は 18.1%で、Wc 基準に寄らず内蔵脂肪蓄積群で有意に高値であった。

5年後の糖尿病発症率: MetS は有意なリスクであったが、FPG 高値に比して、どの Wc 基準を用いても同様で、得意度は高い(IDF Wc、現行日本人 Wc、代替日本人 Wc、vs. FPG 高値;95.0, 96.4, 93.6% vs. 83.7%, p<0.001)ものの、感度は低く(7.7, 0.0, 7.7% vs. 69.2%, p<0.001)、偽陽性率は高かった(95.0, 100, 96.0% vs. 87.2%, p<0.001)。一方、FPG 高値は、内蔵脂肪の蓄積の有無に関わらず有意なリスクであった。

D. 考察

近年のメタ解析の結果では、診断基準に寄らず、MetS は、糖尿病発症の有意な危険因子であると報告されている(IDF 基準での MetS の相対リスクは 4.42)。しかしながら、このメタ解析では、種々の因子での補正(多重解析等)が成されておらず、また、内蔵脂肪蓄積を必須項目として MetS を診断した場合には、MetS を有意なリスクとして認めることが出来なかった。従って、MetS の構成因子の内でも、多くの研究で、糖尿病発症の強いリスクと報告されている、FPG 高値は、単独での糖尿病発症リスクに MetS の診断が付加的価値を持つかどうかは疑問である。非ヒスパニック系白人、及び、メキシコ系アメリカ人での研究では、付加的価値があると報告されているが、糖尿病発症の病態が、これら対象者とは明らかに異なる(インスリン抵抗性よりも、膵β細胞機能低下が主)日本人での報告は成されていなかった。本研究で、日本人では、糖尿病発症に関しては、FPG 高値が強いリスクであり、MetS は、あまり大きな付加的因子とはならない事が示唆された。

E. 結論

FPG 高値は将来の糖尿病発症を予測する因子として MetS より重要と思われた。

G.研究発表

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H.知的財産権の出願・登録状況

無

別紙４

研究成果の刊行に関する一覧表

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Brief report

Raised fasting plasma glucose a better predictor of diabetes than the IDF definition of the metabolic syndrome☆

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ABSTRACT

Raised FPG was better at identifying future diabetes than either IDF MetS or a constellation of risk factors except for raised FPG with and without abdominal adiposity. This should shed light on a screening program for future DM in Japan.

The metabolic syndrome (MetS) concept has been used as a screening test for preventing cardiovascular diseases (CVD) and type 2 diabetes mellitus (DM) in Japan since April 2008 [1]. Abdominal adiposity is a prerequisite of MetS, and in association with a cluster of metabolic abnormalities can be followed to identify subjects at high risk for developing DM [1]. This study aimed at clarifying the extent to which either the MetS or a constellation of risk factors except glucose with or without abdominal adiposity, can be used to identify future DM in comparison with raised fasting plasma glucose (FPG).

The study enrolled 779 non-diabetic subjects aged 40–74 years without a prior CVD event or risk factors, and followed them for 5 years, with 3092 person years accumulated, from the Funagata Diabetes Study [2]. World Health Organization criteria [3] were used to diagnose DM. The FPG ≥ 5.56 mmol/l was used to define raised FPG. The International Diabetes Federation (IDF) definition [4] with three different cut-offs of waist circumference (Wc) for abdominal adiposity was used to identify MetS. The cut-offs were as follows: IDF cut-offs for Japanese (m/f = 90/80 cm) [4]; current cut-offs in Japan

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Table 1 – Incidence density of DM (per 1000 person years) and its 95% confidence interval in subjects with different cluster of metabolic abnormalities using three cut-offs of waist circumference (WC) for diagnosis of abdominal adiposity.

	Abnormal obesity							
	Absent				Present			
	≤1[a]		≥2[a]		≤1[a]		≥2 (MetS)[a]	
	Absent[b]	Present[b]	Absent[b]	Present[b]	Absent[b]	Present[b]	Absent[b]	Present[b]
IDF cut-offs for Japanese								
Number of subjects	461	88	52	12	102	24	23	17
Number of incident case	7	12	0	1	0	4	1	1
Incidence density	3.8 (1.0–6.7)	34.3 (15.2–53.4)	–	20.9 (−19.7–61.5)	–	42.0 (1.7–82.3)	10.9 (−10.4–32.3)	14.7 (−14.0–43.6)
Current Japanese cut-offs								
Number of subjects	494	86	61	16	69	26	14	13
Number of incident case	5	10	1	2	2	6	0	0
Incidence density	2.6 (0.3–4.8)	29.3 (11.4–47.2)	4.1 (−3.9–12.2)	31.4 (−11.4–74.2)	7.3 (−2.8–7.4)	58.1 (13.0–103.2)	–	–
Proposed Japanese cut-offs								
Number of subjects	419	73	45	9	144	39	30	20
Number of incident case	5	9	0	1	2	7	1	1
Incidence density	3.0 (0.4–5.6)	31.0 (11.1–51.0)	–	27.9 (−26.0–81.8)	3.5 (−1.3–8.3)	45.2 (12.5–78.0)	8.4 (−8.0–24.8)	12.6 (−11.9–37.1)

Metabolic abnormalities include: serum triglycerides ≥1.7 mmol/l; high-density cholesterol <1.03/1.29 mmol/l in *m/f*; systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥85 mmHg.
Raised FPG: FPG ≥5.56 mmol/l.
[a] Number of metabolic abnormalities except raised FPG.
[b] Condition of raised FPG.

(*m/f* = 85/90 cm) [1], and proposed cut-offs which corresponded to ≥2 non-essential risk factors (*m/f* = 85/80 cm) [5,6].

The 5-year cumulative incidence of DM was calculated as the number of subjects who developed DM from non-DM divided by the sum of the durations of follow-up for each subject among those with different clusters of metabolic abnormalities.

The prevalence of the MetS according to IDF Wc cut-offs, current and proposed Japanese cut-offs were 5.1, 3.5 and 6.4%, respectively. The prevalence of raised FPG was 18.1% and was higher in subjects with abdominal adiposity than those without, regardless of any of the three Wc cut-offs used (*p*-values <0.05).

Overall, 26 non-DM subjects developed DM within the next 5 years. Raised FPG identified absolute high risk of future DM whereas the constellation of risk factors except raised FPG with or without abdominal adiposity, using any of the three Wc cut-offs, did not (Table 1). As a screening test for future DM, the MetS defined by Wc according to IDF or current and proposed Japanese cut-offs had a significantly lower sensitivity (7.7, 0 and 7.7% vs. 69.2%, all *p*-values <0.001) and false positive test rate (95.0, 100 and 96.0% vs. 87.2%, all *p*-values <0.001) and higher specificity (95.0, 96.4 and 93.6% vs. 83.7%, all *p*-values <0.001) than raised FPG.

