 to 3.58)		1.70 (0.79 to 3.62)	
	23 to	280	23	1.91 (0.91 to 4.04)	0.019	1.49 (0.68 to 3.24)	0.073	1.26 (0.55 to 2.92)	0.17

OR, odds ratio; CI, confidence interval; GGT, γ-glutamyltransferase; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Model 1: adjustment was made for age.

Model 2: adjustment was made for age, family history of diabetes, fasting insulin, BMI, waist-to-hip ratio, total cholesterol, high-density lipoprotein-cholesterol, triglycerides, high-sensitivity C-reactive protein, hypertension, current drinking, current smoking, and physical activity.

Model 3: adjustment was made for the variables used in Model 2 and for the other liver enzymes

Table 3. Age- and sex-adjusted ORs and 95% CIs for the occurrence of diabetes by increments of 1 log in each liver enzyme according to risk factor levels during mean of 9 years of follow-up

	Range	Population at risk (*n*)	Number of events (*n*)	Age- and sex-adjusted [OR (95% CI) for GGT]	*p*	Age- and sex-adjusted [OR (95% CI) for ALT]	*p*	Age- and sex-adjusted [OR (95% CI) for AST]	*p*
Fasting insulin (pM)	0 to 24.0	605	32	2.93 (1.87 to 4.59)	0.0001	2.78 (1.45 to 5.35)	0.0022	2.26 (1.08 to 4.74)	0.031
	24.1 to 36.0	547	36	2.21 (1.38 to 3.52)	0.0009	2.53 (1.39 to 4.63)	0.0025	2.50 (1.26 to 4.96)	0.0087
	36.1 to	651	67	1.86 (1.22 to 2.82)	0.0039	2.07 (1.31 to 3.26)	0.0018	1.93 (1.09 to 3.44)	0.025
BMI (kg/m^2)	0 to 21.5	601	29	2.91 (1.82 to 4.64)	0.0001	2.87 (1.50 to 5.48)	0.0014	3.32 (1.57 to 7.04)	0.0017
	21.6 to 24.2	602	36	2.09 (1.30 to 3.38)	0.0025	3.43 (1.81 to 6.49)	0.0002	2.54 (1.26 to 5.13)	0.0090
	24.3 to	601	70	1.99 (1.32 to 3.00)	0.0010	1.71 (1.10 to 2.65)	0.016	1.72 (0.97 to 3.03)	0.063
Waist-to-hip ratio	0 to 0.88	586	24	3.71 (2.10 to 6.54)	0.0001	2.19 (1.15 to 4.17)	0.017	2.38 (1.09 to 5.22)	0.030
	0.89 to 0.94	583	59	2.28 (1.55 to 3.35)	0.0001	3.19 (1.86 to 5.49)	0.0001	2.83 (1.53 to 5.23)	0.0009
	0.95 to	590	50	1.78 (1.15 to 2.75)	0.01	2.24 (1.37 to 3.67)	0.0014	1.73 (0.91 to 3.30)	0.093
HS-CRP (mg/L)	0 to 0.25	586	21	2.12 (1.21 to 3.73)	0.009	2.49 (1.31 to 4.74)	0.0056	2.68 (1.29 to 5.54)	0.0081
	0.26 to 0.64	587	46	2.62 (1.60 to 4.27)	0.0001	2.78 (1.50 to 5.15)	0.0011	2.45 (1.11 to 5.40)	0.026
	0.65 to	586	64	2.09 (1.45 to 3.02)	0.0001	2.51 (1.59 to 3.96)	0.0001	2.35 (1.32 to 4.17)	0.0038
Alcohol intake (g/day)	0	1,274	79	2.81 (1.90 to 4.15)	0.0001	2.56 (1.73 to 3.79)	0.0001	2.19 (1.29 to 3.72)	0.0036
	1 to 29	289	24	2.86 (1.50 to 5.44)	0.001	3.04 (1.45 to 6.35)	0.0032	2.20 (0.91 to 5.31)	0.079
	30 to	241	32	1.69 (1.08 to 2.64)	0.02	2.49 (1.24 to 5.00)	0.011	2.31 (1.12 to 4.74)	0.023

OR, odds ratio; CI, confidence interval; GGT, γ-glutamyltransferase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HS-CRP, high-sensitivity C-reactive protein.

