Table 1
Baseline characteristics by sex and serum 1,5-anhydro-D-glucitol levels, the Suita study, Japan, 1994–2007.

	Men			
	1,5-Anhydro-D-glucitol (μg/mL)			p
	≥24.5	14.1–24.4	≤14.0	
Number of subjects	423	416	152	
Age (years)	58 (12)	61 (12)	63 (11)	<0.001
Body mass index (kg/m^2)	22.7 (2.7)	22.8 (2.9)	23.1 (2.9)	0.24
HDL cholesterol (mmol/L)	1.4 (0.3)	1.4 (0.4)	1.4 (0.4)	0.48
1,5-Anhydro-D-glucitol (μg/mL)	31.3 (5.6)	19.7 (3.0)	8.8 (3.6)	<0.001
Estimated GFR (mL/min/1.73 m^2)	80.2 (15.6)	78.1 (16.0)	79.0 (18.1)	0.19
Hypertension (%)[a]	32	37	45	0.01
Hypercholesterolemia (%)[b]	23	23	21	0.85
Diabetes (%)[c]	0	3	30	<0.001
Current cigarette smoking (%)	44	39	41	0.36
Alcohol drinking (non/light to moderate/heavy) (%)	29/53/18	29/55/16	35/47/18	0.55
Hypertension medication (%)	13	15	20	0.09
Hypercholesterolemia medication (%)	4	4	5	0.81
Diabetes medication (%)	0	0	20	<0.001
	Women			
	1,5-Anhydro-D-glucitol (μg/mL)			p
	≥21.3	14.1–21.2	≤14.0	
Number of subjects	442	438	224	
Age (years)	59 (12)	55 (12)	58 (12)	<0.001
Body mass index (kg/m^2)	22.2 (3.2)	21.9 (2.7)	22.3 (3.2)	0.12
HDL cholesterol (mmol/L)	1.6 (0.4)	1.6 (0.3)	1.6 (0.3)	0.001
1,5-Anhydro-D-glucitol (μg/mL)	26.7 (4.1)	18.0 (2.0)	10.5 (3.2)	<0.001
Estimated GFR (mL/min/1.73 m^2)	80.2 (19.7)	81.2 (16.8)	81.1 (15.2)	0.71
Hypertension (%)[a]	33	26	31	0.06
Hypercholesterolemia (%)[b]	39	37	38	0.80
Diabetes (%)[c]	1	1	12	<0.001
Current cigarette smoking (%)	11	8	8	0.42
Current alcohol drinking (non/light to moderate/heavy) (%)	75/25/0	72/27/1	72/28/0	0.31
Menopause (%)	76	63	71	<0.001
Hypertension medication (%)	14	12	17	0.17
Hypercholesterolemia medication (%)	7	7	5	0.46
Diabetes medication (%)	0	0	4	<0.001

Mean (standard deviations), or percentage is shown. GFR means glomerular filtration rate.
[a] Hypertension is defined by systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg or the use of antihypertensive medication.
[b] Hypercholesterolemia is defined by total cholesterol ≥5.7 mmol/L (220 mg/dL) or the use of antihypercholesterolemic medication.
[c] Diabetes is defined by fasting plasma glucose ≥7.0 mmol/L (126 mg/dL) in those with fasting time of 8 h or more, postprandial plasma glucose ≥11.1 mmol/L (200 mg/dL) in those with fasting time of less than 8 h, or the use of antidiabetic medication.

tribution (minimum, 25th percentile, median, 75th percentile, maximum) of serum 1,5-AG by sex was 1.2, 17.0, 23.1, 28.9, and 55.3 μg/mL, respectively in men, and 1.7, 15.2, 19.8, 24.8, and 41.5 μg/mL, respectively in women (data not shown). The prevalence of diabetes and medication for diabetes at baseline was highest in the category with the lowest serum 1,5-AG (≤14.0 μg/mL) in both sexes, and was much higher in men (Table 1). Age and prevalence of hypertension increased as serum 1,5-AG decreased in men only.

During the follow-up period (11.1 years average), 147 CVD events (64 CHD and 83 strokes) were observed. The CHD included 14 percutaneous coronary angioplasty, 5 coronary artery bypass grafting, 1 sudden death, 41 myocardial infarctions and 3 unclassified CHD. The strokes included 53 ischemic strokes, 14 hemorrhagic strokes and 16 unclassified strokes. The incidence rates of all CVD and each CVD subtype increased as 1,5-AG levels decreased in men, and the incidence rate of all CVD was 15.1 per 1000 person-years in the lowest 1,5-AG category (Table 2). In model 2, there was a statistically significant linear increase in the adjusted HRs of all CVD in men ($p = 0.004$), and the adjusted HR was 2.22 (95% CI 1.24–3.98) in the lowest 1,5-AG category. In model 3, the adjusted HR of all CVD in the lowest 1,5-AG category was less than model 2. However, the adjusted HR of the middle category (14.1–24.4 μg/mL) was not very different and the elevation of risk was still significant, 1.74 (95% CI 1.07–2.84). In men, similar results were observed for each CVD subtype, although the HRs of CHD were much lower than of all strokes and were not statistically significant. In women, similar results were not observed, although, for CHD, similar trends were observed (Table 3). In the combined analysis of women and men for CHD, the HRs in model 2 increased linearly with decrease in serum 1,5-AG levels ($p = 0.03$), and the adjusted HR in the lowest 1,5-AG category was 2.10 (95% CI 1.10–4.02) (Table 4).

A sensitivity analysis for non-diabetic men with FPG or PPG less than 6.1 mmol/L (110 mg/dL) showed that the adjusted HRs for all CVD in model 2 increased as 1,5-AG levels decreased ($p = 0.03$), and the adjusted HR was 2.00 (95% CI 0.88–4.55) in the lowest 1,5-AG category (Table 5). Similar results were observed with all strokes and ischemic strokes, but such a relationship was not clear in CHD.

In the sensitivity analyses, altering the definition of postprandial, entering waist circumferences or adding triglycerides levels to the models hardly alter the results. In addition, waist circumferences or triglycerides levels were not related with the risk for CVD or each CVD subtype.

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Table 2
Incidence rates and adjusted hazard ratios for cardiovascular diseases by serum 1,5-anhydro-D-glucitol levels in men, the Suita study, Japan, 1994–2007.