A recent meta-analysis has reported that the MetS, regardless of definition, is a significant predictor of incident DM in many populations and the average estimated relative risk of IDF MetS for incident DM was 4.42 [7]. Analysis using a multivariate regression model was not performed in this study due to the limited number of cases, however, the MetS with abdominal adiposity as an essential component, regardless of which cut-off was applied, did not identify a high absolute risk of future DM. Among the MetS components, raised FPG is thought to be the strongest predictor of DM in many studies [8–10], and this was the case in our study. Raised FPG, regardless of the number of other risk factors with and without abdominal adiposity defined by different Wc cut-offs, was a better predictor of DM than the MetS. In contrast, the MetS provided additional prediction beyond that provided by raised FPG in Non-Hispanic White and Mexican Americans [11]. The different characteristics of Japanese in the pathogenesis of type 2 DM, where decreased β-cell function is a major factor rather than insulin resistance, might cause the different impact of raised FPG on the relation between MetS and incident DM. Moreover, the very low sensitivity of the IDF MetS seen in our study has not always been shown in other studies [7]. In contrast, high specificity was commonly observed in many studies [7] including ours. This may suggest the need for population specific prediction models for future type2 DM in Japan.

Conflict of interest

The authors state that they have no conflict of interest.

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ORIGINAL ARTICLE

Angiotensin-converting enzyme gene and retinal arteriolar narrowing: The Funagata Study

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The purpose of this study is to determine whether the angiotensin-converting enzyme (*ACE*) gene polymorphism is associated with retinal arteriolar narrowing, a subclinical marker of chronic hypertension. The Funagata Study examined a population-based sample of Japanese aged 35+ years; 368 participants had both retinal vessel diameter measurements and *ACE* insertion/deletion (*ACE* I/D) polymorphism analyses performed. Assessment of retinal vessel diameter and retinal vessel wall signs followed the protocols used in the Blue Mountains Eye Study. *ACE* gene polymorphisms D/D, I/D and I/I were present in 34 (9.2%), 170 (46.2%) and 164 (44.5%) participants, respectively, distributed in Hardy–Weinberg equilibrium. After multivariable adjustment, retinal arteriolar diameter was significantly narrower in subjects with the D/D genotype compared to subjects with I/D and I/I genotypes (mean difference −6.49 μm, 95% confidence interval (CI): −12.86 μm, −0.11 μm). Our study suggests that the *ACE* I/D polymorphism may be associated with subclinical structural arteriolar changes related to chronic hypertension.
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Keywords: The Funagata Study; angiotensin-converting enzyme polymorphism; retinal arteriolar diameter

Introduction

Retinal arteriolar narrowing is a structural microvascular sign associated with chronic hypertension[1] that predicts the risk of stroke[2] and coronary heart disease.[3] Recent studies suggest that a substantial proportion of the variation in retinal arteriolar diameter might be genetically determined, independent of concomitant risk factors.[4] However, no definite candidate genes associated with retinal arteriolar diameter have yet been consistently identified.

Angiotensin-converting enzyme (*ACE*) is a key component of the renin–angiotensin system and can promote vasoconstriction, inflammation, thrombosis and vascular remodeling. It was reported that there was a high level of ACE expression in the regions of atherosclerotic lesions in human vasculature.[5] Retinal arteriolar narrowing, which reflects intimal thickening, medial hyperplasia and hyalinization and sclerosis of retinal arterioles has also been associated with atherosclerosis.

Polymorphisms in the *ACE* gene, absence (deletion, D allele) rather than presence (insertion, I allele) of the 287-bp Alu insert in intron 16, has been found associated with hypertension,[6] carotid wall thickening[7] and coronary heart disease.[8] The D allele of this polymorphism was also reportedly associated with two-fold higher circulating levels of *ACE*.[9]

It was reported that *ACE* gene and renin mRNA (messenger ribonucleic acid) expressed in the retinal pigment epithelium, the choroid and neural retina of rats.[10] This suggested that the local renin–angiotensin system (RAS) is likely involved in the regulation of the retinal vasculature. Furthermore, one study suggested that patients with hypertensive retinopathy were more likely to have the D/D

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polymorphism than the I/D or I/I polymorphisms.[11] However, there were no studies that had examined the association of the *ACE* gene with quantitatively measured retinal vessel diameter.

The purpose of this study is to determine the independent association of *ACE* I/D polymorphisms and retinal arteriolar narrowing, and whether this association is independent of measured blood pressure and other cardiovascular risk factors.

Materials and methods

Study population

The Funagata study is a population-based epidemiologic study examining diabetes and other vascular disease in adult Japanese persons aged 35 years or older. Details of study participants and research methodology were described elsewhere.[12] In this study, systemic and ophthalmologic data were obtained between June 2000 and June 2002. Of 3676 eligible residents in Funagata community, 743 (20.2%) agreed to participate in the genetic part of the study. Participants included in this current study had a lower frequency of pre-diabetes and diabetes than those excluded (22.8 vs 30.7%; $P=0.003$). There were no significant differences between included and excluded participants in other demographic characteristics, such as age, gender, smoking, body mass index and systolic and diastolic blood pressure. Of the 743, 651 (87.6%) had fundus photographs with sufficient quality for assessment of retinal microvascular structural signs. Only 368 (49.5%) participants with retina–optic disc photographs had adequately captured a sufficient number of retinal vessels within a zone 0.5 disc diameter away from the optic disc margin, to grade retinal vessel diameter using a standardized computer-assisted method.[13] Written consent was obtained from all study participants, the study was conducted according to the recommendation of the Declaration of Helsinki and was approved by the Ethics Committee of the Yamagata University Faculty of Medicine, Yamagata, Japan.