Table 4. Optimal cut-off points of risk factors defined by maximizing sensitivity and specificity to predict future diabetes and their ROC curve areas

	GGT (units/L)	ALT (units/L)	AST (units/L)	Fasting insulin (pM)	BMI (kg/m^2)	Waist-to-hip ratio	HS-CRP (mg/L)
Cut-off point	18	13	19	30.0	24.1	0.91	0.44
Sensitivity (%)	63.3	63.4	48.6	50.7	66.2	47.8	54.8
Specificity (%)	63.7	65.9	71.1	65.2	56.3	69.9	67.9
ROC curve area (%)	67.9	67.4	62.3*†	61.1*†	64.6	60.0*†	61.6*†
(95% CI)	(63.1 to 72.3)	(62.4 to 72.1)	(57.0 to 67.4)	(56.0 to 65.9)	(59.5 to 69.6)	(55.4 to 64.5)	(56.9 to 66.2)

ROC, receiver operating characteristic; GGT, γ-glutamyltransferase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HS-CRP, high-sensitivity C-reactive protein; CI, confidence interval.
* $p < 0.05$ vs. GGT.
† $p < 0.05$ vs. ALT.

related with liver fat measured by proton spectroscopy and, after weight loss, the change in serum ALT correlates with that in liver fat (19).

In our multivariate analysis, serum GGT and ALT were mutually independent in predicting incident diabetes. It is known that serum GGT is not only a marker of liver fat amount but also a marker of oxidative stress (20–22). GGT presenting at the outer side of the cell membrane is thought to maintain cellular glutathione levels, which are the major intracellular defense against free radicals (23). Increased oxidative stress impairs insulin secretion from the islets of Langerhans and insulin action in target tissues by damaging DNA, membranes, enzymes, etc. (24). Decreased insulin secretion and insulin sensitivity are major features of the pathophysiology of type 2 diabetes (25). This may be the reason why GGT and ALT has a highly predictive value for the development of diabetes. On the other hand, several epidemiologic studies examined which of these enzymes was the best marker for incident diabetes. Lee et al. (3,4) reported the dose–response relationship between GGT levels and incidence of diabetes in both Korean male workers and young black and white Americans with ALT or AST levels within the reference interval. Furthermore, in their other study, GGT levels within normal range predicted incidence of chronic elevation of ALT (26). These findings indicate the possibility that GGT is a more powerful predictor of incident diabetes than other liver enzymes. However, we showed in the ROC analysis that ALT and GGT but not AST have equally predictive value for the development of diabetes. These findings should be confirmed in other populations, having different BMI levels and lifestyles.

Some experimental studies have shown that selective deletion of the insulin receptor from muscle results in a slight increase in serum free fatty acid and triglycerides but not in glucose intolerance or diabetes (27), whereas a similar maneuver in the liver leads to marked glucose tolerance (28), suggesting that maintaining normal glucose concentrations is related to the liver rather than to peripheral tissue. Our stratified analysis showed that the associations of both GGT and ALT levels with the occurrence of diabetes were independent of markers of systemic insulin resistance, such as fasting insulin, BMI, waist-to-hip ratio, and HS-CRP. In our subjects, the areas under the ROC curve of GGT and ALT were also significantly larger than that of fasting insulin, waist-to-hip ratio, or HS-CRP. Insulin resistance in the liver through fat accumulation may offer a better explanation of the cause of diabetes than peripheral insulin resistance or systemic inflammation.

Alcohol intake causes fatty change of the liver. In alcoholic fatty liver, serum ALT tends to be depressed relative to serum AST, and serum GGT has the specificity to detect alcohol abuse (29), whereas liver fat accumulation caused by overeating predominantly increases ALT but not AST or GGT (19). However, these findings indicated that both GGT and ALT predict future diabetes, independent of current drinking habits. Additionally, in our stratified analyses, the associations of both GGT and ALT with diabetes were unrelated to alcohol intake levels. These observations suggest that elevated serum levels of GGT and ALT, irrespective of the causes of fatty liver, are associated with incident diabetes.