	1,5-Anhydro-D-glucitol (μg/mL)			*p* for trend
	≥24.5	14.1–24.4	≤14.0	
Person-years	4727	4322	1455	
All cardiovascular diseases				
Cases, *n*	26	49	22	
Incidence rates/1000 person-years	5.5	11.3	15.1	
Model 1[a]	1	1.76 (1.09–2.86)	2.29 (1.29–4.07)	0.003
Model 2[a]	1	1.79 (1.10–2.91)	2.22 (1.24–3.98)	0.004
Model 3[a]	1	1.74 (1.07–2.84)	1.72 (0.89–3.34)	0.049
Coronary heart disease				
Cases, *n*	16	19	10	
Incidence rates/1000 person-years	3.4	4.4	6.9	
Model 1[a]	1	1.21 (0.61–2.38)	1.81 (0.81–4.05)	0.17
Model 2[a]	1	1.14 (0.57–2.25)	1.59 (0.70–3.59)	0.29
Model 3[a]	1	1.13 (0.57–2.24)	1.47 (0.59–3.68)	0.44
All strokes				
Cases, *n*	10	30	12	
Incidence rates/1000 person-years	2.1	6.9	8.2	
Model 1[a]	1	2.56 (1.25–5.25)	3.02 (1.31–7.01)	0.006
Model 2[a]	1	2.64 (1.28–5.45)	3.32 (1.41–7.79)	0.003
Model 3[a]	1	2.53 (1.23–5.23)	2.29 (0.87–6.01)	0.04
Ischemic strokes				
Cases, *n*	8	20	9	
Incidence rates/1000 person-years	1.7	4.6	6.2	
Model 1[a]	1	2.16 (0.95–4.92)	2.84 (1.09–7.37)	0.02
Model 2[a]	1	2.15 (0.94–4.93)	2.86 (1.09–7.49)	0.03
Model 3[a]	1	2.10 (0.92–4.82)	2.28 (0.78–6.67)	0.09

Parentheses indicate 95% confidence intervals.
[a] Model 1: adjusted for age, model 2: adjusted for model 1 plus body mass index, hypertension, hypercholesterolemia, HDL cholesterol, estimated glomerular filtration rate, current cigarette smoking, current alcohol drinking, model 3: adjusted for model 2 plus diabetes.

4. Discussion

This is the first report of a prospective cohort study showing that serum 1,5-AG levels predict CVD incidence in men, similar to HbA_{1c} [15–17] or postload glucose levels in OGTT [4,5]. More subjects with overt diabetes were included in the category with serum 1,5-AG levels of 14.0 μg/mL or less, which would lead to the greatest risk. Those with serum 1,5-AG levels of 14.1 to 24.4 μg/mL, whose preva-

Table 3
Incidence rates and adjusted hazard ratios for cardiovascular diseases by serum 1,5-anhydro-D-glucitol levels in women, the Suita study, Japan, 1994–2007.

	1,5-Anhydro-D-glucitol (μg/mL)			*p* for trend
	≥21.3	14.1–21.2	≤14.0	
Person-years	5077	5293	2424	
All cardiovascular diseases				
Cases, *n*	22	15	13	
Incidence rates/1000 person-years	4.3	2.8	5.4	
Model 1[a]	1	0.83 (0.43–1.60)	1.23 (0.62–2.44)	0.68
Model 2[a]	1	0.92 (0.47–1.79)	1.30 (0.65–2.60)	0.54
Model 3[a]	1	0.91 (0.47–1.77)	1.04 (0.48–2.22)	0.99
Coronary heart disease				
Cases, *n*	7	5	7	
Incidence rates/1000 person-years	1.4	0.9	2.9	
Model 1[a]	1	0.82 (0.26–2.60)	2.09 (0.73–5.96)	0.21
Model 2[a]	1	0.89 (0.28–2.83)	2.33 (0.81–6.71)	0.15
Model 3[a]	1	0.87 (0.27–2.76)	1.74 (0.54–5.56)	0.42
All strokes				
Cases, *n*	15	10	6	
Incidence rates/1000 person-years	3.0	1.9	2.5	
Model 1[a]	1	0.83 (0.37–1.86)	0.83 (0.32–2.14)	0.65
Model 2[a]	1	0.93 (0.41–2.09)	0.88 (0.34–2.27)	0.77
Model 3[a]	1	0.92 (0.41–2.08)	0.75 (0.26–2.12)	0.59
Ischemic strokes				
Cases, *n*	6	7	3	
Incidence rates/1000 person-years	1.2	1.3	1.2	
Model 1[a]	1	1.48 (0.50–4.41)	1.03 (0.26–4.12)	0.84
Model 2[a]	1	2.01 (0.66–6.11)	1.20 (0.29–4.89)	0.60
Model 3[a]	1	1.99 (0.66–6.06)	1.01 (0.22–4.71)	0.71

Parentheses indicate 95% confidence intervals.
[a] Model 1: adjusted for age, model 2: adjusted for model 1 plus body mass index, hypertension, hypercholesterolemia, HDL-cholesterol, estimated glomerular filtration rate, current cigarette smoking, current alcohol drinking, menopause, model 3: adjusted for model 2 plus diabetes.

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Table 4
Incidence rates and adjusted hazard ratios for coronary heart disease and ischemic strokes by serum 1,5-anhydro-D-glucitol levels in men and women, the Suita study, Japan, 1994–2007.

	1,5-Anhydro-D-glucitol (μg/mL)			*p* for trend
	≥23.1	14.1–23.0	≤14.0	
Number of subjects	854	865	376	
Person-years	9606	9814	3878	
Coronary heart diseases				
Cases, *n*	22	25	17	
Incidence rates/1000 person-years	2.3	2.5	4.4	
Model 1[a]	1	1.36 (0.76–2.44)	2.17 (1.14–4.13)	0.02
Model 2[a]	1	1.41 (0.78–2.52)	2.10 (1.10–4.02)	0.03
Model 3[a]	1	1.37 (0.76–2.46)	1.76 (0.85–3.63)	0.12
Ischemic strokes				
Cases, *n*	19	22	12	
Incidence rates/1000 person-years	2.0	2.2	3.1	
Model 1[a]	1	1.25 (0.67–2.31)	1.58 (0.76–3.27)	0.22
Model 2[a]	1	1.24 (0.67–2.31)	1.56 (0.75–3.24)	0.23
Model 3[a]	1	1.21 (0.65–2.25)	1.23 (0.54–2.82)	0.56

Parentheses indicate 95% confidence intervals.
[a] Model 1: adjusted for age, sex, model 2: adjusted for model 1 plus body mass index, hypertension, hypercholesterolemia, HDL cholesterol, estimated glomerular filtration rate, current cigarette smoking, and current alcohol drinking.

lence of diabetes or anti-diabetic medication was clearly lower than those with 14.0 μg/mL or less, also had significantly elevated risks. This suggested the possibility that many subjects without overt diabetes who had postprandial hyperglycemia with excretion of glucose in the urine were included in this middle category. Measurement of serum 1,5-AG levels can be useful to detect individuals at greater risk for CVD even among those without overt diabetes. In fact, the sensitivity analyses in non-diabetic subjects with almost normal plasma glucose levels also showed similar results, which reinforced these findings.

In men, the relationship between serum 1,5-AG levels and stroke was much clearer than that with CHD. The prevalence of hypertension increased with decrease in serum 1,5-AG levels, but the prevalence of hypercholesterolemia did not change, irrespective of serum 1,5-AG levels. Such discrepancies in the relationships between serum 1,5-AG levels and risk factors for CVD may account for the difference observed between risk of stroke and that of CHD.

In women, no significant relationship was observed between serum 1,5-AG levels and the risk for all CVD or each CVD subtype, although a similar increase in the risk for CHD was found. Previous meta-analyses have shown either that women with diabetes have a higher risk for CHD than men with diabetes [18,19], or that there was no sex difference [20]. The DECODE study also showed that the HR of death from CVD in individuals with 2-h glucose levels of 11.1 mmol/L or greater tended to be higher among women than among men [5]. The present results show an opposite sex difference, and the reason is not clear. However, the prevalence of diabetes at baseline was much lower in women than in men, and the incidence rate of all CVD and each CVD subtype was also relatively lower in women. Such discrepancies in basic characteristics

Table 5
Sensitivity analyses of incidence rates and adjusted hazard ratios for cardiovascular diseases by serum 1,5-anhydro-D-glucitol levels in non-diabetic men with fasting or postprandial plasma glucose levels of less than 6.1 mmol/L, the Suita study, Japan, 1994–2007.