Assessment of retinal microvascular changes

Fundus photographs were taken using non-stereoscopic 45° non-mydriatic fundus camera (CR5-NM45, Canon Inc., Tokyo, Japan; and TRC, Topcon Inc., Tokyo, Japan); a single field centered between the macula and optic disc was taken. Fundus photographs were graded for retinal microvascular signs at the Centre for Vision Research, University of Sydney, Australia. Grading was performed by a trained grader following a standard protocol; details of image preparation and grading protocols have been described previously.[13,14] In brief, retinal photographs on 35-mm film were converted to digital images using a high-resolution scanner (LS2000; Nikon, Tokyo, Japan). Digital images were centered on the optic disc, and all vessels passing through the entire zone between 0.5 and 1 disc diameter away from the disc margin were measured using image analysis software (Retinal Analysis, Department of Ophthalmology Visual Science, University of Wisconsin, WI, USA). A trained grader identified each vessel either as an arteriole or venule. The computer program measured and calculated the average width from five equidistant measures of each vessel. The average diameter of retinal vessels was calculated using the Parr–Hubbard formula, and summarized as the central retinal artery equivalent (CRAE) and the central retinal vein equivalent (CRVE), representing the average arteriolar and venular diameter, respectively.[15,16]

Retinal arteriolar wall signs (focal arteriolar narrowing, arterio-venous nicking and enhanced arteriolar wall reflex) and retinopathy signs (microaneurysms, retinal hemorrhages and exudates) were also graded using a light box method following the standard photographs selected by a retinal specialist (PM) from the standard photographic sets developed for the Modified Airlie House Classification of Diabetic Retinopathy[17] and the Wisconsin Age-Related Maculopathy Grading System.[18] All grading was performed by a trained grader and adjudicated by a senior researcher (JJW) and a retinal specialist (PM).[12]

Assessment of systemic characteristics

Blood pressure was measured after rest for 5 min, and using a mercury sphygmomanometer. Hypertension status was defined for systolic blood pressure $\geqslant 140$ mm Hg or diastolic blood pressure $\geqslant 90$ mm Hg, or if persons had a previous diagnosis of hypertension and were using anti-hypertensive medications. Diabetes or pre-diabetes was defined as having fasting plasma glucose $\geqslant 110$ mg dl^{-1} or 2 h post-load glucose $\geqslant 140$ mg dl^{-1}. Smoking status was assessed during an interview. Body mass index was calculated as weight (kg) divided by the square of height (m).

Assessment of insertion/deletion polymorphism of 287 bp Alu insert in intron 16 of ACE gene

Genomic DNA was isolated from peripheral blood leukocytes by proteinase K and the phenol/chloroform extraction procedure. Insertion (I) or deletion (D) of the 287-bp Alu insert in intron 16 of the *ACE* gene was determined by polymerase chain reaction fragment length polymorphism analysis.[19] The frequency of the D and I allele were 32.3% ($n=238$) and 67.6% ($n=498$), respectively. The frequency of D/D, I/D and I/I were 9.2% ($n=34$), 46.2% ($n=170$) and 44.6% ($n=164$), respectively. The genotypes frequency was found to be in Hardy–Weinberg equilibrium.

Statistical analysis
Data analysis was performed by statistical analysis software (Stata 10, StataCorp, TX, USA and SPSS 14.0, SPSS Inc., Chicago, USA). Demographic characteristics among three genotype groups were compared using analysis of variance. To examine whether the *ACE* I/D polymorphism was associated with retinal vessel diameter, linear regression analysis was used, with retinal vessel diameter as the dependent variable, adjusting for cardiovascular risk factors selected based on our previous analysis.[12] Associations between the *ACE* I/D polymorphism and presence of retinal arteriolar wall signs/retinopathy were examined using logistic regression models while adjusting for cardiovascular risk factors. Crude, age–gender adjusted and multivariable (age, gender, systolic blood pressure, smoking status and body mass index) adjusted estimates for the associations are presented. We used models following additive models (I/I vs I/D vs D/D), dominant models (I/I vs I/D or D/D) or recessive models (I/I or I/D vs D/D). Models for CRAE additionally adjusted for CRVE and vice versa.[20] We also analyzed if the interaction between *ACE* I/D polymorphism (D/D vs I/D or I/I) and hypertension status (hypertension vs normotension) affected retinal vessel diameters. We further examined if the *ACE* I/D polymorphism was associated with systolic and diastolic pressure; linear regression was used to estimate the mean differences in systolic and diastolic blood pressure by *ACE* I/D polymorphism, adjusting for other cardiovascular risk factors.

Results

Demographic characteristics by *ACE* I/D polymorphism are presented in Table 1. There were no significant differences in demographic characteristics among *ACE* I/D polymorphism groups.

Difference in systolic and diastolic blood pressure by ACE I/D polymorphisms
Mean systolic and diastolic blood pressure was highest in subjects with I/I polymorphism, although these were not statistically significant (Table 1). Table 2 shows relationships between ACE I/D polymorphism and blood pressure status. Mean diastolic pressure was significantly lower in subjects with D allele (D/D or I/D) compared with that in subjects with I/I (−2.50 mm Hg 95% CI: −4.78 mm Hg, −0.23 mm Hg) after adjusting for age, gender, body mass index and smoking status. However, there was no significant difference in systolic blood pressure (1.43 mm Hg, 95% CI: −4.82 mm Hg, 7.68 mm Hg) and no significant association between the presence of hypertension and the *ACE* I/D polymorphisms (odds ratio for D/D compared with I/I: 1.02, 95% CI: 0.38–73).

Difference in retinal vessel diameters by ACE I/D polymorphisms
Table 3 shows relationships between *ACE* I/D polymorphism and CRAE. Mean CRAE (± s.d.) for subjects with D/D, I/D and I/I polymorphism was 173.77 ± 19.73 μm, 179.46 ± 20.54 μm and 179.50 ± 20.39 μm, respectively. After adjusting for CRVE, CRAE was significantly smaller in subjects with D/D compared with that in subjects with I/I by −6.69 μm (95% confidence interval (CI) for the β coefficient: −12.88 μm, −0.51 μm). This remained significant after age–gender (−6.60 μm, 95% CI: −12.78 μm, −0.42 μm) and multivariable adjustment (−6.86 μm, 95%CI: −13.58 μm, −0.13 μm). Similar findings are obtained when comparing subjects with D/D with those with the I allele (I/D and I/I) after adjusting for CRVE, age–gender or multiple variables (Table 3). There were no significant differences in mean CRAE between subjects with I/I and I/D polymorphism, or between subjects with I/I and those with D allele (I/D and D/D polymorphisms) (Table 3).

Table 3 shows CRVE by *ACE* I/D polymorphism. Mean CRVE for the subjects with D/D, I/D and I/I polymorphisms was 217.37 ± 20.07 μm, 216.12 ± 20.37 μm and 215.61 ± 21.52 μm, respectively Mean CRVE was non-significantly larger in subjects with D/D compared with that in subjects with I/I or I/D.

