Table 1 Baseline characteristics of patients

Variable	Men	Women	Total
n	1374	2628	4002
Age, years	55.5 ± 8.1	59.8 ± 6.0	58.3 ± 7.1
BMI, kg/m^2	24.1 ± 2.8	23.8 ± 3.4	23.9 ± 3.2
Diabetes, *n* (%)	626 (45.6)	870 (33.1)	1496 (37.4)
Hypertension, *n* (%)	514 (37.4)	1108 (42.2)	1622 (40.5)
Current smoker, *n* (%)	518 (37.7)	145 (5.5)	663 (16.6)
TC, mmol/L	6.24 ± 0.31	6.29 ± 0.32	6.27 ± 0.32
LDL-C, mmol/L	4.01 ± 0.47	4.08 ± 0.43	4.06 ± 0.45
HDL-C, mmol/L	1.36 ± 0.36	1.54 ± 0.38	1.48 ± 0.38
Non-HDL, mmol/L	4.88 ± 0.46	4.76 ± 0.48	4.80 ± 0.48
TG (median [IQR]), mmol/L	1.71 (1.26-2.45)	1.33 (1.01-1.80)	1.44 (1.08-2.01)
FPG, mmol/L	6.80 ± 2.27	6.15 ± 1.80	6.37 ± 2.00
HbA1c, %	6.47 ± 1.38	6.22 ± 1.16	6.31 ± 1.24
Oral hypoglycemic agent, *n* (%)	291 (21.2)	423 (16.1)	714 (17.8)
Insulin, *n* (%)	55 (4.0)	98 (3.7)	153 (3.8)

Values are mean ± SD unless otherwise indicated.

Diabetes and hypertension defined by physician diagnosis. BMI, body mass index; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triacylglycerides; FPG, fasting plasma glucose; IQR, interquartile range.

was slightly higher in the HbA1c ≥6.5% group for the total population and in men and in women, although it did not reach statistical significance. In men, but not women, there was a significant trend for increased mortality as HbA1c levels increased.

Comparing patients whose HbA1c was ≥6.5% versus <6.0% by treatment arm revealed that CVD was significantly increased in the diet alone group (HR, 2.2, p <0.001) and similarly in diet plus pravastatin group (HR, 1.8; p = 0.02; Figure 1) in patients with HbA1c ≥6.5%. The spline curves for CVD exhibited a linear increase in risk as HbA1c increased until approximately HbA1c <6.0%; thereafter the risk increased more gently (Figure 2). Although CVD risk was proportionally lower in women than men, no large difference in the shape of the spline curves was found between the two sexes.

Discussion

We found a significant relation between having an HbA1c level ≥6.5% and risk of CVD in Japanese patients with hypercholesterolemia. This analysis compared three categories of HbA1c levels as measured according to new International Expert Committee criteria. Significant relations between increased HbA1c level and CHD and CVD were observed in men and women. A continuous increase in CVD risk as HbA1c level rose was confirmed by the spline method, which indicated that there is no threshold between CVD risk and HbA1c level. Recent reports have demonstrated that including HbA1c level in the assessment model could help to identify subjects at high risk, and that the predictability was improved by also including lipid levels [14]. Therefore, evaluating the relationship between HbA1c and CVD in patients with hypercholesterolemia is important to identify patients in a high-risk population.

The incidence of microvascular disease is known to increase with higher HbA1c levels. For instance, diabetic retinopathy occurs at a high rate in persons with HbA1c >6.0%-7.0% [15]. The Kumamoto Study in Japan demonstrated that the risk of retinopathy and nephropathy starts to increase as HbA1c rises above 6.6%-6.7% (NGSP) [16]. Macrovascular disease also is affected by a high HbA1c. In the Framingham Heart Study, a 1% increase in HbA1c was associated with a 1.39-fold increased risk of CVD [17]. A graded association between HbA1c and carotid intima-media thickness was found in the Atherosclerosis Risk in Communities (ARIC) study [18]. The Suita Study [11] recently reported a significantly increased risk of CVD associated with high HbA1c. Although it appears clear from these epidemiologic data and interventional studies that increased HbA1c levels are associated with raised CVD risk, we believe that the present findings are the first such demonstration in the setting of hypercholesterolemia, which itself confers high risk for CVD. Our data indicate that the significant relation between CVD risk and HbA1c ≥6.5% observed in hypercholesterolemia is similar to that seen in the general population.

In our previous report, we stated that the incidence of CVD in patients with or without abnormal fasting glucose was 16.5 and 5.7 per 1000 patient-years, respectively. In the present study, the incidences of CVD in patients with HbA1c ≥ 6.1% and <6.1% were 16.9 and 6.1 per 1000 patient-years, respectively [19]. Although the results are broadly consistent when using fasting glucose and HbA1c as markers for glucose abnormalities to determine the HRs, 5% of the patients with HbA1c ≥6.1% actually had normal fasting glucose levels (data not shown). Since the HbA1c level is affected by postprandial glucose excursions more than the fasting glucose level [20], evaluating HbA1c in addition to fasting glucose is useful to identify people at high risk.

Statins can reduce CVD onset in the settings of primary and secondary prevention [21-25]. Benefits of statin therapy have been reported in patients with diabetes [9,19,26] and confirmed in a large-scale meta-analysis that implied that statins reduce CVD risk in diabetic and nondiabetic populations [27]. In this study, although statistical significance was not reached probably due to the small number of events, we nonetheless observed a proportional risk reduction in each HbA1c category in the diet plus pravastatin group compared with diet alone group (in patients with HbA1c <6.0%, 6.0%-<6.5%, and ≥6.5%, HR = 0.64, 0.72, and 0.81, respectively).