	1,5-Anhydro-D-glucitol (μg/mL)			*p* for trend
	≥24.5	14.1–24.4	≤14.0	
Number of subjects	388	349	77	
Person-years	4326	3636	703	
All cardiovascular diseases				
Cases, *n*	22	40	8	
Incidence rates/1000 person-years	5.1	11.0	11.4	
Model 1[a]	1	1.75 (1.04–2.96)	1.65 (0.73–3.72)	0.07
Model 2[a]	1	1.76 (1.04–2.98)	2.00 (0.88–4.55)	0.03
Coronary heart diseases				
Cases, *n*	14	17	2	
Incidence rates/1000 person-years	3.2	4.7	2.8	
Model 1[a]	1	1.26 (0.62–2.57)	0.71 (0.16–3.15)	0.96
Model 2[a]	1	1.18 (0.57–2.43)	0. 86 (0.19–3.86)	0.89
All strokes				
Cases, *n*	8	23	6	
Incidence rates/1000 person-years	1.8	6.3	8.5	
Model 1[a]	1	2.58 (1.15–5.79)	3.11 (1.07–9.00)	0.01
Model 2[a]	1	2.51 (1.11–5.66)	3.68 (1.26–10.75)	0.01
Ischemic strokes				
Cases, *n*	7	15	5	
Incidence rates/1000 person-years	1.6	4.1	7.1	
Model 1[a]	1	1.97 (0.80–4.85)	3.05 (0.96–9.69)	0.045
Model 2[a]	1	1.92 (0.77–4.75)	3.45 (1.08–11.05)	0.03

Parentheses indicate 95% confidence intervals.
[a] Model 1: adjusted for age, model 2: adjusted for model 1 plus body mass index, hypertension, hypercholesterolemia, HDL cholesterol, estimated glomerular filtration rate, current cigarette smoking, and current alcohol drinking.

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between men and women might result in the sex difference. In addition, the involvement of selection bias cannot be completely eliminated in women. Further studies with sufficient samples and CVD events in women are necessary to clarify this problem.

Measurement of serum 1,5-AG levels could detect not only those with persistent hyperglycemia but also those with transient postprandial hyperglycemia who are likely to be at higher risk for development of diabetes in the near future. Accordingly, decrease in serum 1,5-AG levels might be related with the elevated risk of CVD. The previous epidemiological studies also reported the association of postprandial hyperglycemia with risk of CVD [4–6], and the present results are not inconsistent with them. However, the mechanism remains still inconclusive, and two hypotheses could be considered. First, hyperglycemia itself is a risk for atherosclerotic diseases. Second, hyperglycemia is just a reflection of insulin resistance which is closely related to risk factors for atherosclerotic diseases. In the present study, adjustments for insulin resistance-related factors, waist circumferences or triglycerides, hardly changed the results. This indirectly suggests that serum 1,5-AG levels are independently related with a risk for CVD from insulin resistance, and we infer that hyperglycemia itself might be a risk.

OGTT cannot be conducted easily in the routine clinical setting or during health check-ups because it requires overnight fasting in blood sampling, longer time and extra costs. Conversely, measurement of serum 1,5-AG can be performed easily with a single non-fasting blood sample and is relatively low cost. Serum 1,5-AG levels do not fluctuate very much within an individual if glucose is not excreted into urine; however, it varies widely among individuals [1–3,13,21,22]. Accordingly, periodic measurement of serum 1,5-AG might be important for the early detection of a decrease from the normal level in each individual.

It is also well known that hemoglobin A_{1c} (HbA_{1c}) is useful for the diagnosis of diabetes or as a marker of glycemic control, and elevated HbA_{1c} is associated with increased risk for macro- and micro-complications [15–17,23]. HbA_{1c} can also be measured in a single non-fasting blood sample. However, red cell turnover and hemoglobinopathies influence HbA_{1c} levels, and this has been often identified as a problem [23,24]. In contrast, serum 1,5-AG levels are not affected by red cell turnover and hemoglobinopathies. In terms of screening higher risk individuals among the general population, a combination of HbA_{1c} and serum 1,5-AG measurements might be better choice.

The present analysis had several limitations. First, some aspects of medical history were unknown, including gastric resection, hyperthyroidism and renal glycosuria, which can lower 1,5-AG levels. Second, the present dataset did not include measurement of HbA_{1c} levels or OGTT; therefore, comparison of HbA_{1c} or OGTT with serum 1,5-AG was not possible. Third, a single serum 1,5-AG measurement at baseline may have lead to an underestimation of the association between serum 1,5-AG levels and CVD due to regression dilution bias [25].

In conclusion, the present analyses suggest that in men measurement of serum 1,5-AG was useful to detect individuals at increased risk for CVD, regardless of the presence or absence of diabetes. Measurement of serum 1,5-AG levels might be a useful tool for screening in the clinical setting or during health check-ups. However, this is the first report with a limited population of Japanese, and these findings should be further investigated by studies with sufficient samples and CVD events among various populations, races and geographical areas.

Conflict of interest

None to be declared.

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分担研究報告書

大阪府八尾市南高安地区地域コホート研究

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研究要旨

大阪府Y市M地区の特定健診受診者30-89歳の男女1965人を対象として、臍部レベルと中点レベルそれぞれで腹囲測定を行い、両測定値の差および各測定値とメタボリック症候群のリスク因子との関連を検討した。中点レベルの腹囲に比し臍部レベルの腹囲は、男性では平均1.2cm、女性では平均6.0cm大きく、男性よりも女性で差が大きかった。臍部レベルと中点レベルの腹囲の差が小さい者ほど、男女ともにトリグリセライド値が高く、HDLコレステロール値が低い傾向を認め、さらに女性では収縮期血圧値が高い傾向を示した。

A．研究目的

2008年度より、日本ではメタボリック症候群に着目した特定健診・特定保健指導が開始され、メタボリック症候群を中心とした高リスク者同定の妥当性および有効性に関する議論が活発になっている。特に腹囲測定は、海外における測定方法の多くが中点レベルでの腹囲を採用しているに対して、日本のメタボリック症候群では臍点レベルでの腹囲を採用しており、その比較可能性についての課題がある。

そこで、本年度は、一般住民を対象として、臍部レベルと中点レベルそれぞれで腹囲測定を行い、両測定値の差に関連する因子の検討、および各測定値とメタボリック症候群のリスク因子との関連の差について横断的に検討した。

B．研究方法

本研究の対象者は大阪府Y市M地区住民の30-89歳の男女1965人である。2010年度の健診時に、測定の研修を受けた熟練者が、受診者の臍部レベルと中点レベルのそれぞれでの腹囲測定を行った。