Viral hepatitis infection often increases liver enzyme levels without hepatic fat accumulation, and several clinical studies have shown that chronic hepatitis C virus infection is linked to type 2 diabetes (30,31). In our study, however, the distribution of hepatitis B and C virus positive markers

did not differ between subjects who developed diabetes and those who did not, indicating that viral hepatitis infection did not affect our findings.

A limitation of our study is that a diagnosis of diabetes was not based on a 75-gram oral glucose tolerance test, but on a single reading of fasting glucose level, as has been the case in other epidemiologic studies (3–5,9). Thus, subjects with diabetes having normal fasting glucose levels were misdiagnosed in our study. In addition, some of the participants who were classified as having worsening fasting glucose status may not have been so categorized after repeated testing. These misclassifications may have weakened the associations found in this study, and the true associations may, in fact, be stronger than those shown in our data.

In conclusion, we have shown that elevated serum GGT and ALT levels, even in the normal range, are better predictors of diabetes than the known risk factors except for BMI in a general Japanese population. The association between these enzymes and diabetes was found to be independent of insulin resistance, inflammation markers, and alcohol consumption levels. These results support the hypothesis that the liver is more important than previously thought in the pathogenesis of type 2 diabetes.

Acknowledgments

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別紙3

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）
分担研究報告書

メタボリックシンドロームの診断における内臓脂肪面積値の意義に関する研究

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研究要旨
MONK研究集団でCTで測定した内臓脂肪面積値と、メタボリックシンドロームの血圧、血糖、血清脂質との関係を横断的に解析した。日本の診断基準では、内臓脂肪面積のカットオフ値は感度と特異度から男性100cm^2、女性65cm^{2}が最適で、IDFおよびAHA/NHLBI基準では、男性98cm^2、女性60cm^{2}が最適であった。男性≥ 100cm^2、女性≥ 65cm^{2}と判定された被験者は、HOMA-R≥ 1.6の被験者との重なりが大きかった。

A．研究目的
MONK研究集団でのメタボリックシンドロームの日本、IDFおよびAHA/NHLBI診断基準に適切な内臓脂肪面積値を明らかにする。また、インスリン抵抗性の指標であるHOMA-Rと内臓脂肪面積の基準値の関係を解析する。

B．研究方法
MONK研究集団の、CTで内臓脂肪面積測定を受けた40-59歳の被験者につき、血圧、血糖、血清脂質、服薬から、メタボリックシンドローム診断基準に該当する項目に関する横断的解析を行ない、複数の項目を満たす例を診断する内臓脂肪面積値をROC解析で検討した。空腹時インスリンと血糖を同時測定した被験者で、男性100cm^2、女性65cm^{2}の基準値がHOMA-Rの上昇を検出する感度と特異度を求めた。
（倫理面への配慮）
書面で同意を得た被験者のみについて、データを匿名化して解析した。

C．研究結果
ROC解析の結果、日本の診断基準では、男性100cm^2、女性65cm^{2}が最適で、IDF及びAHA/NHLBI基準では、男性98cm^2、女性60cm^{2}が最適な値であった。また、この基準値で判定したメタボリックシンドロームの有病率は、IDF基準で男性36.1%、女性20.7%、AHA/NHLBI基準で男性41.3%、女性22.2%であった。男性100cm^{2}と女性65cm^{2}を基準値とすると、HOMA-R≥ 1.6の被験者は男性で感度0.67、特異度0.67、女性で感度0.70、特異度0.66で検出された。