After adjusting for CRVE, subjects with hypertension had significantly smaller CRAE than those who were normotensive by −3.63μm (95% CI; −7.11 μm,

Table 1 Demographic characteristics by polymorphism of insertion (I) or deletion (D) of the 287 bp Alu insert in intron 16 of the angiotensin-converting enzyme (ACE) gene, The Funagata Study, Japan, 2000–02

	D/D polymorphism N = *34*	*I/D polymorphism* N = *170*	*I/I polymorphism* N = *164*	P-*value*
Male gender (%)	17 (50)	67 (39.4)	67 (40.9)	0.518
Hypertension (%)	13 (38.2)	70 (41.2)	64 (39.0)	0.915
Pre-diabetes or diabetes (%)	6 (17.6)	39 (22.9)	39 (23.7)	0.739
Current smoker (%)	3 (8.8)	32 (18.8)	25 (15.2)	0.313
		Mean (s.d.)		
Age, years	58.9 (11.6)	60.1 (11.6)	60.5 (10.9)	0.776
Body mass index, kg m^{-2}	24.5 (3.2)	23.4 (3.1)	24.0 (3.5)	0.159
Systolic blood pressure, mm Hg	127.8 (17.0)	125.9 (15.5)	128.0 (15.5)	0.447
Diastolic blood pressure, mm Hg	75.3 (8.8)	75.1 (9.7)	77.2 (10.6)	0.169

Table 2 Difference in systolic and diastolic blood pressure (mm Hg) and odds ratio in hypertension , by angiotensin-converting enzyme insertion/deletion polymorphisms, the Funagata Study, Japan, 2000–02

	N	*Mean blood pressure (mm Hg)*	*Crude difference (95%CI) (mm Hg)*	*Age–gender-adjusted (95%CI) (mm Hg)*	*Multivariable adjusted (95%CI) (mm Hg)*[a]
Systolic blood pressure					
D)I/I polymorphism	164	128.0 ± 15.5	(reference)	(reference)	(reference)
I/D or D/D	204	126.2 ± 15.8	−2.67 (−6.27, 0.93)	−2.32 (−5.70, 1.07)	−1.76 (−5.00, 1.48)
R)I/D or I/I polymorphism	334	126.9 ± 15.5	(reference)	(reference)	(reference)
D/D	34	127.8 ± 17.0	2.06 (−4.09, 8.21)	3.06 (−2.73, 8.85)	2.16 (−3.46, 7.79)
Diastolic blood pressure					
D)I/I polymorphism	164	77.2 ± 10.6	(reference)	(reference)	(reference)
I/D or D/D	204	75.2 ± 9.6	−2.98 (−5.36, −0.59)*	−2.88 (−5.24, −0.51)*	−2.50 (−4.78, −0.23)*
R)I/D or I/I polymorphism	334	76.1 ± 10.2	(reference)	(reference)	(reference)
D/D	34	75.3 ± 8.8	−0.06 (−4.17, 4.04)	0.16 (−3.93, 4.24)	−0.45 (−4.43, 3.53)
	N	*Prevalence (%)*	*Crude (95%CI)*	*Age–gender-adjusted (95% CI)*	*Multivariable adjusted (95% CI)*[a]
Hypertension					
A)I/I polymorphism	164	64 (39.0)	(reference)	(reference)	(reference)
I/D	170	70 (41.2)	1.09 (0.71, 1.70)	1.07 (0.48, 2.42)	0.91 (0.37, 2.58)
D/D	34	13 (38.2)	0.97 (0.45, 2.07)	1.12 (0.70, 1.79)	0.98 (0.52, 1.60)
D)I/I polymorphism	164	64 (39.0)	(reference)	(reference)	(reference)
I/D or D/D	204	83 (40.7)	1.07 (0.70, 1.63)	1.11 (0.71, 1.74)	0.92 (0.54, 1.58)
R)I/D or I/I polymorphism	334	134 (40.1)	(reference)	(reference)	(reference)
D/D	34	13 (38.2)	0.92 (0.45, 1.91)	1.01 (0.46, 2.20)	1.03 (0.41, 2.59)

Abbreviations: D, deletion polymorphism; I, insertion polymorphism.
[a]Adjusted for age, gender, systolic blood pressure, body mass index and smoking status.
*$P<0.05$.

−0.14 μm). However, the interaction between D/D polymorphism and hypertension was not significantly associated with CRAE after adjusting for CRVE (−8.71 μm, 95% CI; −20.76 μm, 3.34 μm).

Association of retinal arteriolar wall signs/retinopathy and ACE I/D polymorphism

There was no significant association between focal retinal arteriolar wall signs (focal arteriolar narrowing, arterio-venous nicking and enhanced arteriolar wall reflex) or retinopathy and the *ACE* I/D polymorphisms (data not shown).

Discussion

In this population-based study of adult Japanese, we reported associations between the *ACE* I/D polymorphism and retinal arteriolar narrowing, a subclinical structural microvascular sign associated with chronic hypertension. We found that retinal arteriolar diameter was smaller in subjects with D/D than those with the I allele after adjusting for systolic blood pressure and other cardiovascular risk factors. We also found that diastolic blood pressure was significantly lower in subjects with D allele polymorphism compared with I/I polymorphism, but there was no difference in systolic blood pressure and no association for the presence of hypertension by the *ACE* I/D polymorphism.

Retinal arteriolar narrowing is a structural microvascular sign associated with chronic hypertension;[1] it has been shown to predict the incidence of stroke[2] and coronary heart disease.[3] On the other hand, other studies suggested that retinal arteriolar narrowing might be antecedent of the hypertension, and involved in the pathogenesis of hypertension itself. If retinal arteriolar narrowing is associated with genetic disposition, such as *ACE* I/D polymorphism, which we have examined assessing the retinal vessel diameters will enable us to stratify those who are vulnerable to developing hypertension or further cardiovascular diseases. The Beaver Dam Eye Study showed that genetic factors affected retinal vessel diameters in a genome-wide linkage analysis.[4] Within or near the linkage regions with retinal vessel diameter, there were genes associated with endothelial function, vasculogenesis, hypertension and coronary heart disease.[4] However, to date, exact genes associated with retinal vessel diameter have not been identified.