本研究では、臍部レベルと中点レベルでの腹囲測定値の差についての特徴を検討することを目的として、①腹囲の差（臍部－中点）に関連する対象者の特性、②腹囲の差に関連するメタボリック症候群のリスク因子、③臍部と中点のそれぞれの腹囲とメタボリック症候群のリスク因子との関連について検討した。

統計解析は、一般化線形モデルを用いて、腹囲の差または腹囲区分ごとに各リスク因子の多変量調整平均値を求めた。交絡因子としては、性別、年齢(10歳ごと)、臍部における腹囲(5分位)、喫煙状況（喫煙なし、過去喫煙あり、現在喫煙あり)、飲酒状況(飲酒なし、過去飲酒あり、現在飲酒あり）を採用した。統計解析には SAS version 9.13 (SAS Institute, Inc., Cary, NC, USA)を用いた。

（倫理面への配慮）本研究は、「疫学研究に関する倫理指針」ならびに個人情報保護に関する国のガイドラインや指針等に則ってデータ解析を行ない、大阪府立健康科学センター倫理審査委員会の承認を得た。

C．研究結果

Table 1に腹囲の差に関連する対象者特性についての分析結果を示した。中点レベルの腹囲に比し臍部レベルの腹囲は、男性では平均1.2cm、女性では平均6.0cm大きく、男性よりも女性で差が大きかった。また、年齢区分および臍部における腹囲区分の値が大きくなるにつれて、腹囲の差は大きくなる傾向が見られた。

Table 2に腹囲の差の5分位区分別の各リスク因子の平均値を示す。女性では、腹囲の差が小さい区分ほど、収縮期血圧値と中性脂肪値の平均値が高く、HDLコレステロール平均値が低い傾向が認められた（腹囲調整後）。男性でも、腹囲の差が小さい区分ほど、トリグリセライド値の平均値が高く、HDLコレステロール平均値が低い傾向が認められた。

Table 3-4に臍部レベルの腹囲（Table 3）、および中点レベルの腹囲（Table 4）の5分位区分別の各リスク因子の平均値を示す。女性、男性どもに、臍部レベルまたは中点レベルの腹囲区分と、総コレステロールを除く全てのリスク因子の平均値との間に有意な傾向性が認められた。すなわち、腹囲区分が大きいほど、血圧値、トリグリセライド値、LDLコレステロール値、HbAlc値の平均値は高く、HDLコレステロール平均値が低い値を示した。臍部レベルと中点レベルの腹囲の間で、各リスク因子の関連性に大きな相違は認められなかった。

Table 5に臍部レベルと中点レベルのそれぞれの腹囲と各リスク因子との関連性に関し、重回帰分析にて年齢、喫煙状況、飲酒状況を調整した後の回帰係数（β）値と寄与率（R^2）を示した。本分析の結果からも、臍部レベルと中点レベルの腹囲の間で各リスク因子との関連に大きな相違は認められなかった。

D．考察

今回の一般住民を対象とした検討により、臍部レベルと中点レベルの腹囲の差は、女性、高齢者、および臍部レベルの腹囲が高値の者でより大きいことが明らかとなった。また、臍部レベルと中点レベルの腹囲の差が小さいほど、男女ともにトリグリセライド値が高く、HDLコレステロール値が低い傾向が示され、さらに女性では収縮期血圧値が高い傾向を示した。すなわち、臍部レベルと中点レベルの腹囲の差が少ない体型は、腹囲とは独立して、メタボリック症候群のリスク因子と関連していることが示唆された。

また、臍部レベルの腹囲と中点レベルの腹囲の各々とリスク因子との関連性には大差がなかったことから、どちらの腹囲でもメタボリック症候群の指標として使用することは妥当であると考えられた。

E．結論

本研究結果により、海外において主流である中点レベルの腹囲を用いた研究成績とわが国の臍部レベルの腹囲を用いた研究成績を比較する際には性、年齢等の影響の考慮を要すると考えられた。また、特に臍部レベルの腹囲と中点レベルの腹囲が男性よりも大きい女性において、臍部レベルと中点レベルの腹囲の差が少ない体型は、腹囲とは独立したメタボリック症候群の惹起因子である可能性が示唆された。

F．健康危険情報

なし

G．研究発表

1．論文発表

なし

2．学会発表

1) 北村明彦. 疫学研究と予防対策の現状からみた特定健診・特定保健指導への考察. 第69回日本公衆衛生学会総会フォーラム（2010.10.28）. 日本公衛誌. 2010;57(特別附録）:99.

2) 北村明彦. 地域・職域・ドック研究よりみた心血管病の疫学的エビデンス. 第21回日本疫学会学術総会シンポジウム（2011.1.22）. 総会講演集 2011;21;66-67.

H. 知的財産権の出願・登録状況

なし

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Table 1. Multivariable adjusted mean values (95% confidence intervals) of gap of waist circumference between navel and midpoint [†], Yao, 2010

		Number at risk	Mean (95% CI)	$P_{\text{for trend}}$ [§]
Gender				
	Male	701	1.2 (0.0-2.4)	
	Female	1261	6.0 (4.8-7.2)**	<0.001
Age				
	30-39 years	124	2.9 (1.6-4.3)	
	40-49 years	228	3.1 (1.8-4.3)	
	50-59 years	300	3.5 (2.3-4.7)	
	60-69 years	757	4.1 (2.9-5.2)**	
	70-79 years	487	3.9 (2.7-5.1)*	
	80-89 years	66	4.2 (2.8-5.6)*	<0.001
Waist circumference				
	58-74 cm	410	2.9 (1.6-4.1)	
	75-79 cm	319	3.5 (2.3-4.7)*	
	80-84 cm	469	3.8 (2.6-5.0)**	
	85-89 cm	372	3.8 (2.6-5.0)**	
	90-112 cm	392	4.1 (2.9-5.3)**	<0.001
Smoking status				
	Never-smokers	1227	3.5 (2.5-4.5)	
	Former-smokers	453	3.1 (2.1-4.1)	
	Current-smokers	280	3.3 (2.2-4.3)	0.47
Drinking status				
	Never-drinkers	1048	3.7 (2.2-5.2)	
	Former-drinkers	134	3.0 (1.4-4.5)*	
	Current-drinkers	775	3.4 (1.9-4.9)	0.07

[†] The gap of waist circumferences are calculated by the values measured at navel substracting the values measured at the level midway between the lowest rib and the iliac crest.