Table 2 Incidence of CVD events in relation to HbA1c level

% HbA1c	Men				Women				All			
	Events/pts, n (/1000 py)	HR (95%CI)	p-value	Trend-p	Events/pts, n (/1000 py)	HR (95%CI)	p-value	Trend-p	Events/pts, n (/1000 py)	HR (95% CI)	p-value	Trend-p
CHD				<0.01				<0.01				<0.01
<6.0	16/630 (5.6)	1.0	–		9/1481 (1.3)	1.0	–		25/2111 (2.6)	1.0	–	
6.0-< 6.5	7/226 (7.1)	1.2 (0.5-2.9)	0.73		6/419 (3.2)	2.1 (0.7-6.0)	0.16		13/645 (4.5)	1.5 (0.8-2.9)	0.24	
≥6.5	33/518 (14.7)	2.3 (1.3-4.2)	<0.01		24/728 (7.2)	4.9 (2.2-10.6)	<0.01		57/1246 (10.3)	3.1 (1.9-5.0)	<0.01	
Stroke (all)				0.33				0.14				0.07
<6.0	11/630 (3.9)	1.0	–		13/1481 (1.9)	1.0	–		24/2111 (2.5)	1.0	–	
6.0-< 6.5	5/226 (5.0)	1.1 (0.4-3.3)	0.82		4/419 (2.1)	1.0 (0.3-3.0)	0.94		9/645 (3.1)	1.1 (0.5-2.3)	0.85	
≥6.5	15/518 (6.5)	1.5 (0.7-3.2)	0.33		14/728 (4.2)	1.8 (0.8-3.9)	0.13		29/1246 (5.1)	1.7 (1.0-2.9)	0.07	
CVD				<0.01				<0.01				<0.01
<6.0	27/630 (9.6)	1.0	–		26/1481 (3.9)	1.0	–		53/2111 (5.6)	1.0	–	
6.0-< 6.5	12/226 (12.2)	1.2 (0.6-2.3)	0.69		10/419 (5.4)	1.2 (0.6-2.5)	0.64		22/645 (7.7)	1.2 (0.7-2.0)	0.48	
≥6.5	50/518 (22.9)	2.1 (1.3-3.4)	<0.01		42/728 (12.8)	2.9 (1.8-4.7)	<0.01		92/1246 (16.9)	2.4 (1.7-3.4)	<0.01	
Death (total)				0.01				0.53				0.04
<6.0	4/630 (1.4)	1.0	–		16/1481 (2.3)	1.0	–		20/2111 (2.1)	1.0	–	
6.0-< 6.5	5/226 (4.9)	3.4 (0.9-12.9)	0.07		10/419 (5.2)	2.2 (1.0-4.9)	0.05		15/645 (5.1)	2.3 (1.2-4.4)	0.02	
≥6.5	16/518 (6.7)	4.1 (1.3-12.5)	0.01		10/728 (2.9)	1.2 (0.5-2.6)	0.68		26/1246 (4.5)	1.9 (1.0-3.4)	0.04	

HR, 95%CI estimated by Cox proportional model adjusted by sex, age, treatment arm, baseline LDL-C, baseline HDL-C, hypertension, chronic kidney disease (estimated glomerular filtration rate <60), and smoking status.

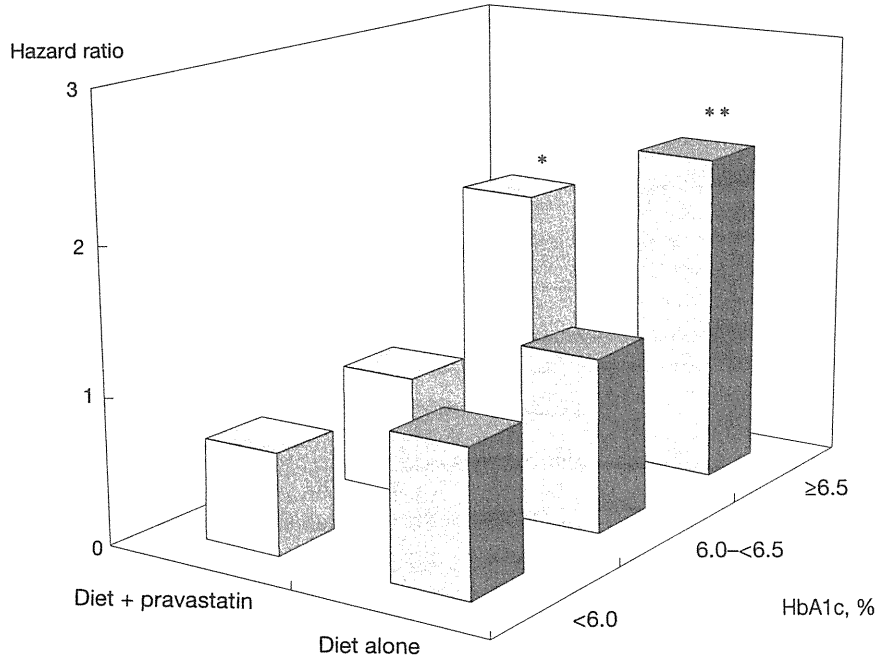

Figure 1 Relation between HbA1c and CVD according to treatment arms. P-values were calculated against <6.0% in each group by Cox proportional hazard model adjusted for sex, age, baseline LDL-C, baseline HDL-C, hypertension, chronic kidney disease (estimated glomerular filtration rate <60), and smoking. *p <0.05; **p <0.01.

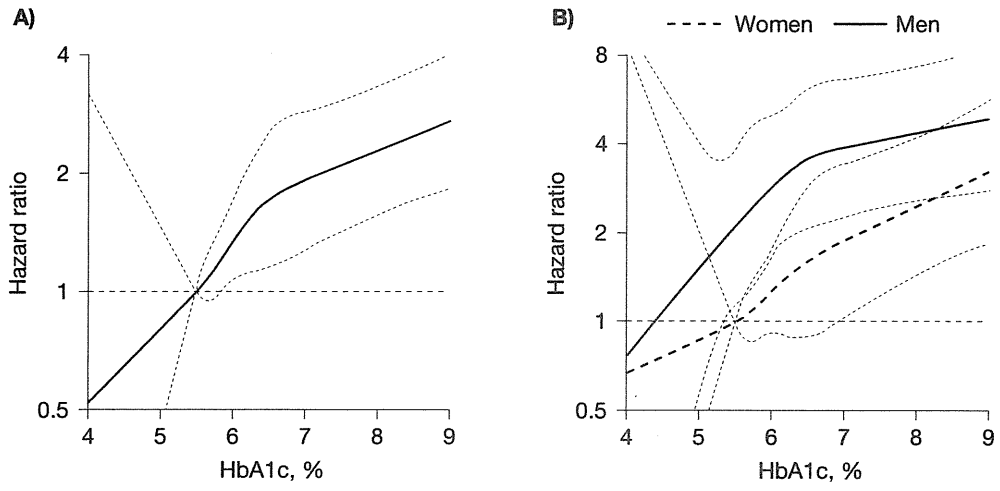

Figure 2 Spline curves for CVD in total population (A) and in men and women (B). Knots are quartiles of HbA1c in the total population. A) Dashed lines = 95%CI. B) Solid lines = 95%CI for men; dashed lines = women.