The RAS and endothelial cells are intimately involved in atherosclerosis.[5] It is known that local RAS exists in the eye,[10] and retinal vascular endothelial cells can express angiotensin type 1 receptors.[21] Previous experimental reports in studies of streptozocin-induced diabetic rats revealed that RAS inhibition ameliorates endothelial dysfunction.[22] Retinal vessel diameter has also been linked with endothelial dysfunction, with studies showing association of retinal arteriolar narrowing with von Willebrand factor and factor VIII, which are systemic markers of endothelial dysfunction.[23] Therefore, our findings that D/D polymorphism is associated with narrower retinal arteriolar diameters

Table 3 Difference in central retinal artery and vein equivalent (μm), by angiotensin converting enzyme insertion/deletion polymorphisms, the Funagata study, Japan, 2000–02

	N	*Mean vessel diameter (s.d.) (μm)*	*Crude difference (95% CI) (μm)*[a]	*Age–gender-adjusted (95% CI) (μm)*	*Multivariate adjusted*[b] *(95% CI) (μm)*
Central retinal artery equivalent					
(A) I/I polymorphism	164	179.50 (20.39)	(reference)	(reference)	(reference)
I/D	170	179.46 (20.54)	−0.33 (−3.92, 3.26)	−0.43 (−3.98, 3.13)	−0.32 (−4.15, 3.51)
D/D	34	173.77 (19.73)	−6.69 (−12.88, −0.51)*	−6.60 (−12.78, −0.42)*	−6.86 (−13.58, −0.13)*
(D) I/I polymorphism	164	179.50 (20.39)	(reference)	(reference)	(reference)
I/D or D/D	204	178.51 (20.47)	−1.39 (−4.84, 2.06)	−1.50 (−4.90, 1.91)	−1.51 (−5.21, 2.19)
(R) I/I or I/D polymorphisms	334	179.48 (20.44)	(reference)	(reference)	(reference)
D/D	34	173.77 (19.73)	−6.56 (−12.45, −0.67)*	−6.61 (−12.43, −0.79)*	−6.49 (−12.86, −0.11)*
Central retinal vein equivalent					
(A) I/I polymorphism	164	215.61 (21.52)	(reference)	(reference)	(reference)
I/D	170	216.12 (20.37)	0.54 (−3.14, 4.21)	0.60 (−3.05, 4.26)	−0.07 (−3.87, 3.73)
D/D	34	217.37 (20.07)	5.22 (−1.31, 11.74)	4.75 (−1.78, 11.28)	3.93 (−3.01, 10.88)
(D) I/I polymorphism	164	215.61 (21.52)	(reference)	(reference)	(reference)
I/D or D/D	204	216.33 (20.28)	1.30 (−2.22, 4.82)	1.31 (−2.19, 4.81)	0.69 (−2.78, 4.35)
(R) I/I or I/D polymorphisms	334	215.87 (20.92)	(reference)	(reference)	(reference)
D/D	34	217.37 (20.07)	4.88 (−1.16, 10.92)	4.55 (−1.48, 10.58)	3.84 (−2.51, 10.20)

Abbreviations: D, deletion polymorphism; I, insertion polymorphism.
Estimated β coefficient, using multiple linear regression models, represents a mean difference in retinal arteriolar diameter and venular diameter by each unit change in genotype or allele, in additive (A), dominant (D) and recessive (R) models.
[a]Adjusted for central retinal vein equivalent in models of central retinal artery equivalent, and for central retinal artery equivalent in models of central retinal vein equivalent, respectively.
[b]Adjusted for age, gender, systolic blood pressure, body mass index and smoking status.
*$P<0.05$.

might be explained by the activation of RAS in retinal vasculature.

Our study shows both *ACE* I/D polymorphism and hypertension-influenced retinal arteriolar diameters. However, we could not confirm whether an interaction between the D/D polymorphism and the presence of hypertension affecting retinal arteriolar diameters exists. Because there were only 13 subjects (38.2%) with D/D polymorphism who have hypertension in this study, a statistical power may be weak to prove this association.

In this older Japanese population, presence of the I allele is associated with essential hypertension.[24] In contrast, the D allele of the *ACE* I/D polymorphism has been associated with atherosclerosis.[7] Retinal arteriolar narrowing, which reflects intimal thickening, medial hyperplasia and hyalinization and sclerosis of retinal arterioles has also been associated with atherosclerosis.[25] Our findings that the *ACE* I/D polymorphism is linked to retinal arteriolar narrowing may also be explained by its association with atherosclerotic processes.

Limitations and potential biases of this study should be mentioned. First, only 20.2% of total eligible subjects were included in this genetic analysis. Low participant rate of genetic analysis may affect the statistical power to prove associations. Furthermore, only 49.5% of this subsample had fundus photographs with sufficient quality for computer-assisted measurement of retinal vessels. Thus, unknown selection biases could have altered these results. Second, we did not have a detailed history of medications, including use of antihypertensive agents. Current use of ACE inhibitors to lower blood pressure could have influenced our findings of an association between the *ACE* I/D polymorphism and retinal vessel caliber. Also, we were not able to measure plasma ACE levels in this study.

In conclusion, we found that subjects with D/D of the *ACE* I/D polymorphism had significant retinal arteriolar narrowing, a subclinical structural marker of chronic hypertension in this adult Japanese population. This association was stronger in subjects with a known history of hypertension. Our finding suggests that the *ACE* I/D polymorphism may influence the microvasculature, thereby possibly contributing to genetic susceptibility for the development of hypertension. Definitely, further research is needed to confirm this finding in other population-based samples.

What is known about this topic

- Retinal arteriolar narrowing is a structural sign associated with chronic hypertension.[1]
- A substantial proportion of the variation in retinal arteriolar diameter might be genetically determined, independent of concomitant risk factors.[4]
- *ACE* I/D polymorphism is associated with hypertension[5] and atherosclerosis, such as carotid wall thickness[6] and coronary heart disease.[7]

What this study adds

- Subjects with D/D of the *ACE* I/D polymorphism had significantly narrower retinal arteriolar caliber in this adult Japanese population.
- *ACE* I/D polymorphism may influence the peripheral microcirculation, thereby possibly contributing to genetic susceptibility for the development of hypertension.