[§] P values are from multiple analysis of variance (MANOVA)

* p <0.05 are from MANOVA by using the first categories as reference for each variables

** p<0.001 are from MANOVA by using the first categories as reference for each variables

Table 2. Multivariable adjusted mean values (95% confidence intervals) of cardiovascular risk factors according to quintiles of gap of waist circumference†, Yao, 2010

	Quintiles of gap of waist circumference†					
	Q1	Q2	Q3	Q4	Q5	$P_{\text{for trend}}$§
Female						
Range	[-10, 2]	[3, 4]	[5, 6]	[7, 9]	[10, 22]	
Median, cm	2	4	5	8	12	
Number of subjects	223	286	287	250	215	
Systolic blood pressure, mmHg	124.5 (117.4-131.7)	121.4 (114.3-128.5)*	122.2 (115.1-129.4)	119.6 (112.4-126.7)**	121.6 (114.5-128.7)*	0.004
Diastolic blood pressure, mmHg	74.9 (70.3-79.6)	74.3 (69.7-78.9)	74.3 (69.7-79.0)	72.8 (68.2-77.5)*	73.4 (68.8-78.0)	0.10
Serum triglycerides, mg/dL	114.7 (85.8-143.7)	108.9 (80.2-137.5)	106.0 (77.3-134.7)	105.6 (76.7-134.4)	99.6 (71.0-128.2)*	0.09
Serum high-density lipoprotein, mg/dL	69.1 (61.2-77.0)	70.1 (62.3-77.9)	69.7 (61.9-77.5)	70.8 (62.9-78.6)	72.7 (64.9-80.5)*	0.14
Serum total cholesterol, mg/dL	211.8 (194.1-229.5)	213.0 (195.5-230.6)	212.2 (194.6-229.8)	214.9 (197.2-232.5)	211.9 (194.4-229.4)	0.85
Serum low-density lipoprotein, mg/dL	121.3 (105.1-137.4)	121.7 (105.7-137.7)	121.7 (105.7-137.8)	122.8 (106.7-138.9)	118.0 (102.0-134.0)	0.56
Hemoglobin A1c (%)	5.2 (4.9-5.5)	5.2 (4.9-5.5)	5.1 (4.8-5.4)	5.1 (4.8-5.4)*	5.1 (4.8-5.4)	0.07
Male						
Median (cm)	-1	0	1	2	4	
Range	[-5, -1]	[0, 0]	[1, 1]	[2, 2]	[3, 12]	
Number of subjects	145	174	154	106	122	
Systolic blood pressure, mmHg	120.6 (112.9-128.3)	120.4 (113.0-127.9)	118.7 (111.1-126.4)	118.7 (110.9-126.5)	118.6 (110.8-126.3)	0.62
Diastolic blood pressure, mmHg	76.7 (71.7-81.6)	74.7 (70.0-79.5)	74.6 (69.7-79.5)	75.7 (70.7-80.7)	74.8 (69.8-79.7)	0.29
Serum triglycerides, mg/dL	167.3 (116.0-218.7)	156.4 (107.0-205.8)	154.2 (103.3-205.1)	159.9 (107.9-211.8)	140.1 (88.6-191.7)*	0.25
Serum high-density lipoprotein, mg/dL	51.2 (43.8-58.7)	52.9 (45.8-60.1)	55.1 (47.8-62.5)*	54.3 (46.8-61.8)	53.4 (46.0-60.9)	0.19
Serum total cholesterol, mg/dL	201.1 (183.5-218.7)	202.6 (185.7-219.6)	204.2 (186.8-221.7)	199.3 (181.5-217.2)	202.9 (185.3-220.6)	0.81
Serum low-density lipoprotein, mg/dL	125.4 (109.3-141.5)	127.1 (111.6-142.6)	125.4 (109.4-141.3)	122.5 (106.2-138.8)	128.8 (112.7-145.0)	0.59
Hemoglobin A1c (%)	5.3 (4.9-5.7)	5.2 (4.8-5.6)	5.1 (4.8-5.5)	5.3 (4.9-5.6)	5.2 (4.8-5.5)	0.37

† The gap of waist circumferences are calculated by the values measured at navel substracting those at the level midway between the lowest rib and the iliac crest.

§ *P* values are from multiple analysis of variance (MANOVA), adjusted for age, waist circumference measured at the level of navel, smoking status and drinking status.

* $p<0.05$ are from MANOVA by using the first categories as reference for each variables

** $p<0.001$ are from MANOVA by using the first categories as reference for each variables

Table 3. Partial regression coefficients (β) (95% confidence interval: 95% CI) for the values of waist circumference by multiple liner regression analysis with cardiovascular risk factors as dependent variable with adjustment for age, smoking status and drinking status

	Waist circumference measured at the level of navel			Waist circumference measured at the at the level midway between the lowest rib and the iliac crest		
	β (95% CI)	*p*	R^2	β (95% CI)	*p*	R^2
Female						
Systolic blood pressure	0.37 (0.27, 0.48)	<0.001	0.23	0.39 (0.28, 0.50)	<0.001	0.23
Diastolic blood pressure	0.17 (0.11, 0.24)	<0.001	0.05	0.18 (0.12, 0.25)	<0.001	0.05
Serum triglycerides	1.88 (1.53, 2.23)	<0.001	0.12	1.96 (1.61, 2.31)	<0.001	0.13
Serum total cholesterol	-0.06 (-0.28, 0.17)	0.62	0.03	-0.10 (-0.33, 0.12)	0.36	0.03
Serum high-density lipoprotein	-0.63 (0.73, -0.53)	<0.001	0.15	-0.64 (-0.73, -0.54)	<0.001	0.15
Serum low-density lipoprotein	0.41 (0.21, 0.61)	<0.001	0.04	0.38 (0.17, 0.58)	<0.001	0.04
Hemoglobin A1c	0.02 (0.01, 0.02)	<0.001	0.11	0.02 (0.01, 0.02)	<0.001	0.12
Male						
Systolic blood pressure	0.24 (0.07, 0.41)	0.006	0.11	0.25 (0.09, 0.40)	0.002	0.11
Diastolic blood pressure	0.24 (0.14, 0.34)	<0.001	0.04	0.24 (0.15, 0.33)	<0.001	0.04
Serum triglycerides	2.67 (1.76, 3.58)	<0.001	0.08	2.65 (1.80, 3.50)	<0.001	0.09
Serum total cholesterol	0.05 (, 0.26, 0.36)	0.75	0.01	0.07 (, 0.22, 0.36)	0.64	0.01
Serum high-density lipoprotein	-0.64 (0.78, -0.51)	<0.001	0.17	-0.60 (-0.72, -0.47)	<0.001	0.17
Serum low-density lipoprotein	0.46 (0.18, 0.74)	0.002	0.04	0.42 (0.16, 0.69)	0.002	0.04
Hemoglobin A1c	0.01 (0.00, 0.02)	0.007	0.04	0.01 (0.00, 0.02)	0.004	0.04

Table 4. Multivariable adjusted mean values (95% confidence intervals) of cardiovascular risk factors according to quintiles of waist circumference, Yao, 2010