National guidelines recommend the aggressive management of CVD in patients with type 2 diabetes and that multidisciplinary interventions that includes weight, lipid and blood pressure control are needed to minimize the CVD risk, in addition to glucose lowering[28]. Statins offer an important therapeutic option for the management of lipids, particularly in type 2 diabetes. However, the relation between HbA1c and CVD was unaltered suggesting that appropriate HbA1c management is required in addition to lipids reduction. There are some hypotheses for the mechanisms by which hydrophilic statins may attenuate the deterioration of abnormal glucose metabolism in diabetic patients [29]. However, the HbA1c level was not significantly different between the diet plus pravastatin group and the diet alone group throughout the study period, as we have previously reported [19]. It is possible that adherence to diet therapy was somewhat worse in the diet plus pravastatin group than in the diet alone group, which may or may not influence the HbA1c level. However, we do not think we should focus on the effects of pravastatin on HbA1c levels in this analysis because there was no difference in HbA1c levels between the two groups.

There are two important limitations to the present analysis. First, it was conducted in patients whose TC was 5.7-6.0 mmol/L, and extrapolating these results to patients with higher TC concentrations should be done with caution. On the other hand, our patients had a broad range of LDL-C levels (1.4-4.6 mmol/L). Thus it appears that our findings may be quite generalizable. Second, the small number of events in the MEGA Study may affect the accuracy of the spline method. Therefore the tail analysis of data for sex, LDL-C level, and treatment arm were exploratory, especially in sparse tail area. In addition, an earlier study showed that all-cause mortality was increased in people with low HbA1c levels (<4.0%) [30]. Although we cannot assess the relationship between low HbA1c and high mortality because few patients with low HbA1c levels were included in this analysis, we should take this into account in clinical practice.

In conclusion, our results suggest that the HbA1c level should be included in prediction models for CVD risk. Controlling HbA1c independently of lipid management is necessary to reduce the risk of CVD in diabetic patients with elevated HbA1c.

Acknowledgements and funding

The authors sincerely thank the MEGA Study Group for providing their data. Financial support for this retrospective subanalysis was provided by Daiichi-Sankyo Co, Ltd.

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Authors' contributions

RN carried out interpreting the data and writing the manuscript; TN, HS and NT carried out interpreting the data and reviewing the manuscript; YO carried out analyzing and reviewing the manuscript. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

Received: 1 March 2011 Accepted: 30 June 2011
Published: 30 June 2011

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doi:10.1186/1475-2840-10-58
Cite this article as: Nishimura *et al.*: **Relationship between hemoglobin A1c and cardiovascular disease in mild-to-moderate hypercholesterolemic Japanese individuals: subanalysis of a large-scale randomized controlled trial.** *Cardiovascular Diabetology* 2011 **10**:58.

[J Tokyo Wom Med Univ 81 (Extra) E189~E196 (2011)]

Original

Total and Differential White Blood Cell Counts, Fasting Insulin Concentrations, and Components of Metabolic Syndrome in Japanese Men and Women: the Kurihashi Lifestyle Cohort Study

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(Accepted December 29, 2010)

We examined the cross-sectional association between fasting insulin, metabolic syndrome (MetS), and total and differential white blood cell (WBC) counts in Japanese men and women. Middle-aged and apparently healthy subjects (1,910 men, 849 women) who participated in a general health check-up were included. The International Diabetes Federation definition was adopted to identify subjects with MetS. The prevalence of MetS was 12.4% among men and 10.4% among women. Multivariate logistic regression model showed that men and women in the highest quartile of total WBC counts had a 2.26-fold and 2.71-fold increased risk of MetS, respectively, compared to those in the lowest quartile. Similarly, men and women in the highest quartile of neutrophil count had a 2.17-fold and 4.08-fold increased risk of MetS, respectively, compared to those in the lowest quartile of neutrophil count. Lymphocyte count was an independent risk factor for MetS only in men. These associations were all independent of the fasting insulin. Our data suggests that MetS relates to total and differential WBC counts, independent from fasting insulin in both sexes. However, it is unknown whether sex differences in the association between MetS and WBC subtypes relate to sex differences in incident cardiovascular diseases and diabetes.

Key Words: white blood cell count, insulin, metabolic syndrome

Introduction

Recently, evidence has shown that chronic inflammation is an important factor associated with the progression of atherosclerosis[1] and insulin resistance[2]. White blood cell (WBC) count is a well-known objective biological marker of acute infection, tissue damage, and other systemic inflammatory conditions. Several studies have shown that increased WBC counts are associated with components of metabolic syndrome (MetS)[3], type 2 diabetes mellitus (DM)[4], and coronary heart disease[5]. Some Japanese studies have also shown a significant association between WBC counts and MetS[6]~[9]. Thus, the WBC count may be a powerful predictor of several atherosclerotic diseases. Regarding WBC subtypes, recent studies suggest that elevated neutrophil or granulocyte counts may be the strongest predictor of carotid arteriosclerosis, coronary heart disease (CHD), and cardiovascular disease (CVD) mortality[10]~[12]. However, few studies have investigated the relationship between MetS and differential WBC count[13]~[15].

MetS, which comprises various metabolic disorders, is a known risk factor for CVD and DM[16][17]. Insulin sensitivity is closely related to MetS[18], CVD[19], and DM[20]. However, little is known regarding the relationship between WBC subtypes and MetS via insulin resistance. Thus, the aim of this study was to assess the relationship between total and differential WBC counts and MetS and to test whether this relationship was independent of insulin concentrations in Japanese men and women.

Subjects and Methods

Study subjects

From February 2006 to January 2007, Saitama-ken Saiseikai Kurihashi (SSK) Hospital conducted a health check-up program in which 3,825 subjects aged 30-76 years participated and were followed up in the Kurihashi Lifestyle Cohort Study. Subjects were excluded if they had DM, CVD, cancer, asthma, or certain infectious diseases or if they were under pharmacological treatment for hypertension or dyslipidemia. Moreover, 234 subjects with abnormal WBC counts ($\geq 10 \times 10^9$ cells/L or $< 4.0 \times 10^9$ cells/L), indicative of an infectious disease or pathological state of leucopenia, were later excluded from the study. The remaining 2,759 subjects were included in the study.