Conflict of interest

The authors declare no conflict of interest

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分担研究報告書

腹部内臓脂肪蓄積が5年後の糖尿病発症に与える影響に関する研究

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研究要旨

職場の人間ドックにおいて、2008年の糖尿病治療者を除く3513人では、JDS診断基準で糖尿病と診断される被験者を予測する場合HbA1cのcut off 値 は5.6%（感度85.4%、特異度89.7%）であった。2003年から5年以内に新規に糖尿病を発症した男性受診者の糖代謝パラメータの特徴について調べたところ、糖尿病発症前の平均値は、BMI 24.7 kg/m^2、HbA1c 5.62%、1日目FPG 119.0 mg/dl、1hPG 222.9mg/dl、2hPG 166.9mg/dlであった。職場健診でHbA1cが5.6%程度の場合、5年後に糖尿病を発症する可能性があると思われる。また、2003年に糖尿病未発症でありかつ腹部CTによる内臓脂肪面積（CT-VFA）を測定できた人間ドック男性受診者126名を<A群>CT-VFA100 cm^{2}未満と<B群>CT-VFA100 cm^{2}以上の2群分けて、5年後の糖代謝パラメータの変化について検討した。5年後に糖尿病を発症したのは<A群>で1名、<B群>で4名であった。腹部CTで測定した内臓脂肪面積が100 cm^{2}以上の受診者では糖尿病をより発症しやすい可能性がある。

A．研究目的

2003年から5年間経過を追うことができた人間ドック男性受診者のうち、新規に糖尿病を発症した受診者の糖代謝パラメータの特徴について検討した。また、腹部内臓脂肪蓄積が糖代謝異常に与える影響を検討するために、2003年に糖尿病未発症でありかつ腹部CTによる内臓脂肪面積（CT-VFA）を測定できた職場の人間ドック男性受診者の5年後の糖代謝異常の特徴について検討した。

B．研究方法

近畿地方の通信会社の職員とその家族を対象とした人間ドックの男性受診者において、1日目に午前9時に空腹時血糖（FPG）を測定し、任意で2日目午前9時より75gOGTTを施行した。JDSによる糖尿病診断基準に基づき(a)1日目FPG≧126mg/dlかつ2日目FPG≧126mg/dl、(b)1日目FPG≧126mg/dlかつ2hPG≧200mg/dlのいずれかを満たす場合を糖尿病と診断した。

【方法1】対象は2008年の男性受診者6636名から糖尿病治療中の受診者を除き、75gOGTTを施行できた3513人（50.6±7.3歳）。HbA1cにより糖尿病と診断する場合のHbA1cのcutoff値について感度と特異度から検討した。

【方法2】2003年１月～12月の人間ドックの男性受診者6110名のうち、2003年に糖尿病未発症かつ未治療で5年後にも経過を追うことができた1048名（平均年齢歳、BMI g/m^2）について、5年以内の新規糖尿病発症者の特徴を調べた。

【方法3】2003年の人間ドック男性受診者で75gOGTTを施行した3020名のうち糖尿病未発症かつCT-VFAを測定できた男性126名（平均年齢 48.8歳、BMI 24.4kg/m^2）について、<A群>内臓脂肪面積が100cm^{2}未満の66名（平均BMI 23.2 kg/m^2、平均CT－VFA 70.8cm^2）と<B群>100cm^{2}以上の60名（平均BMI 25.6 kg/m^2、平均CT-VFA 135.7cm^2）の2群に分け、5年後の糖代謝パラメータの変化と新規糖尿病発症者の有無について検討した。

（倫理面への配慮）
書面で同意を得た被験者のみで測定を行ない、匿名化したうえで、解析した。

C．研究結果
【方法1】2008年の糖尿病治療者を除く3513人では、JDS診断基準で糖尿病と診断される被験者を予測する場合HbA1cのcut off 値は5.6%（感度85.4%、特異度89.7%）であった。HbA1cのcutoff値が5.6%のとき、PPV（陽性的中率）は16.6%、1-NPV（疾患あるがHbA1c検査で陰性になる率）は0.39%であった。
【方法2】5年以内に新規に糖尿病を発症したと確認できたのは、34名（ 未治療16名、治療中18名）であり、発症前(2003年)の平均値は、BMI 24.7±3.4 kg/m^2 、HbA1c 5.62±0.35%、FPG 119.0±9.2mg/dl、1hPG 222.9±36.3mg/dl、2hPG 166.9±41.1mg/dl であった。
【方法3】5年以内の新規糖尿病発症者は<A群>では1名、<B群>では4名であった。5年間で両群ともに平均BMIは変化がなかったが、<A群>では、HbA1c(5.05→5.17%)・FPG(100.6→104.8mg/dl)・1hPG(141.5→150.4mg/dl)が有意に増加し、<B群>ではHbA1c(5.25→5.41%)・FPG(108.6→111.3mg/dl)・2hPG(128.6→138.8mg/dl)が有意に増加した。

D．考察
糖尿病の見逃しを減らしながら、特異度を下げない、要精査する基準としてDM診断基準値よりも低い5.6%を健診では採用しても良いかもしれない。

E．結論
2003年から5年以内の新規糖尿病発症者の発症前の平均値は、BMI 24.7 kg/m^2、HbA1c5.62%、1日目FPG 119.0 mg/dl、1hPG 222.9mg/dl、2hPG 166.9mg/dlであった。職場健診でHbA1c5.6%程度の場合、5年以内に糖尿病を発症する可能性があると思われる。腹部CTでの内臓脂肪面積が100cm^{2}以上の受診者の方が、100 cm^{2}未満の受診者に比べて、将来、糖尿病を発症しやすい可能性が考えられた。

G．研究発表
1． 論文発表
投稿準備中
2． 学会発表
井田みどり、他.日本内分泌学会雑誌 86巻1号Page163(2010.3)

H．知的財産権の出願・登録状況
なし

研究成果の刊行に関する一覧表

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
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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）
分担研究抄録

総アディポネクチン・高分子量アディポネクチン濃度と関連する要因に関する検討

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研究要旨：総・高分子量アディポネクチン(T.ADIP, HMW）を測定した3,373例について内臓脂肪面積、血清脂質、血糖値、IRI、総・高アディポネクチン値、血圧値等との関連を検討した。T.ADIP・HMWともにMetabolic syndromeの病態を表現していると解釈され、低下群では糖尿病発症率が高いことが明らかになった。アディポネクチン低下群への積極的な介入は増加する生活習慣病対策として有意義と思われる。

A. 研究目的

わが国における生活習慣病の増加は著しく、Metabolic syndromeの病態はじめとするこれら疾病の予備軍に如何にして早期に生活習慣の是正を行うかが極めて重要である。

今回は内臓脂肪面積と関連する血中の総および高分子量アディポネクチンを測定し、これら疾病の予測の可能性を検討した。

B. 研究方法

対象は2005年10月～2010年2月に当所で人間ドック健診を受診した者のうち血中の総アディポネクチン（T.ADIP）および高分子量アディポネクチン（HMW）を測定した3,373例（男性 1,856例、女性 1,517例）である。このうち経過観察例は747例であった。対象の平均年齢は男性46.0±9.5、女性45.0±9.2歳であった。早朝空腹時の血清脂質、血糖値、IRI、総・高アディポネクチン値、血圧値等を測定した。腹囲径は3か所で測定し低線量CTで内臓脂肪面積を測定した。経過観察例についてはT.ADIP濃度別に糖尿病発症率を比較した。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