	Quintiles of waist circumference measured at the level of navel					$P_{\text{for trend}}$ †
	Q1	Q2	Q3	Q4	Q5	
Female						
Range	59-74	75-79	80-84	85-89	90-112	
Median, cm	70	77	82	87	93	
Number of subjects	327	224	282	210	218	
Systolic blood pressure, mmHg	121.1 (112.4-129.9)	124.8 (116.0-133.6)	127.1 (118.3-135.8)	129.4 (120.5-138.2)	131.1 (122.4-139.8)	<0.001
Diastolic blood pressure, mmHg	72.4 (67.5-77.4)	74.1 (69.1-79.1)	75.0 (70.0-80.0)	76.3 (71.3-81.4)	77.0 (72.0-82.0)	<0.001
Serum triglycerides, mg/dL	81.3 (52.7-110.0)	99.2 (70.2-128.1)	103.0 (74.3-131.8)	120.4 (91.3-149.5)	125.2 (96.6-153.7)	<0.001
Serum high-density lipoprotein, mg/dL	79.6 (71.8-87.4)	73.5 (65.6-81.4)	69.1 (61.3-77.0)	67.4 (59.5-75.3)	64.4 (56.6-72.1)	<0.001
Serum total cholesterol, mg/dL	211.7 (194.2-229.2)	213.7 (196.0-231.4)	213.6 (196.0-231.2)	213.0 (195.2-230.8)	211.0 (193.5-228.4)	0.88
Serum low-density lipoprotein, mg/dL	113.4 (97.5-129.4)	119.5 (103.4-135.6)	123.7 (107.7-139.7)	122.2 (106.0-138.4)	124.2 (108.3-140.1)	<0.001
Hemoglobin A1c (%)	5.0 (4.7-5.3)	5.0 (4.7-5.3)	5.1 (4.8-5.4)	5.2 (4.9-5.5)	5.3 (5.0-5.6)	<0.001
Male						
Range	58-74	75-79	80-84	85-89	90-112	
Median, cm	72	77	82	87	93	
Number of subjects	83	95	187	162	174	
Systolic blood pressure, mmHg	118.7 (109.1-128.3)	124.1 (114.5-133.7)	123.7 (114.5-132.9)	121.4 (112.3-130.5)	125.7 (116.5-135.0)	0.03
Diastolic blood pressure, mmHg	73.6 (68.1-79.2)	75.8 (70.3-81.4)	76.2 (70.9-81.5)	76.1 (70.8-81.4)	78.9 (73.6-84.2)	0.002
Serum triglycerides, mg/dL	109.4 (57.0-161.8)	156.0 (103.6-208.3)	161.7 (111.5-211.9)	165.3 (115.5-215.1)	186.4 (136.0-236.8)	<0.001
Serum high-density lipoprotein, mg/dL	64.0 (56.5-71.6)	57.2 (49.6-64.7)	49.6 (42.3-56.8)	49.6 (42.4-56.8)	46.1 (38.9-53.4)	<0.001
Serum total cholesterol, mg/dL	203.2 (185.2-221.1)	205.1 (187.3-223.0)	195.9 (178.8-213.1)	203.9 (186.9-221.0)	203.6 (186.4-220.8)	0.09
Serum low-density lipoprotein, mg/dL	121.4 (105.1-137.8)	123.8 (107.4-140.1)	123.4 (107.7-139.1)	130.8 (115.3-146.4)	132.0 (116.2-147.7)	0.01
Hemoglobin A1c (%)	5.0 (4.6-5.4)	5.2 (4.8-5.6)	5.2 (4.8-5.6)	5.3 (4.9-5.7)	5.3 (4.9-5.7)	0.04

† *P* values are from multiple analysis of variance (MANOVA), adjusted for age, waist circumference measured at the level of navel, smoking status and drinking status.

Table 5. Multivariable adjusted mean values (95% confidence intervals) of cardiovascular risk factors according to quintiles of waist circumference, Yao, 2010

	Quintiles of waist circumference measured at the at the level midway between the lowest rib and the iliac crest					$P_{\text{for trend}}$ †
	Q1	Q2	Q3	Q4	Q5	
Female						
Range	54-74	75-79	80-84	85-89	90-110	
Median, cm	68	77	81	86	93	
Number of subjects	617	269	186	111	78	
Systolic blood pressure, mmHg	123.1 (114.4-131.7)	127.3 (118.5-136.1)	129.4 (120.5-138.3)	129.9 (121.0-138.8)	135.0 (125.7-144.3)	
Diastolic blood pressure, mmHg	73.0 (68.1-77.9)	75.3 (70.3-80.3)	76.1 (71.1-81.2)	76.8 (71.8-81.9)	78.7 (73.4-84.0)	<0.001
Serum triglycerides, mg/dL	89.6 (61.5-117.8)	109.6 (80.9-138.3)	118.3 (89.3-147.2)	116.7 (87.8-145.6)	152.4 (122.0-182.9)	<0.001
Serum high-density lipoprotein, mg/dL	76.8 (69.1-84.6)	68.5 (60.7-76.4)	66.8 (58.8-74.7)	65.3 (57.4-73.3)	61.7 (53.4-70.1)	<0.001
Serum total cholesterol, mg/dL	212.6 (195.3-229.9)	216.8 (199.2-234.4)	209.2 (191.5-227.0)	210.3 (192.6-228.1)	213.4 (194.7-232.1)	0.18
Serum low-density lipoprotein, mg/dL	115.9 (100.1-131.7)	126.2 (110.1-142.2)	120.3 (104.1-136.5)	124.0 (107.8-140.2)	125.7 (108.6-142.7)	<0.001
Hemoglobin A1c (%)	5.0 (4.7-5.3)	5.1 (4.8-5.4)	5.2 (4.9-5.5)	5.3 (5.0-5.6)	5.6 (5.3-6.0)	<0.001
Male						
Range	58-74	75-79	80-84	85-89	90-111	
Median, cm	71	78	82	87	94	
Number of subjects	107	120	163	153	158	
Systolic blood pressure, mmHg	120.0 (110.6-129.5)	123.4 (114.0-132.9)	121.7 (112.4-131.0)	122.3 (113.1-131.4)	126.1 (116.8-135.4)	0.07
Diastolic blood pressure, mmHg	73.2 (67.7-78.6)	75.3 (69.9-80.8)	76.1 (70.8-81.5)	76.9 (71.6-82.1)	78.6 (73.3-84.0)	<0.001
Serum triglycerides, mg/dL	117.2 (65.7-168.7)	150.2 (98.7-201.8)	156.2 (105.7-206.6)	169.7 (119.9-219.4)	188.5 (137.9-239.1)	<0.001
Serum high-density lipoprotein, mg/dL	62.2 (54.7-69.7)	54.5 (47.0-62.0)	48.8 (41.4-56.1)	50.6 (43.4-57.9)	45.2 (37.8-52.5)	<0.001
Serum total cholesterol, mg/dL	201.8 (184.1-219.5)	200.3 (182.7-218.0)	197.0 (179.7-214.3)	205.4 (188.3-222.4)	201.6 (184.3-219.0)	0.28
Serum low-density lipoprotein, mg/dL	120.5 (104.4-136.6)	123.9 (107.8-140.1)	126.1 (110.3-141.9)	130.3 (114.7-145.9)	131.4 (115.5-147.2)	0.03
Hemoglobin A1c (%)	5.1 (4.7-5.4)	5.3 (4.9-5.7)	5.2 (4.8-5.6)	5.2 (4.9-5.6)	5.4 (5.0-5.8)	0.02

† *P* values are from multiple analysis of variance (MANOVA), adjusted for age, waist circumference measured at the level of navel, smoking status and drinking status.