Data collection

The general health check-up examination procedure at SSK Hospital included biochemical laboratory tests and a self-administered questionnaire regarding smoking status, physical activities during leisure time, medical history, alcohol habits, and in women, menopausal status. Smoking status was classified into three categories (never, past, and current smoker). Physical activity status during leisure time was classified as sedentary, occasionally, or active. Alcohol habits were divided into three categories (never, occasionally, and regularly). The height, weight, blood pressure, and waist circumference (WC) of all subjects were measured. Body height was measured to the nearest 0.1 cm with the subject standing without shoes. The subjects were requested to wear light indoor clothes before the body weight was measured to the nearest 0.1 kg. Blood pressure was measured in a sitting position after 5 min of rest by using an automatic sphygmomanometer. WC was measured to the nearest 0.1 cm at the navel level at the end of the expiration of a normal breath and with the subject in a standing position. Blood samples were collected in the morning after a 10-h fast. Fasting plasma glucose (FPG) (glucose oxidase method), triglyceride (enzymatic method), and high-density lipoprotein cholesterol (HDL-C) (direct method) levels and WBC counts (Kinetic WBC optical count, CELL-DYN, Abbott Japan) were measured at the hospital laboratory. Insulin concentration was measured by an immunoradiometric assay at a commercial laboratory.

Statistical analysis

Statistical analyses were performed and reported separately for men and women. MetS was defined using International Diabetes Federation (IDF) criteria. To investigate the possible relationship between anthropometric measurements, metabolic activities, and lifestyle characteristics and WBC counts, data were divided into quartiles of WBC counts. The equality of means of each variable across quartiles of WBC counts was tested by analysis of variance (ANOVA). The chi-squared test was used to compare the proportions. Subjects with different numbers of MetS components were divided into six groups by numbers 0-5. The components of MetS included central obesity, high fasting glucose levels, high triglyceride levels, low HDL-C levels, and high blood pressure. Means of total WBC counts and WBC subtypes were calculated for each group and groups with and without MetS by means of a multiple linear regression model. The multivariate adjusted odds ratios and their 95% confidence intervals associated with the presence of MetS were calculated for each quartile category of total WBC and WBC subtype counts by using logistic regression models. In the multivariate model, age (continuous), physical activity during leisure time (categorical), alcohol habits (categorical), smoking status (categorical), fasting insulin concentration, and (in women only) menopause status (categorical) were included as confounding factors.

Statistical Package for Social Sciences (SPSS) for Windows (version 14.0, Chicago, IL, USA) was used for all statistical analyses. All reported p values are two-tailed, and $p < 0.05$ was considered statistically significant. The study was approved by the Institutional Review Board of SSK Hospital, and informed consent was obtained from the study participants.

Results

Anthropometric, metabolic, and lifestyle characteristics in relation to WBC counts

The classical CVD risk factors deteriorated with increasing WBC counts in both men and women,

Table 1 Relationships between anthropometric measurements, metabolic activity and lifestyle characteristics, and quartiles of white blood cell counts (/μl)

Men	Quartile 1 (n=478) ≤4.98	Quartile 2 (n=481) 4.99-5.71	Quartile 3 (n=474) 5.72-6.59	Quartile 4 (n=477) ≥6.70	p value
Age (years)	51 ± 9	51 ± 8	50 ± 9	50 ± 8	0.039
Body mass index (kg/m²)	22.9 ± 2.7	23.6 ± 2.9	23.9 ± 3.0	24.2 ± 3.4	<0.001
Waist circumference (cm)	83.1 ± 7.3	84.8 ± 7.7	86.0 ± 7.8	86.6 ± 8.3	<0.001
Systolic blood pressure (mmHg)	123 ±15	125 ± 15	127 ±16	125 ± 18	0.018
Diastolic blood pressure (mmHg)	78 ±12	79 ± 12	81 ±13	80 ± 13	0.001
High-density lipoprotein cholesterol (mg/dl)	60 ±15	56 ± 15	53 ±14	50 ± 13	<0.001
Triglyceride (mg/dl)	100 ±61	123 ±118	133 ±86	147 ±108	<0.001
Fasting plasma glucose (mg/dl)	94 ±11	94 ± 12	95 ±14	95 ± 15	0.687
Fasting insulin (μU/ml)	5.62± 3.20	6.58± 4.30	6.77± 3.82	7.48± 4.57	<0.001
Alcohol intake regularly (%)	42.6	45.7	44.7	43.7	0.799
Current smoker (%)	21.5	36.4	47.0	65.6	<0.001
Physically active during leisure time (%)	22.1	19.9	17.4	12.9	<0.001
Metabolic syndrome (%)	5.9	10.0	15.4	18.2	<0.001
Women	Quartile 1 (n=216) ≤4.46	Quartile 2 (n=210) 4.47-5.07	Quartile 3 (n=211) 5.08-5.85	Quartile 4 (n=212) ≥5.86	p value
Age (years)	51 ± 8	52 ± 8	50 ± 8	49 ± 7	0.037
Body mass index (kg/m²)	21.8 ± 3.0	22.3 ± 2.9	22.5 ± 3.1	23.1 ± 3.5	<0.001
Waist circumference (cm)	78.4 ± 8.8	80.4 ± 8.1	80.1 ± 8.5	81.8 ± 9.4	<0.001
Systolic blood pressure (mmHg)	120 ±16	121 ±15	122 ±17	120 ±17	0.421
Diastolic blood pressure (mmHg)	72 ±11	72 ±12	74 ±12	72 ±12	0.267
High-density lipoprotein cholesterol (mg/dl)	70 ±15	68 ±15	67 ±16	62 ±14	<0.001
Triglyceride (mg/dl)	79 ±46	87 ±39	95 ±51	102 ±47	<0.001
Fasting plasma glucose (mg/dl)	89 ±10	89 ± 9	89 ± 9	90 ±13	0.135
Fasting insulin (μU/ml)	4.86± 2.51	5.50± 2.88	5.90± 3.24	6.37± 3.77	<0.001
Alcohol intake regularly (%)	13.2	13.9	11.3	14.9	0.709
Current smoker (%)	8.8	7.1	10.0	17.9	0.009
Physically active during leisure time (%)	14.5	19.0	13.9	15.2	0.447
Menopause (%)	46.9	51.7	50.5	43.2	0.304
Metabolic syndrome (%)	5.1	7.6	12.8	16.0	0.001

Variables are the mean ± SD for continuous variables and percentages of subjects for categorical variables.
p values were for the equality of quartile group means determined by ANOVA.
Chi-squared tests of independence were tested between alcohol habits, smoking status, physical activity, and menopausal status and quartile groups.

except for FPG and alcohol habits in men and blood pressure, FPG, alcohol habits, physical activity at leisure time, and menopause in women (Table 1). Fasting insulin concentrations and the prevalence of MetS increased with increase of total WBC counts in both sexes.