1) 総アディポネクチン濃度とMetabolic syndromeの要因との関連

T.ADIP濃度とMetabolic syndromeの要因との単相関をみると、男性では内臓脂肪面積（VFA）とは$r=0.281(p<0.0001)$、F-IRI（対数変換）$r=0.322(p<0.0001)$、TG（対数変換）$r=0.338(p<0.0001)$、また、HMWとの関連はそれぞれ $r=0.237(p<0.0001)$、F-IRI $r=0.286(p<0.0001)$、TG $r=0.285$ $(p<0.0001)$、と何れも有意な関連がみられた。女性についてみるとT.ADIP濃度とはVFA $r=0.304(p<0.0001)$、F-IRI $r=0.317(p<0.0001)$、TG $r=0.313(p<0.0001)$、また、HMWとの関連はそれぞれ $r=0.288$ $(p<0.0001)$、$r=0.297(p<0.0001)$、$r=0.293(p<0.0001)$で何れも有意な相関であった。また、T.ADIPおよびHMWを対数変換して相関を求めたが結果は同様であった。

2) 空腹時血糖値（FPG）に関連する要因の分析

VFA、F-IRI、T.ADIP、BMI、血圧、TGについて重回帰分析でFPGと関連する要因を分析した。それぞれの要因は以下のカテゴリーに区分して分析した。VFAは$<100cm^2$、100～149、≧150に3区分、F-IRIは$<8\mu u/ml$と≧8、T.ADIPは4分位、BMIは$<25kg/m^2$と≧25、血圧値 収縮期<130で拡張期<85 mm Hg、159～130または94～85、≧160または≧95、に3区分した。TGは<150mg/dl、150～199、≧200に区分して重回帰分析を行った。男性では回帰係数はVFA 6.390 $(p<0.0001)$、F-IRI 4.638 $(p<0.0001)$、T.ADIP 0.764 $(p=0.0636)$、BMI -0.770 $(p=0.4940)$、血圧 1.532$(p=0.0410)$、TG 1.538 $(p=0.0147)$であった。女性ではVFA 7.953$(p<0.0001)$、F-IRI 5.619 $(p<0.0001)$、T.ADIP 0.589 $(p=0.0371)$、BMI 3.037 $(p=0.0055)$、血圧 2873$(p<0.0001)$、TG 2.807$(p=0.0020)$であり、男女ともVFAの増加、血圧上昇、TG上昇、F-IRIの上昇と大きく関連していた。T.ADIPは男性ではFPGの上昇で低下傾向を示し、女性では有意に低

下した。

3) Metabolic syndrome の有無別にみたアディポネクチン濃度

VFA が≧100cm^2 で TG、血圧、FPG の 3 項目のうち 1 項目のみの群、2 項目以上の群と VFA<100 で risk もない群について T.ADIP および HMW を比較した。男性についてみると risk が 1 個の場合の T.ADIP の Mean±S.D. は 4.094±2.002 ng/ml (n=1181)、HMW は 1.392±1.290 ng/ml (n=1181)、2 個以上の場合は 3.690±1.739 ng/ml (n=280)、HMW は 1.191±1.005 ng/ml (n=280)、VFA<100 cm^2 で risk (-) の場合は 5.015±2.171 ng/ml (n=637)、HMW は 1.861±1.446 ng/ml (n=636)であった。女性についてみると risk が 1 個の場合の T.ADIP の Mean±S.D.は 6.736±3.543 (n=377)、HMW は 3.173±2.552 ng/ml (n=377)、2 個以上の場合は 5.364±2.292 ng/ml (n=28)、HMW は 2.289±1.755 ng/ml (n=28)、VFA<100 cm^2 で risk (-) の場合は 7.637±3.111 ng/ml (n=1129)、HMW は 3.805±2.334 ng/ml (n=1129)であった。この様に男女とも risk もなく VFA<100 cm^2 の群に比して VFA≧100 cm^2 で risk が 1 個のもの、2 個以上のものの順に有意に T.ADIP および HMW ともに有意に低下した。また、女性では何れも男性に比して高値を示した。

4) 糖尿病発症率の比較

初診時に FPG≧126mg/dl または HbA1c≧6.1%であったものを除いて 747 例(男性 389 例、女性 358 例について経過観察 (平均 1.6 年) を行い糖尿病発症率を T.ADIP 別に比較した。なお、初診時の平均年齢は男性 44.0 歳、女性 44.1 歳であった。T.ADIP 濃度によって 2 分位、即ち、男性では T.ADIP<4.1ng/ml と≧4.1 群、女性は<7.0 と≧7.0 に区分した。糖尿病発症率は男性では低 T.ADIP 群からは 38.2/1000 人年で高 T.ADIP 群からは 14.4 と低率であった (p=0.0637)。女性では糖尿病発症例が 1 例と低率であったために T.ADIP<7.0 では 0%、≧7.0 では 3.6%であった。

C. 考察

アディポネクチン濃度と Metabolic syndrome の要因との関連をみると、内臓脂肪面積、インスリン抵抗性、高 TG 血症との関連が有意であり、Metabolic syndrome の病態の一部はアディポネクチン濃度で表現できると思われる。さすれば 1 回の採血で判定することが可能となり更に生活指導へと繋ぐことができる大きなメリットがある。しかもアディポネクチン濃度の測定は比較的安定しており精度的には問題ない。FPG が上昇する要因をみると、内臓脂肪面積の上昇、インスリン抵抗性、肥満、血圧上昇、高 TG 血症である。一方アディポネクチン濃度をみると女では FPG の上昇と共に有意に低下し、男性においてもその傾向がみられる。

また、Metabolic syndrome の risk factor 数別に T.ADIP と HMW の平均値をみると、男女とも Non-metabolic syndrome 群、risk が 1 個の群、risk が 2 個以上の群の順に低下していた。糖尿病発症率をみてもアディポネクチン濃度が低い群から高くなっていたが、対象の年齢が若いために全般的に低率であったので、follow-up 期間を延長して確定的な結論を得る必要がある。