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

沖縄県における心臓血管イベント発症要因の解明(沖縄豊見城研究)

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研究要旨:
【背景、目的】これまで、沖縄県の人間ドック受診者において、生活習慣病関連の危険因子の心臓血管イベント発症に及ぼす影響を調査、解析してきた。その結果、内臓肥満症、高血圧、耐糖能異常、脂質異常症のいずれも全国平均より高いことがわかった。急性心筋梗塞の発症率は、男性2.01、女性1.03(千人年)、冠動脈疾患(急性心筋梗塞+労作性狭心症)男性3.40、女性2.06(千人年)、脳卒中3.47、女性2.49(千人年)であった。腹部肥満、高血圧、高血糖、高中性脂肪、低HDL血症の陽性率、喫煙率、習慣飲酒率でも、男性が女性に比較して高く、高コレステロール血症は男女で有病率に差がなかった。心血管イベントの発生率には男女差があり、その発生要因も明らかな差があった。本年は以下の点につき実施もしくは着手した、第一、沖縄住民の内臓肥満症、高インスリン血症・インスリン抵抗性の実態を、性別、世代別に大規模集団で明らかにする。第二、内臓肥満症を基盤とする血圧上昇が、血管機能障害(血管機能障害、頸動脈プラーク形成、微量アルブミン尿)に及ぼすインパクトを明らかにする、第三、内臓肥満症を基盤とする血圧上昇が、血管機能障害、心臓血管イベントを発症させるメカニズムを検証した。【方法】方法1:血圧、脈拍、高インスリン血症・インスリン抵抗性評価、腹部脂肪・異所性脂肪蓄積、血管内皮機能、尿中微量アルブミン、頸動脈プラーク、心臓血管イベントの有病率、発症率を調べ、長野県と比較。方法2:持続血糖モニタリング、血管内皮機能モニターを併用し、内臓肥満症にともなう血圧上昇の要因を調べた。【結果】1 沖縄住民は長野県に比べ、肥満、高インスリン血症・インスリン抵抗性の頻度が大。2 腹囲増加は特に男性で血圧分布を右にシフトした(平均±SD mmHg、高血圧(≥130mmHg)頻度%、男性:腹囲85cm未満 126±79、38% vs 85cm以上 133±16、57%;女性 90cm未満 121±17、16% vs 腹囲90cm以上 134±17、57%)。3 血圧上昇にともなう血管機能障害の程度、冠動脈疾患有病率は、内臓肥満症の程度、酸化ストレス増加と強く相関した。【結論】内臓肥満症に起因する血圧上昇は、酸化ストレス上昇および内臓脂肪由来分子の調節異常により、血管内皮機能障害、臓器障害を来すこと、これらが冠動脈疾患発症に関与することが強く示唆された。

A. 研究目的

沖縄県における心臓血管イベント発症要因を解明する。メタボリックシンドロームのコンポーネントを含めた動脈硬化性疾患リスクファクターの陽性率と心血管イベントの発生率との関係を明らかにする。

B. 研究方法

研究1: 2003年5月から2004年3月まで豊見城中央病院健康管理センターを人間ドックのため受診した者6985名(年齢30～69才、男性3839名、女性3146名)。メタボリックシンドロームの各コンポーネントの陽性率と他の動脈硬化危険因子の陽性率を調査する。研究2:研究1で対象となった症例につき、毎年の受診歴をカルテ上で確認し、受診歴の不明なものに対して、往復はがきで健康状態、死別の有無に関する調査を行う。メタボリックシンドロームに対して、食事療法、運動療法、薬物療法の有無を調査し、プライマリーエンドポイントおよびセカンダリーエンドポイントを判定する。研究3:血圧、脈拍、高インスリン血症・インスリン抵抗性評価、腹部脂肪・異所性脂肪蓄積、血管内皮機能、尿中微量アルブミン、頸動脈プラーク、心臓血管イベントの有病率、発症率を調べ、長野県と比較。研究4:持続血糖モニタリング、糖・脂肪クランプモデル、血管内皮機能モニターを併用し、内臓肥満症にともなう血圧上昇の要因を調べた。

(倫理面への配慮)
ヘルシンキ宣言(http://www.wma.net/e/policy/b3.htm)を遵守している。予後問い合わせのはがきでは、調査に関する情報保護シールを貼ることで、また、統計解析ならびに中央の疫学解析委員会におけるデータ提供の際は、連結不可匿名化をおこない個人が特定されない処理を厳重におこない、個人情報の遺漏がないことに徹底して留意した。

C. 研究結果

研究1および2:対象とした者人間ドック受診者6985名のメリスクファクターの頻度は以下の通りである。腹部肥満陽性率は、男性58%(≥85cm)31%(≥90cm)、女性53% (≥80cm)17%(≥90cm)。空腹時高血糖または血糖降下薬内服の率は、男性53%(≥100mg/dl)、21%(≥110)、女性24%(≥100)、8%(≥110)であった。総これてすロール血症(≥220mg/dlまたは内服中)は男性32%、女性33%、高中性脂肪血症(≥150または脂質異常症治療薬内服)は、男性41%、女性18%であった。低HDL血症(<40または脂質異常症治療薬内服)の有病率は、男性20%、女性11%(<50だと25%)であった。高血圧症(≥130/85mmHgまたは内服)の有病率は、男性55%、女性38%であった。メタボリックシンドロームの陽性率は男性は、27%(日本基準_腹囲85cm)23%(IDF_腹囲90cm)、14%(AHA/NHLBI_2005年改訂_腹囲90cm)であった。。女性は、6%(日本基準_腹囲90cm)24%(IDF_腹囲80cm)、24%(AHA/NHLBI_2005年改訂_腹囲80cm)であった。喫煙率(男性喫煙中34%＋既往喫煙25%、女性喫煙中5%＋既往喫煙2%)、習慣飲酒率(週1回以上、男性81%、女性31%)であった。

平均観察期間(男性1346日、女性1358日)で、初発心筋梗塞(男性21例、女性12例)、初発労作性狭心症(男性227例、女性12例)、初回冠動脈インターベンション(男性221例、女性6例)、初発脳卒中(男性49例、女性29例)、急性死(男女とも0例)、死亡(男性4例、女性0例)であった。 急性心筋梗塞の発症率は、男性2.01、女性1.03(千人年)、冠動脈疾患(急性心筋梗塞＋労作性狭心症)男性3.40、女性2.06(千人年)、脳卒中3.47、女性2.49(千人年)であった。内服薬服用率は、降圧薬(男性17%、女性16%)、脂質異常症治療薬(男性6%、女性7%)、糖尿病治療薬(男性5%、女性2%)であった。

研究3:沖縄住民は長野県に比べ、肥満、高インスリン血症・インスリン抵抗性の頻度が大。2 腹囲増加は特に男性で血圧分布を右にシフトした(平均±SD mmHg、高血圧(≥130 mmHg)頻度%、男性:腹囲85cm未満 126±79、38% vs 85cm以上 133±16、57%;女性90cm未満 121±17、16% vs 腹囲90cm以上

134±17、57%)。3 血圧上昇にともなう血管機能障害の程度、冠動脈疾患有病率は、内臓肥満症の程度、酸化ストレス増加と強く相関した。

D. 考察

メタボリックシンドロームのコンポーネントを含めた動脈硬化性疾患リスクファクターの陽性率と心血管イベントの発生を全件調査した。

平均観察期間男性1346日、女性1358日で、急性心筋梗塞の発症率は、男性2.01、女性1.03(千人年)、冠動脈疾患(急性心筋梗塞+労作性狭心症)男性3.40、女性2.06(千人年)、脳卒中3.47、女性2.49(千人年)といずれも男性が女性に比較して、高率であった。