Total and differential WBC counts and MetS

The overall prevalence of MetS was 12.4% in men and 10.4% in women. Total WBC and neutrophil counts increased with increasing numbers of components of MetS, after adjusting for confounding factors in both men and women (Table 2). In men, total WBC, neutrophil, lymphocyte, eosinophil, and basophil counts were elevated in subjects with MetS. In women, total WBC, neutrophil, and lymphocyte counts were elevated in subjects with MetS (Table 2).

According to the multivariate logistic regression model, total WBC and neutrophil counts showed statistically significant linear positive relationships with MetS in both men and women (p for linear trend = 0.004 and 0.022 and 0.046 and 0.045, respectively), and the lymphocyte count showed a statistically significant linear positive relationship with MetS in men (p for trend = 0.01) (Table 3). However, fasting insulin concentrations were not independent risk factors for total and differential WBC counts in men and women. Men in the highest quartiles of to-

Table 2 Adjusted means of total and differential white blood cell counts for clustered components of metabolic syndrome

Men								
Number of components	n	%	Total WBC (/μl)	Neutrophil (/μl)	Lymphocyte (/μl)	Monocyte (/μl)	Eosinophil (/μl)	Basophil (/μl)
0	555	29.1	5,525±1,331	3,114± 882	1,844± 599	240±157	148±148	22±2
1	619	32.4	5,707±1,230	3,278± 870	1,871± 592	248±159	153±138	23±2
2	413	21.6	5,887±1,280	3,356± 928	1,967± 646	263±166	148±132	22±2
3	230	12.0	6,292±1,316	3,535± 879	2,069± 639	283±171	176±158	26±2
4	79	4.1	6,240±1,212	3,673± 966	2,113± 573	274±171	178±218	27±2
5	14	0.7	6,514±1,128	3,488±1,166	2,292±1,099	252±179	223±282	21±2
	Trend		<0.001	0.005	0.110	0.053	0.062	0.062
non-MetS	1,674	87.6	5,723±1,290	3,249± 897	1,894± 610	250±161	151±143	22±2
MetS	236	12.4	6,282±1,281	3,597± 899	2,097± 669	280±170	184±173	27±2
	Trend		<0.001	0.002	0.003	0.077	0.004	0.002
Women								
Number of components	n	%	Total WBC (/μl)	Neutrophil (/μl)	Lymphocyte (/μl)	Monocyte (/μl)	Eosinophil (/μl)	Basophil (/μl)
0	283	33.3	4,804±1,069	2,679± 686	1,674±588	199±129	132±141	21±2
1	288	33.9	5,013±1,027	2,871± 770	1,631±477	192±129	121±123	21±2
2	184	21.7	5,242±1,176	2,961± 760	1,670±567	219±115	148±142	23±2
3	71	8.4	5,461±1,208	3,251± 837	1,757±547	194±128	124±136	22±2
4	18	2.1	5,832±1,165	3,434±1,074	1,827±478	240±133	158±139	23±2
5	5	0.6	5,822±1,066	2,919± 361	2,488±978	266±133	300±360	22±2
			0.012	0.045	0.230	0.152	0.057	0.832
non-MetS	761	89.6	4,995±1,086	2,831± 740	1,655±536	201±126	131±135	21±2
MetS	88	10.4	5,561±1,218	3,267± 881	1,839±607	210±123	142±157	22±2
			0.018	0.017	0.030	0.541	0.933	0.813

WBC, white blood cell; MetS, metabolic syndrome.

Components of MetS: central obesity, high blood pressure, high triglyceride, low high-density lipoprotein cholesterol, and high fasting plasma glucose.

Variables are the means±SD.

Adjusted for age, smoking status, alcohol intake, physical activity during leisure time, fasting insulin concentration in both men and women, and in women only, menopausal status.

tal WBC, neutrophil, and lymphocyte counts had a 2.26-, 2.17-, and 2.32-fold increased risk for MetS, respectively, relative to men in the lowest quartiles of those counts, and this finding was independent of the fasting insulin concentration. Women in the highest quartiles of total WBC and neutrophil counts had a 2.71- and 4.08-fold increased risk for MetS, respectively, relative to women in the lowest quartiles of those counts (Table 3).

Discussion

Recent studies have shown that chronic inflammation is associated with the progression of atherosclerosis[1]and insulin resistance[2]. Insulin resistance plays an important role in the progression of MetS, CVD and DM[18)~20)]. In our study, fasting insulin concentrations were not independently related to total and differential WBC counts in both sexes. However, the significant relation between IDF-MetS and total WBC and neutrophil counts in both sexes and lymphocyte count in men were significantly independent from confounding factors including fasting insulin concentrations. Thus, IDF-MetS seems to be an insulin independent inflammatory condition leading to atherosclerotic diseases. However, it was unknown to what extent the sex difference in the effect of IDF-MetS on WBC subtypes relates to the sex difference in incident CVD and DM.