D．考察
日本の基準とIDFの判定基準は、血糖値と脂質の基準が異なっているが、最適な内臓脂肪面積値に大きな差はなかった。IDF基準と腹部肥満基準を必須としないAHA/NHLBI基準での有病率の差が小さいことは、最適化された基準での腹部肥満の判定がメタボリックシンドロームの病態とよく合致することを示唆する。MONK研究集団は40-59歳にほぼ限られるため、他の年齢層等も含めた検討が必要であるが、わが国の基準を考える上で有意義な結果である。内臓脂肪蓄積と判定される被験者とインスリン抵抗性を有する被験者の重なりが大きいことが確認された。

E．結論
メタボリックシンドロームの診断基準にいて、腹部肥満の判定には、最適化された内臓脂肪面積値を定めることが重要で、さらなるデータの蓄積と解析が必要と考えられる。

G. 研究発表
1. 論文発表
投稿準備中
2. 学会発表
平田雅一、他. 糖尿病 50巻 suppl. S-108, 2007.
平田雅一、他. 肥満研究 13巻 suppl. pp292, 2007.

H. 知的財産権の出願・登録状況
なし

別紙４

研究成果の刊行に関する一覧表

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ
平田雅一、宮脇尚志、細田公則、小鳥真司、近藤絵里、志賀利一、大島秀武、中尾一和	副肥満の評価としてのウエスト、内臓脂肪面積測定，超音波法、生体インピーダンス法	門脇孝、小川佳宏	脂肪細胞と脂肪組織	文光堂	東京	2007	211-215

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年

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）
分担研究報告

内臓脂肪面積と危険因子からみたメタボリックシンドローム診断基準に関する研究

分担研究者　伊藤千賀子　ｸﾞﾗﾝﾄﾞﾀﾜｰ　ﾒﾃﾞｨｶﾙｺｰﾄ　所長

研究要旨：1,787 人（男性 1,101 人、女性 686 人）について CT による内臓脂肪面積(VFA)からメタボリックシンドローム（MS）を診断するために虚血性心疾患等の危険因子を考慮して腹囲径を検討し、男性 85.0cm、女性 80.0cm が適切と判断した。

A. 研究目的

メタボリックシンドローム（MS）診断基準の腹囲は女性が男性より大きくなっており、この理由が明らかでないことから内臓脂肪面積（VFA）と危険因子数から検討した

B. 研究方法

対象は、2005 年 10 月から 2008 年 2 月の間、当所で人間ドックを受けた 1,787 例（男性 1,101 例、女性 686 例）である。早朝空腹時の血清脂質、血糖値、IRI、アディポネクチン値、座位の血圧値を測定した。腹囲径は臍周囲及び WHO 基準（肋骨下縁と腸骨上縁の中間点）で測定した。低線量 CT で VFA、皮下脂肪面積を測定した。高血圧、脂質代謝異常、空腹時高血糖のうち 2 個以上有するものをスクリーニングする精度を VFA 別に比較した。

本研究は Grand Tower Medical Court Life Care Clinic 治験審査委員会で承認を受け、対象例は全て文書による同意を得ている。

C. 研究結果

男性では精度が最も高いのは VFA 94cm^2 で、感度・特異度がともに 69%であった。

女性では精度が最も高いのは VFA 46cm^2 で、感度と特異度はともに 75%であった。

臍周囲径と VFA は高い相関がみられ、男性では VFA 94cm^2 に対する腹囲径は 86.0cm であり、女性では内臓脂肪面積 46cm^2 に対する腹囲は 78.5cm であった。

D.考察

VFA が 100cm^2 を越すと、空腹時高血糖、脂質代謝異常、高血圧症の合併頻度が増加するとの報告を基に、VFA が 100cm^2 に相当する腹囲径が男性 85cm、女性 90cm が日本の MS 診断基準の必須項目となっている。

今回の結果から男性では VFA 94cm^2 が MS をスクリーニングする精度が最も高く、VFA 94cm^2 に対する腹囲径は 86.0cm であった。すなわち従来の VFA100cm^2、腹囲 85cm と大差はないと考えた。