一方で、腹部肥満、高血圧、高血糖、高中性脂肪、低HDL血症の陽性率、喫煙率、習慣飲酒率でも、男性が女性に比較して高く、高コレステロール血症は男女で有病率に差がなかった。

内臓肥満症に起因する血圧上昇は、酸化ストレス上昇および内臓脂肪由来分子の調節異常により、血管内皮機能障害、臓器障害を来すこと、これらが冠動脈疾患発症に関与することが強く示唆された。

E. 結論

心血管イベントの発生率には男女差があり、その発生要因も明らかな差がある。メタボリックシンドロームの診断・管理のためには、男女差を考慮にいれて個別のアプローチ基準を設定する必要があると考えられた。さまざまリスクひとつずつにつき、その病態における関与、マーカーとしての有用性につき慎重に検討を進める必要がある。

F. 健康危険情報

問題となる健康危険情報はない。

G. 研究発表

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H. 知的財産権の出願・登録状況

1. 特許取得

なし

2. 実用新案登録

なし

3. その他

なし

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

血圧に関する診断のエビデンスに関する研究

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研究要旨：DPP-4阻害薬Sitagliptin（SGT）は最近開発された経口血糖降下薬である。SGTはGLP-１を増加させるが、GLP-1は食塩摂取を減少させ、ナトリウム排泄を促進する。したがって、SGTは血圧を減少させる可能性がある。本試験では、十分な血糖コントロールが得られていない2型糖尿病患者17人にSGTを6ヶ月間投与して、前後における血圧の変化を観察した。BMIに変化は無く、HbA1cは6.5%から5.8%へ減少した。収縮血圧は130mmHgから120mmHgまで低下した。HbA1cの変化と血圧の変化には相関が見られなかった。以上より、SGTは血糖降下作用とは独立した降圧作用があると考えられる。

A．研究目的
DPP-４阻害薬Sitagliptin（SGT）に降圧作用があるかどうかを明らかにする。

B．研究方法
血糖及び降圧治療を受けており、十分な血糖管理が達成されていない2型糖尿病患者17人にSGT50mgを隔日に投与して、6ヶ月間血圧の変化を観察した。
（倫理面への配慮）
倫理委員会の承認を得ている。

C．研究結果
対象患者は男性6人、女性9人で、平均年齢は76歳であった。SGTの投与によりHbA1cは6.5±0.3%から5.8±0.3%間で減少した。収縮期血圧130.0±37.2mmHgから119.7±9.4mmHg間で減少した（P<0.01）。血圧の変化とHbA1cの変化の間には相関が見られなかった。

D．考察
SGTには血糖降下作用とは独立した機序による狡猾作用がある。

E．結論
どの年代層においても、血圧レベルは重要な心血管病のリスクとなる。少なくても140/90mmHg未満への降圧を達成すべきである。

G．研究発表
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2.　学会発表

H．知的財産権の出願・登録状況
（予定を含む。）
1．特許取得
なし
2．実用新案登録
なし
3．その他
なし

別紙４

雑誌

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Methylglyoxal Is a Predictor in Type 2 Diabetic Patients of Intima-Media Thickening and Elevation of Blood Pressure

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Methylglyoxal Is a Predictor in Type 2 Diabetic Patients of Intima-Media Thickening and Elevation of Blood Pressure

Susumu Ogawa, Keisuke Nakayama, Masaaki Nakayama, Takefumi Mori, Masato Matsushima, Masashi Okamura, Miho Senda, Kazuhiro Nako, Toshio Miyata, Sadayoshi Ito

Abstract—We test whether plasma level of methylglyoxal (MG) is an independent risk factor predicting the progression of diabetic macroangiopathy or microangiopathy in type 2 diabetic patients. We measured in 50 type 2 diabetic patients plasma levels of MG and 3-deoxyglucosone (DG) using an electrospray ionization-liquid chromatography-mass spectrometry. We assessed the correlations between baseline levels of MG or DG and the percentage changes after 5 years of clinical parameters linked to diabetic macroangiopathy or microangiopathy, that is, intima-media thickness (IMT), systolic blood pressure (SBP), the amount of urinary albumin excretion (ACR), pulse wave velocity (PWV), and estimated glomerular filtration rate (eGFR). Multiple regression analysis was performed using the percentage changes in IMT, SBP, ACR, PWV, and eGFR over the 5-year period as the independent or objective variables and the values of MG, DG, glycohemoglobin A1c, body mass index, triglyceride, and diabetic duration at the baseline as the dependent variables. The values of IMT, PWV, SBP, and ACR all increase, but eGFR reduces with time during the 5-year period. Baseline level of MG correlates significantly with the percentage changes of IMT, SBP, ACR, PWV, and eGFR, whereas that of DG does only with ACR. A multiple regression analysis reveals that MG is an independent risk factor for the percentage changes of IMT, PWV, and SBP but not for those of ACR and eGFR. DG is an independent risk factor for the percentage change of ACR. MG is a predictor in type 2 diabetic patients of intima-media thickening, of increase of PWV, and of elevation of SBP. (***Hypertension*. 2010;56:471-476.**)

Key Words: methylglyoxal ■ 3-deoxyglucosone ■ diabetic macroangiopathy ■ hypertension ■ intima-media thickness ■ pulse wave velocity

Under hyperglycemia and/or oxidative stress in diabetes mellitus, a variety of toxic α-oxoaldehydes are produced, and these in turn react with protein amino groups, eventually leading to formation of advanced glycation end products (AGEs).[1–3] These α-oxoaldehydes also interfere with various cellular functions, independent of their effect on AGE modification of proteins, and influence the intracellular signaling by multiple pathways.[1–3]

Among toxic α-oxoaldehydes, the present studies were focused on methylglyoxal (MG), because the in vitro studies and animal experiments in experimental diabetic models by us and others have suggested that MG is pathologically involved in the progression of both macroangiopathy and microangiopathy: MG plays a major role in vascular damage to endothelial cells and in the development of hypertension, of insulin resistance, and of nephropathy.[1–10]

The primary biosynthetic pathway of MG in diabetic patients remains elusive, but MG is known to be produced from a variety of sources. That is, MG can be produced not only from glucose but also from a variety of substances and is not necessarily produced from hyperglycemia only.[1,2,11]

Elevated blood concentrations of MG have been reported in type 2 diabetics,[5,12] and it has been reported that plasma-free MG-derived hydroimidazolone was higher in the type 1 diabetics as compared with the nondiabetics.[13] An 18-year follow-up study showed that high baseline serum levels of the MG-derived hydroimidazolone type of AGE-modified proteins were associated with cardiovascular disease mortality in nondiabetic women.[14]

Interestingly, postprandial hyperglycemia, a factor contributing to the development of macroangiopathy, dramatically increases the intracellular accumulation of MG.[15,16] Furthermore, biguanide, an agent that effectively suppresses macroangiopathy independent of its blood glucose–lowering effect, significantly lowers the production of MG.[17–19]

Taken together, these findings strongly suggest the contribution of MG to diabetic angiopathy, especially macroangiopathy. Unfortunately, there have been no studies examining whether elevated plasma MG levels are an independent risk factor predicting the progression of diabetic macroangiopathy or microangiopathy.

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