E. 結論

アディポネクチン濃度は T.ADIP・HMW ともに従来から報告されている様に本データにおいても Metabolic syndrome の病態を表現していると解釈される。一方ではアディポネクチン濃度が低い群では糖尿病発症率が高いことが明らかになった。アディポネクチン濃度が低下している群への積極的な介入は増加する生活習慣病対策として有意義と思われる。今回は対象の年齢が若いために糖尿病発症率が低い若・中年層が対象であり、follow-up 期間を延ばすことにとって確定的な結論が得られると確信している。

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
伊藤千賀子	ﾒﾀﾎﾞﾘｯｸｼﾝﾄﾞﾛｰﾑ予備軍とその管理・治療	堀田饒・清野裕・門脇孝他	糖尿病 UP・DATE 25	時事通信社	東京	2009	28-35
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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」分担報告書

地域における睡眠呼吸障害とメタボリックシンドロームとの関連
CIRCS : Circulatory Risk in Communities Study

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研究要旨：地域における睡眠呼吸障害とメタボリックシンドロームとそのリスクファクターの集積との関連を調べるため、秋田、茨城、大阪3地域住民40～69歳の男性1,710人、女性2,896人を対象として、パルスオキシメトリ検査を実施し、睡眠呼吸障害の指標として酸素飽和度低下指数3%ODI（oxygen desaturation index)値を3群（5回未満/時間、5回以上15回未満/時間、15回以上/時間）に分け、睡眠呼吸障害の程度とメタボリックシンドロームとそのリスクファクターの集積との関連を分析した。本検討では、メタボリックシンドロームリスクファクターのカウントにおいて、ＢＭＩ≧25kg/m^2、高血糖については空腹時血糖≧110mg/dL、非空腹時血糖≧140mg/dL または服薬者、血圧高値は SBP≧130mmHg かつ DBP≧85mmHg または服薬者、トリグリセライド高値は空腹時・非空腹時ともにトリグリセライド≧150mg/dL、HDL-コレステロール低値についてはHDL-コレステロール値を男性で＜40mg/dl、女性で＜50mg/dl とした。その結果、睡眠呼吸障害がない群に比べ、男女とも睡眠呼吸障害がメタボリックシンドロームとの関連を認められ、この関連は非肥満群で肥満群に比べより明らかであった。

A．研究目的

我が国において平成17年にメタボリックシンドロームに関する診断基準が策定され、平成20年度よりメタボリックシンドロームの概念に着目した特定健診・特定保健指導が開始された。そのため、メタボリックシンドロームと循環器疾患に関する研究が進められているが、循環器疾患の発症との関連が欧米で報告されている。睡眠呼吸障害に関する研究がまた少ない。我々は地域住民を対象とした睡眠呼吸障害とメタボリックシンドロームとの関連を明らかにすることを目的とし、横断研究を行った。

B．研究対象と方法

対象集団は、CIRCS（Circulatory Risk in Communities Study；大阪大学と大阪府立成人病センター集団検診第Ｉ部〔現・大阪府立健康科学センター〕が主体となって実施している5地域コホートの疫学研究の総称）における、井川町（秋田県秋人口約6千人の平地農村)、協和地区（茨城県筑西市

人口約1.7万人の平地農村)、八尾市南高安地区（大阪府八尾市人口約2.3万人の都市近郊）の3地域の住民である。そのうち40-69歳男女住民で、2001年～2005年の住民循環器健診を受診してかつ睡眠検査を実施した男性1,710人（八尾で448人、井川で397人、協和で917人)、女性2,896人(それぞれに853人、571人と1,507人）を分析対象とした。脳卒中および虚血性心疾患の既往者は解析から除外した。

血清脂質の測定は、国内唯一のCRMLNの血清脂質標準化認定機関である脂質基準分析室を有する大阪府立健康科学センターにおいて、Liebermann-Burchard 直接法（LB直接法）で測定した。併せて、血清中の総コレステロール（LB 直接法)、トリグリセライド（蛍光法)、血糖（ネオカプロインCu法）の測定、および身長、体重、水銀血圧計を用いた聴診法による血圧の測定を行った。また、既往歴、飲酒習慣および喫煙習慣に関する問診を実施した。

パルスオキシメトリ検査は、自宅で睡眠中の睡眠呼吸障害の程度を調べるもので、末梢動脈血酸素飽和度を測定する検査である。睡眠呼吸障害の指標としてパルスオキシメトリ検査における酸素飽和度低下指数（3%ODI 値、末梢動脈血酸素飽和度曲線において直前値に比べ３％以上低下し元の数値に戻った１時間あたりの回数）を用いた。メタボリックシンドロームリスクファクターのカウントにおいて ECEP/ATP Ⅲ（Circulation 2002; 106: 3143-3421）を基準とした。Body mass index (BMI=体重〔kg〕/身長^2〔m^2〕) ≧25、高血糖については空腹時血糖≧110mg/dL、非空腹時血糖≧140mg/dL または服薬者、血圧高値は SBP≧130mmHg and/or DBP≧85mmHg または服薬者、トリグリセライド高値については空腹時・非空腹時ともにトリグリセライド≧150mg/dL、HDL-コレステロール低値は HDL-コレステロール値を男性で＜40mg/dl、女性で＜50mg/dl とした。

解析において、3%ODI 値を3群（5回未満/時間、5回以上15回未満/時間、15回以上/時間）に、メタボリックシンドロームとの関連を年齢、性、喫煙有無、飲酒量(グラム/日)、食後時間(2時間未満、2時間以上3時間未満、3時間以上8時間未満、8 時間以上)、女性の閉経有無を共変量として分析した。統計解析には、SAS ver.9.1.3 (SAS Institute Inc.)を用いた。

C．研究結果

（１）年齢調整した睡眠呼吸障害の頻度が3地域の間に差はなかった。男女ともに3%ODIの増加に伴い、年齢、BMI、SBP、DBP、血糖値、トリグリセライドの平均値や降圧剤の服薬者頻度の増加とHDL－コレステロール値の低下を認めた。男性では現在飲酒・喫煙が3%ODIと正の相関を示した。

（2）非睡眠呼吸障害群（3%ODI＜5）に比べ、年齢や多変量調整した肥満、血圧高値、HDL－コレステロール低値とトリグリセライドの高値とメタボリックシンドロームと有意な関連を示した。多変量調整したオッズ比はそれぞれに、

（3）非睡眠呼吸障害群（3%ODI＜5）に比べ、睡眠呼吸障害群（3%ODI≧15）のメタボリックシンドロームのリスクファクターの2個以上集積のオッズ比が非肥満群では1.9（1.2-3.1）であり、肥満群では1.4（0.9-2.1）であった（交互作用のp値は0.002）（表２）。

D．考察

本研究により、男女ともに睡眠呼吸障害