一方、女性では VFA 46 cm^2 が MS をスクリーニングする精度が最も高く、VFA 46cm^2 に対する腹囲径は 78.5cm であった。従来の日本の基準と今回の結果には大きな差が認められたが、これは今まで多数例について女性の VFA とリスクの検討が十分なされなかったためと考える。女性の VFA 100cm^2 に対する腹囲径は 90cm であることが示されたが、VFA100 cm^2 以上の女性の症例は全体の 4.8%とごく 1 部に過ぎない。

本研究は MS の判定基準であり冠動脈疾患の危険因子でもある空腹時高血糖、脂質代謝異常、高血圧症を満たす項目数で分析を行った。本来の MS は VFA を基盤にリスクの上昇をみており、本研究は腹囲からではなく VFA を基本として腹囲を求めたことは極めて意義深い。

E. 結論

CT で測定した VFA をもとに MS をスクリーニングする精度を VFA 別に比較し、男性では VFA 94cm^2、女性では 46cm^2 が最も精度が高かった。それに対応する腹囲径は男性 86.0cm、女性 78.5cm であった。しかしながら一般に用いるのは端数でないのがよいことから、MS をスクリーニングする腹囲の基準に男性 85cm、女性 80cm を提案したい。

別紙４

研究成果の刊行に関する一覧表

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
伊藤　千賀子 藤川　るみ	メタボリックシンドロームにおける「糖尿病」発症のリスク	診断と治療	96巻・第2号	41-46	2008
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保健指導への活用を前提としたメタボリックシンドロームの診断・管理のエビデンス創出のための縦断・横断研究

—茨城県筑西市協和地区における疫学研究—

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研究要旨

茨城県筑西市協和地区では、昭和56年より脳卒中を中心とした循環器疾患病予防対策事業が開始され、現在まで継続している。本研究では、地域住民におけるメタボリックシンドロームが循環器疾患発症リスクに及ぼす影響について前向きに分析することを目的とした。メタボリックシンドロームと循環器疾患発症との関連を検討した結果、NCEP-ATPIIIの診断基準で判定されたメタボリックシンドロームは虚血性心疾患と脳卒中発症の予測因子であったが、日本8学会の基準によるメタボリックシンドロームは脳卒中発症と有意に関連したものの、虚血性心疾患との関連はみられなかった。日本8学会の基準では1990-93年にメタボリックシンドロームと判定された者は男性30%、女性9%であった。一方、2003-05年に判定された者は男性28%、女性7%であり、メタボリックシンドロームの有病率に大きな変化はみられなかった。

A．研究目的

茨城県筑西市協和地区（旧・真壁郡協和町）では、1981年より健診による高血圧の把握と高血圧管理、食事改善指導を中心とする脳卒中の一次・二次予防対策を、町、医師会、保健所、健診機関、住民組織および大阪府立成人病センター（現・大阪府立健康科学センター）、筑波大学、大阪大学等の研究機関の組織的な協力の下に進めてきた。

わが国では平成20年度より特定健康診査・特定保険指導制度を導入し、メタボリックシンドローム予防の観点から、内臓肥満の指標としてウエスト周囲径の測定を実施することとなったが、肥満の割合が未だ低い日本人において、肥満やメタボリックシンドロームが循環器疾患にどのような影響を与えるのかは未だ明らかでない。また、メタボリック症候群の診断基準として、海外のNCEP-ATPⅢ, AHA/NHLBI, IDFの基準に加え、2005年の日本8学会合同基準が策定されたが、わが国の一般集団において、どの診断基準が疾病予測に有用であるかについても明らかでない。コホート研究においては、ベースライン調査においてウエスト周囲径を計測している研究は多くない、メタボリックシンドロームに関するエビデンスはこれまで十分でなかった。そこで、本研究では、1990年代前半のベースライン調査におけるウエスト周囲径とリスクファクターのデータを用い、国内外のそれぞれの基準で、農村地域住民におけるメタボリック症候群と循環器疾患発症リスクとの関連、並びにメタボリック症候群の推移を分析した。