Previous cross-sectional studies have shown an association between total WBC counts and MetS in subjects from Japan. Nagasawa et al. reported an association between WBC counts and MetS by using body mass index (BMI) as an obesity criterion instead of WC in men but not in women[6]. However, fasting insulin concentrations were not significantly

Table 3 Odds ratios with the 95% confidence intervals for MetS according to the quartiles of total and differential WBC counts

		Men Odds ratio (95% confidence interval)	Women Odds ratio (95% confidence interval)
Total WBC	Quartile 1	1.00 (Reference)	1.00 (Reference)
	Quartile 2	1.28 (0.72-2.29)	1.22 (0.51-2.95)
	Quartile 3	2.26 (1.29-3.93)	1.97 (0.86-4.49)
	Quartile 4	2.26 (1.30-3.96)	2.71 (1.20-6.10)
	p for trend	0.004	0.046
Neutrophil	Quartile 1	1.00 (Reference)	1.00 (Reference)
	Quartile 2	1.28 (0.70-2.35)	2.84 (0.81-9.95)
	Quartile 3	1.94 (1.10-3.43)	3.43 (0.99-11.76)
	Quartile 4	2.17 (1.23-3.82)	4.08 (1.19-13.95)
	p for trend	0.022	0.045
Lymphocyte	Quartile 1	1.00 (Reference)	1.00 (Reference)
	Quartile 2	1.22 (0.68-2.21)	0.98 (0.34-2.82)
	Quartile 3	1.63 (0.93-2.87)	1.41 (0.54-3.65)
	Quartile 4	2.32 (1.33-4.04)	2.04 (0.83-5.05)
	p for trend	0.010	0.332
Monocyte	Quartile 1	1.00 (Reference)	1.00 (Reference)
	Quartile 2	1.16 (0.68-1.98)	1.17 (0.61-2.23)
	Quartile 3	1.55 (0.93-2.59)	1.19 (0.62-2.27)
	Quartile 4	1.68 (0.99-2.83)	1.34 (0.72-2.52)
	p for trend	0.172	0.838
Eosinophil	Quartile 1	1.00 (Reference)	1.00 (Reference)
	Quartile 2	1.59 (0.95-2.66)	1.06 (0.54-2.08)
	Quartile 3	1.63 (0.97-2.74)	1.13 (0.58-2.20)
	Quartile 4	1.93 (1.16-3.22)	1.87 (1.01-3.45)
	p for trend	0.091	0.130
Basophil	Quartile 1	1.00 (Reference)	1.00 (Reference)
	Quartile 2	1.32 (0.78-2.25)	1.01 (0.53-1.92)
	Quartile 3	1.86 (1.12-3.08)	1.07 (0.56-2.03)
	Quartile 4	2.03 (1.23-3.36)	1.36 (0.73-2.52)
	p for trend	0.022	0.724

WBC, white blood cell; MetS, metabolic syndrome.
Adjusted for age, smoking status, alcohol intake, physical activity during leisure time, fasting insulin concentration in both men and women, and only in women, menopausal status.

related to WBC count in this study. Their finding was partly accordance with our result. Ishizaka et al reported that high WBC counts are independent risk factors for MetS, after adjusting for age and total cholesterol in both men and women; however, BMI was used for the diagnosis of MetS in women because WC data were not available[7][8]. Oda et al reported that the prevalence of MetS increased through the quartiles of WBC counts in Japanese men and women[9]. This was accordance with our result. In our study, IDF-MetS was a significant, positive, and an independent risk factor for total and differential WBC counts. To our knowledge, this is the first study, using complete data of defined MetS and after adjusting for confounding factors related to lifestyle in Japanese men and women, to show a positive association between total WBC counts and MetS in both sexes. The MetS may directly increase WBC counts, since MetS comprises abdominal obesity which cause insulin resistance.

A few studies have analyzed an association between WBC subtype counts and components of

MetS. Kim et al showed that the numbers of total WBCs, neutrophils, and lymphocytes were elevated in men with MetS but not in women[13]. Another large study from Korea suggested that total and all differential WBC counts were associated with the presence of MetS[14] in men and women. One Japanese study showed that total WBC and lymphocyte counts were elevated with clustered features of MetS[15] only in men. The reasons for differences between these findings and the present data are unclear, but possible reasons include differences in sample size, age distribution, and adjustment of different confounding factors. Recent prospective studies have shown an association between total and differential WBC counts and CVD, IFG, DM, and all-cause mortality[4)10)~12)]. To our knowledge, however, no studies have analyzed impact of WBC counts on various end points independent from insulin concentrations. Further prospective studies are needed to clarify the role of total and differential WBC counts, MetS, and insulin in the development of atherosclerotic diseases.

There is a sex difference in the progression of DM and CVD[21]. A similar sex difference has been reported in total and differential WBC counts[22)23)]. In our study, lymphocyte count was not an independent risk factor for MetS in women. The reason for this is unclear. However, the number of women in our study was less than half of that of men, and thus, our findings in women might be weakened by the sample size. There may be environmental sex differences in lifestyle such as smoking status and physical activity. In our study, men include a higher proportion of smokers and physically active persons during leisure time than women. A female sex hormone, estrogen, may protect from atherosclerosis by decreasing the inflammatory cell adhesion[24], since we have adjusted for menopausal status in the current study.

Despite the mounting evidence of associations between total and differential WBC counts and the risk of MetS, explanatory biological mechanisms remain unclear. Vascular endothelial cells are activated by the presence of atherosclerotic risk factors, such as hypertension, dyslipidemia, and hyperglycemia, thus promoting increased production and release of proinflammatory cytokines and chemokines. Proinflammatory T cell cytokines, interleukin-2 (IL-2) and interferon-γ, were found in atherosclerotic lesion, which demonstrates the presence of Th1-type T cell response[25]. Thus, the atherosclerotic lesion contains large numbers of T lymphocytes. Additionally, proinflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and IL-6, which are secreted from adipose tissue, are known to increase WBC counts[26]. TNF-α is a potent stimulator of IL-6 production, and IL-6 stimulates neutrophils directly[27]. Leptin, which is also released from adipocytes, activates neutrophils via the induction of TNF-α[28]. Moreover, it has been reported that adipose tissue secretes IL-8 and monocyte chemoattractant protein-1, which contribute to the migration of granulocytes and activated T lymphocytes[29]. Thus, human adipose tissue, which is a major concept of MetS, could play an important role in increasing total and differential WBC counts.

There were several limitations in our study. Firstly, this study had a cross-sectional design, thus a temporal relationship between total and differential WBC counts and MetS could not be established. Secondly, though the hyperinsulinemic-euglycemic clamp is the standard technique to measure insulin sensitivity, we used the fasting insulin concentration as a surrogate measure of insulin resistance. As our subjects were participants in general health check-ups, it was impossible to perform such expensive, invasive, and long-sustained examinations. Thirdly, the questionnaire of physical activity, alcohol consumption, and smoking status was self-reported and not validated. Fourthly, high-sensitivity C-reactive protein (hs-CRP) is superior to WBC as an inflammatory component of MetS[30]. However, data of hs-CRP was not available because it was expensive whereas WBC was a stable, well-standardized, and inexpensive marker of routine health care data. Further researches are needed to examine the relation between inflammation and MetS using more sensitive marker. In addition to the limitations, our study has some major advantages. Firstly, we excluded subjects whose WBC

counts exceeded 10×10^9 cells/L or were lower than 4×10^9 cells/L, thus we examined subjects whose WBC counts were within the normal range. Secondly, to avoid systematic bias, we were extremely careful in data collection. We excluded subjects who had previous medical histories of diseases associated with low-grade inflammation. Thirdly, we adjusted for many confounding factors considered to have influence on MetS and insulin resistance in our data analysis.