B．研究対象と方法

対象は茨城農村の筑西市K地区（人口1.7万人）の住民で、1990～1993年の循環器検診で腹囲を測定し、虚血性心疾患と脳卒中の既往がある者を除く2,613人である。1990～1993年から10.5年間（2003年12月末まで）追跡し、NCEP-ATPⅢ, AHA/NHLBI, IDFの診断基準（いずれもアジア人基準の腹囲：男≧90cm、女≧80cm）と日本8学会の診断基準（腹囲：男≧85cm、女≧90cm）によるメタボリック症候群とその後の虚血性心疾患、脳卒中の発症との関連をCox比例ハザードモデルにより分

析した。また、1990～1993年と2003～2005年の検診で腹囲を測定した40～69歳の男女、それぞれ2,660(男998、女1,662)人と2,845人(男1,092、女1,753)人についてNCEP-ATPⅢ, AHA/NHLBI, IDFと日本８学会の診断基準によるメタボリック症候群の有病率をそれぞれ算出し、その推移を分析した。

C．研究結果

（１） メタボリック症候群と虚血性心疾患・脳卒中発症

平均10.5年間の追跡調査の結果、虚血性心疾患42人、全脳卒中73人（脳梗塞54人、出血性脳卒中18人、その他１名)、全循環器疾患（虚血性心疾患＋脳卒中）115人の発症が認められた。NCEP-ATPⅢの診断基準によるメタボリック症候群がある群の多変量調整ハザード比(95%信頼区間)は、虚血性心疾患で2.1(1.1-4.0)、全脳卒中で1.7(1.0-2.7)、脳梗塞で2.0(1.2-3.5)、全循環器疾患で1.7(1.2-2.5) であった。出血性脳卒中については有意な関連を認めなかった。AHA/NHLBIの診断基準では、脳梗塞は1.8(1.0-3.1)、全循環器疾患は1.6 (1.1-2.3) であり、IDFの診断基準では、脳梗塞は2.2(1.2-3.9)、全循環器疾患は1.6(1.1-2.4)であった。AHA/NHLBIとIDFの診断基準では虚血性心疾患、全脳卒中と出血性脳卒中については有意な関連を認めなかった。一方、日本８学会の診断基準では虚血性心疾患で1.0(0.5-2.2)、全脳卒中は1.8(1.1-3.1)、脳梗塞は2.0(1.1-3.6) 、全循環器疾患は1.4(0.9-2.1)であり、虚血性心疾患、出血性脳卒中と全循環器疾患については有意な関連を認めなかった。また、肥満度の有無別に解析した結果、肥満のない危険因子保持者においても肥満の者と同じように循環器疾患発症リスクの増加が認められた。

（２） メタボリック症候群の推移

1990-93年における腹囲の平均値は男性で83.9cm、女性で81.1cmであり、男性で85cm以上の者は49%、女性で90cm以上の者は19%にみられた。一方、2003-05年における腹囲の平均値は男性で86.9cm、女性で83.3cm、男性で85cm以上の者は64%、女性で90cm以上の者は25%にみられ、日本8学会の腹囲の基準にあてはまる者の割合は増加していた。NCEP-ATPⅢの診断基準によるメタボリック症候群の有病率については、1990-1993年から2003～2005年にかけて、男性が29%から23%、女性が33%から21%との減少が認められた。日本8学会の基準による有病率については、1990-93年では男性が30%、女性が9%だったのに対し、2003-05年はそれぞれ28%、7%であり、有意な増加はみられなかった。

D. 考察

本研究により、NCEP-ATPⅢの基準によるメタボリック症候群は虚血性心疾患と脳梗塞の発症リスクと有意な関連を示し、他の基準よりも虚血性心疾患の予測能がやや高かった。脳梗塞についてはいずれの基準でも予測能に大きな違いは認められなかった。

NCEP-ATPⅢの診断基準によるメタボリック症候群の有病率は減少したが、その減少はメタボリック症候群の構成因子である高血圧、高トリグリセライド血症、低HDLコレステロール、高血糖の割合が減少したことによるものであり、ウエスト高値の割合は有意に増加した。一方、他の基準による有病率の減少はみられなかった。

E. 結論

茨城県農村の一般住民において、NCEP-ATPⅢの診断基準で判定されたメタボリック症候群は虚血性心疾患と脳梗塞発症の予測因子として有用であった。また、肥満の有無に関係なく、メタボリックシンドローム構成因子の集積によって循環器疾患発症リスクの上昇が認められた。メタボリックシンドロームの有病率の推移については、この地域住民においては過去10年間でメタボリックシンドロームの有病率は増加していなかった。

都市部住民におけるメタボリックシンドロームと循環器疾患発症の関連(吹田研究)

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研究要旨:平成20年から施行される「高齢者医療確保法」に伴い保険者の責務においてメタボリック症候群に着目した特定健診が必須化される。しかし、現在のわが国のメタボリックシンドロームの基準は2005年に公表されていたエビデンスに基づいており、今後、新しい知見に基づいてUP-DATEしていく必要がある。本研究は、本邦唯一の都市住民コホートである吹田研究のデータを用い、メタボリックシンドローム(2005年日本基準)と循環器疾患発症の関連を明らかにすることを目的とした。1989～1993年の初回健診受診日をベースラインとして、脳卒中・心筋梗塞の既往のない男性2,730名(平均年齢55.9歳)、女性3,117名(平均年齢54.5歳)を1997年度末まで追跡した。平均追跡期間は5.8年であり、脳卒中79人、心筋梗塞39人の発症が確認された。メタボリックシンドローム発症の相対危険度(性・年齢・喫煙・飲酒を調整)は、全脳卒中で1.74(1.14-2.66)、心筋梗塞で2.43(1.60-3.70)であった。メタボリックシンドロームと出血性脳卒中とは関連を認めなかった。都市部の住民においてメタボリックシンドロームは循環器疾患の危険因子であったが、特に女性ではメタボリックシンドロームの頻度が低く発症に対する寄与危険度は小さかった。今後は他の診断基準との比較やLDLなど他の危険因子との交互作用も検討していく予定である。

A. 研究目的

平成20年から施行される「高齢者医療確保法」に伴い保険者の責務においてメタボリック症候群に着目した特定健診が必須化される。同時に特定保健指導も実施され、メタボリック症候群の予防・治療法として食事・運動療法の有効性が強調されている。しかし現在のわが国のメタボリックシンドロームの基準は2005年に公表されていたエビデンスに基づいており、今後、新しい知見に基づいてUP-DATEしていく必要がある。本研究は、本邦唯一の都市住民コホートである吹田研究の追跡調査データを用いて、都市部におけるメタボリックシンドロームと循環器疾患発症の関連を明らかにすることを目的とした。

B. 研究方法

吹田研究は、平成元年に吹田市の住民台帳より12,200名を無作為抽出し、その中で同意が得られた6,485名が一次コホート集団として設定されている。

1)わが国の地域ベースの循環器疾患の疫学研究のほとんどは、人の異動が少ない、研究への協力が得やすい、発症等の追跡調査が行いやすい、などの理由でほとんどが非都市部に集中している。本研究は本邦唯一の都市部における循環器コホート研究である。ベースライン調査(初回健診):1989年から2年ごとに対象者の循環器健診を老人保健法に基づく基本健康診査として実施しており、それに合わせて糖負荷検査、アンケート調査(身体活動問診・ストレス問診、判定量食物摂取頻度調査)、頚部超音波検査などの研究検査を本人の同意にもとに実施している。今回、初期の1989～1993年の初回受診日をベースラインとしたコホート解析を実施した。

2)追跡方法:コホート研究で最も重要なのは参加者の転帰の把握である。そのため全員を対象とした健康アンケートを年1回実施し、また脳卒中・心筋梗塞発症状況を健診案内時(2年に1回)に送付して、脳卒中・心筋梗塞の発症を把握している。さらに健診受診時に脳卒中調査票・胸部症状についての問診票をとり、発症状況を把握している。発症の記載のある者に対して、診療情報提供に関するお願い、診療情報の提供に関する同意書