In conclusion, IDF-MetS relates to inflammatory condition, increased total and differential WBC counts, independent from fasting insulin concentrations in both sexes. However, it is a future challenge to examine to what extent sex differences in the association between MetS and WBC subtypes relates to sex differences in the incident atherosclerotic diseases including CVD and DM.

Acknowledgments

This study was supported by grants from the Japanese Ministry of Health, Labour, and Welfare, the Japan Medical Women's Association, the Tokyo Women's Medical University Association, the Yayoi Yoshioka Research Fund, and the Yazuya Food and Health Research Foundation for T.N.

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総白血球数とその分画，空腹時インスリン，メタボリックシンドロームの関係

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日本人において，総白血球数とその分画，インスリン，メタボリックシンドロームの関係を横断的に検討した．対象は，埼玉県済生会栗橋病院の人間ドックを受診した日本人男女（男性 1,910 人，女性 849 人）で，慢性的に炎症を引き起こす可能性のある疾患の既往歴や糖尿病，高血圧，脂質異常症の内服がなく，白血球数が正常範囲内の者である．メタボリックシンドロームの診断には国際糖尿病連合の診断基準を用いた．メタボリックシンドロームの有病率は，男性で 12.4%，女性で 10.4% であった．男女とも，白血球数の増加に従い，肥満度や心血管危険因子は悪化し空腹時インスリン値は上昇した．また，空腹時インスリン値を含む交絡因子で補正後の総白血球数，好中球数は，メタボリックシンドロームの構成因子数の増加に従い増加した．空腹時インスリン値を含む多因子補正後のロジスティック回帰分析では，総白血球数の 4 分位において，最上位群では最下位群と比較し男女それぞれ，メタボリックシンドロームの相対危険度が 2.26 倍，2.71 倍であった．同様に，好中球数の 4 分位において，最上位群では最下位群と比較し男女それぞれ，メタボリックシンドロームの相対危険度が 2.17 倍，4.08 倍であった．また，男性でのみ，リンパ球数はメタボリックシンドロームの独立した危険因子であった．本横断研究において，メタボリックシンドロームはインスリンから独立した炎症状態（総白血球数とその分画）を示唆していた．しかし本関係には男女差があり，この点が心血管疾患や糖尿病の発症の性差にどの程度関連しているのかは不明であり，今後の検討課題である．

日本病態栄養学会誌14(1)：25－32, 2011

原著

特定健診・特定保健指導区分からみた栄養摂取状況、運動習慣の特徴：栗橋ライフスタイルコホート研究データの検討

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要旨：40-74歳のドック受診者2,108名（男1,231名）の横断データを、特定健診・保健指導区分別に分類し、指導区分間で生活習慣、栄養素摂取量を比較検討した。ドック受診時、1ケ月間の食事内容を簡易型自記式食事歴法質問票で調査し、対象者を保健指導区分に応じて、心血管危険因子非合併非肥満情報提供（N）群、心血管危険因子合併非肥満情報提供（I）群、支援（S）群の3群に分類、N群と各階層間で生活習慣、栄養素摂取量を男女別に比較した。男性で多因子補正後もS群はN群と比べてアルコール摂取量が高値であったが、女性に有意差はなかった。男女ともに、I、S群間で栄養素摂取量に有意差は認めなかった。男性ではI群と比較し食事摂取速度が速い、仕事の強度が低いことがS群の独立した寄与因子であった。この栄養素摂取量、生活習慣の特徴が将来の動脈硬化性疾患の発症に関係するのか、調査を継続予定である。

Key Words：生活習慣、集団検診、肥満、メタボリックシンドローム、疫学

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受付日：平成22年1月12日
採択日：平成22年10月22日

緒言

平成20年4月から「高齢者の医療確保に関する法律」に即して、医療保険者に対して保険加入者を対象としたメタボリックシンドロームに着目した生活習慣病予防のための特定健診・特定保健指導の実施が義務付けられた。受診者は健診後、肥満の有無と心血管危険因子の数で規定される保健指導区分に分類される。指導区分別に支援の形態や内容は異なるが、指導区分には、生活習慣病予防の上で、生活習慣上の問題点を鋭敏に抽出するだけでなく、減量による保健指導の効果が期

待できる群を抽出することが期待される。

栄養・食生活は、生活習慣病や肥満と関連が深く、健康日本21でも脂肪や塩分等の摂取量の目標が挙げられている[1]。脂質摂取量、アルコール摂取量が低く、野菜や果物摂取が多い食事パターンは典型的な欧米型の食事パターンと比較し冠動脈疾患や糖尿病の発症を減少させたとの報告がある[2]。また、食事摂取速度が速い者では肥満になりやすい可能性が示されており[3][4]、食習慣も生活習慣病に深く関係していると考えられる。しかし、成人男性の約3割、成人女性の約1割は食習慣や栄養摂取内容についてあまり意識しておらず、必要な情報を得る機会も少ないため[5]、本保健指導の支援により食事習慣が修正されれば生活習慣病の罹患率が減少することが期待される。一方、肥満がなくとも、心血管危険因子の重複が心血管疾患[6]や糖尿病[7]の発症リスクを高めることが報告されたが、特定健診の結果、情報提供と分類される群にも、心血管疾患や糖尿病の高リスク者が含まれることとなる。本研究では、既存の人間ドック受診者のデータを用いて、ドック受診者を特定健診・特定保健指導における保健指導区分毎に分類し、要支援群あるいは肥満はないが心血管危険因子を持つ者の群間で、食を中心とした生活習慣を比較し、特定健診の指導区分の意義を生活習慣の点から検証した。