を送付し、吹田コホート脳卒中調査票・心筋梗塞調査票を用いてカルテ調査を行っている。
3)エンドポイント(観察打ち切り):発症の追跡研究の場合、脳卒中及び心筋梗塞の発症、市外転出、または最後に非発症生存を確認できた時点をもってエンドポイントとしている。

今回の解析は、一次コホートの対象者のうち脳卒中・心筋梗塞の既往のない男性 2,730 名(平均年齢 55.9 歳)、女性 3,117 名(平均年齢 54.5 歳)を 1997 年度末まで追跡したデータを用いた。メタボリックシンドロームの定義は日本の診断基準を用い、メタボリックシンドロームと循環器疾患との関係は、性年齢、喫煙、飲酒を調整した Cox の比例ハザードモデルを用いて解析した。

C. 研究結果

ベースライン時のメタボリックシンドローム(日本基準による)の割合は、30 歳代から 70 歳代まで、男性で 7.3%、8.0%、15.0%、23.5%、17.6%、女性で 0.2%、1.4%、3.4%、7.2%、9.7%であった。平均追跡期間は 5.8 年であり(男性 15,550 人年、女性 18,203 人年)、脳梗塞 55 人、脳出血 18 人、くも膜下出血 6 人、心筋梗塞 39 人の発症が確認された。メタボリックシンドローム発症の調整相対危険度は全脳卒中で 1.74 (1.14-2.66)、心筋梗塞で 2.43 (1.60-3.70)であったが(性・年齢・喫煙・飲酒を調整)、出血性脳卒中とは関連を認めなかった。しかし女性ではメタボリックシンドロームの人口寄与危険度は小さかった。

D. 考察

吹田研究は、遺伝子多型と循環器疾患の危険因子の関連についての association study で多くの研究成果をあげてきた (Suita study)。しかしこの研究の本来の目的は、都市部一般集団を対象としたコホート研究を通じて、広く国民一般に還元可能な循環器疾患の予防方法を開発、提示していくことにある。しかしながら地域でのコホート研究では成果が得られるようになるまでに多大の年数と労力がかかる。また臨床試験とは異なり、患者ではない一般集団の追跡には相当の公衆衛生学的、疫学的スキルが要求され、特に循環器疾患の発症をエンドポイントとして実施できているところは数えるほどしかない。自由行動下にある非患者集団は通常、医療関係者との接点がないため、健診やアンケート、電話調査などあらゆる手段で接触を保つ必要がある。もし健診を受診しない者がいた場合、受診していないだけで元気なのか、発症して別の病院を受診しているのか、死亡したのか、転居したのかを継続的に確認することによって初めてコホートの維持が可能である。また他の病院を受診した者に対しては、本人の許可を得てカルテ調査を行う必要がある。さらに死亡者に対しては遺族の同意を得てカルテ調査をしたり、死亡小票を調べたりする必要も出てくる。

都市部の場合、住民の異動が頻繁にある上、個人情報の保護等にも非常に敏感な社会的背景があり、通常、コホート研究の実施は困難を極める。吹田研究は、長年、培った吹田市医師会や市保健センターとの協力を得て大阪都市部での長年のコホート研究を継続できている。現在、複雑な解析に十分耐える追跡期間にほぼ達したと考えられるため、成果が期待される。吹田研究はベースライン時からほぼ全対象者に空腹採血を実施し、さらにウェストを測定しているのが特徴である。今後、他のメタボリックシンドロームの基準と日本基準の比較、LDL-C など他の危険因子を考慮した解析などを実施する予定である

E. 結論

都市部の 6 年間のコホート研究の結果、日本基準のメタボリックシンドロームは、脳卒中、脳梗塞、心筋梗塞の発症と有意な関連を示した。しかし特に女性ではメタボリックシンドロームの頻度が低く、予防対策を考えていく上では寄与危険度を考慮する必要があると考えられた。またより発症予測能の高い診断基準についても検討していく必要がある。

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F．健康危険情報

なし

G. 研究発表

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H．知的財産権の出願・登録状況

なし