方 法

対象は、2006年2月から2007年1月の間に埼玉県済生会栗橋病院において人間ドックを受診した40-74歳の男女である。この中で、糖尿病や高血圧、脂質異常症の薬物療法を受けておらず、健診時の各成績が特定健診の受診勧奨判定値を超えない2,108名（男性1,231名、女性877名、平均年齢52±7歳）を本研究の解析対象とした。

人間ドック受診時、身長、体重、腹囲等身体測定、空腹時血液検査の他、問診票により喫煙や運動習慣を含む生活習慣、既往歴、家族歴を調査した。喫煙は「現在吸っている」「過去吸っていた」「吸わない」の中から、前者を「喫煙習慣あり」、後2者を「喫煙習慣なし」とカテゴリー化して扱った。運動習慣については、余暇と労働時間の身体活動を調査した。余暇の運動習慣において「運動する」「時々運動する」「運動しない」の中から、前2者を余暇の「運動習慣あり」、後者を「運動習慣なし」とカテゴリー化して扱った。労働時間の身体活動は「重労働」「中等度」「軽労働」「座業または仕事をしていない」の中から前2者を「活動的」、後2者を「非活動的」とカテゴリー化して扱った。過去1ケ月間の習慣的な栄養素摂取量など食習慣について簡易型自記式食事歴法質問票（Brief-type self-administered diet history questionnaire；BDHQ）で調査した返答率は80.9%であった。BDHQは、すでに妥当性研究が存在している自記式食事歴法質問票[8]-[11]を基として開発された簡易型の質問票で、食事の習慣や調理法の他58種類の食品と99種類の栄養素摂取量を得られるものである。BDHQの妥当性の検証は逐次行っているが、現時点で完了していないため、本研究では2004年度総合研究報告書（佐々木敏ら、厚生労働省）において、16日間の秤量式食事記録との比較で相関係数が男女とも0.46～0.85である栄養素のみを採用した。食事摂取速度については「かなり速い」「やや速い」「普通」「やや遅い」「かなり遅い」から前2者を「速い」、後3者を「速くない」とカテゴリー化して扱った。また、肥満や性別による食事摂取量の過小申告[12]-[14]があるとの報告があり、それにともなって栄養素摂取量も過小申告される可能性があった。この影響をできるだけ取り除くため、本研究では密度法を用い、具体的には次の2つの方法によってエネルギー調整済栄養素摂取量を算出し使用した。エネルギーを産生する栄養素（炭水化物、総脂質、アルコール、飽和脂肪酸、一価不飽和脂肪酸、多価不飽和脂肪酸）については、総エネルギー摂取量にしめるエネルギー寄与率（%エネルギー）として示した。この場合、各栄養素単位重量(g)当たりのエネルギー産生量(kcal)はAtwaterの係数を用い、たんぱく質、炭水化物、脂質（脂肪酸を含む）、アルコールについてそれぞれ順に4、4、9、7とした。また、総エネルギー摂取量には上記の計算によって各栄養素から得られるエネルギーの総和を用いた。エネルギーを産生しない栄養素（食物繊維、ビタミンC、カルシウム）については、1000kcalを摂取したときに摂取した摂取量として表現した。具体的には、次の式によって算出した。

$$X_{adj} = X_{BDHQ} \times (1000/EI_{BDHQ})$$

表1　Comparison of lifestyle behaviors, laboratory data and nutrient intakes between each groups in men

	Normal	Information	Support	p for linear trend
Number of subjects	252	422	300	
Clinical and laboratory data				
Age (years)	51±7	52±8*	52±7*	0.009
Body mass index (kg/m²)	21.2±1.9	21.7±1.6*##	25.2±2.2***	<0.001
Waist circumference (cm)	77.2±5.0	79.3±4.0*###	90.6±4.7***	<0.001
Systolic blood pressure (mmHg)	113±9	121±12*##	123±11***	<0.001
Diastolic blood pressure (mmHg)	68±8	74±9*###	77±9***	<0.001
Fasting plasma glucose (mg/dl)	89±5	95±9*###	98±9***	<0.001
HbA1c (%)	4.9±0.2	5.2±0.3*##	5.3±0.3***	<0.001
Triglyceride (mg/dl)	83±26	104±46*###	126±52***	<0.001
High-density lipoprotein cholesterol (mg/dl)	61±12	57±16*###	50±11***	<0.001
Physically active during their leisure time (%)	73.8	68.0	67.3*	0.032
Physically active during work (%)	32.5	46.2*##	30.7	0.472
Current smoker (%)	36.1	77.3*##	60.3***	<0.001
Eating quickly (%)	42.1	41.2	52.3***	0.012
Supplement users (%)	31.3	25.8	28.0	0.424
Energy intake (kcal/day)	2136±601	2099±562	2118±571	0.708
Nutrient intake				
Carbohydrate (%energy)	56.7±7.7	56.3±8.1	55.5±7.9	0.196
Total fat (%energy)	24.4±5.2	23.0±5.2**	23.0±4.9	0.003
Alcohol (%energy)	5.1±6.6	7.3±8.1***	7.3±7.6**	<0.001
Saturated fatty acid (%energy)	6.2±1.6	5.7±1.5***	5.9±1.5	<0.001
Monounsaturated fatty acid (%energy)	8.7±2.0	8.2±2.0**	8.4±2.0	0.021
Polyunsaturated fatty acid (%energy)	6.5±1.5	6.2±1.5*	6.2±1.4*	0.045
Total dietary fiber (g/1000kcal)	5.9±1.5	5.5±1.6*	5.6±1.7*	0.012
Vitamin C (mg/1000kcal)	52.3±20.9	47.3±22.4*	49.4±22.1	0.017
Calcium (mg/1000kcal)	262.2±83.1	243.1±84.5**	249.3±88.6	0.019

The values are means±SD or percentages.
*：p<0.05, **：p<0.01, ***：p<0.001 vs. Normal
#：p<0.05, ##：p<0.01, ###：p<0.001 vs. Support

ここで、X_{adj}＝エネルギー調整後の栄養素Xの摂取量、X_{BDHQ}＝BDHQで測定された栄養素Xの摂取量、EI_{BDHQ}＝BDHQで測定されたエネルギー摂取量（エネルギーを産生する栄養素から得られたエネルギーの総和）、
である。

対象者を特定健診後の保健指導区分に応じて，心血管危険因子非合併非肥満情報提供（Normal：N）群、心血管危険因子合併非肥満情報提供（Information：I）群、要支援（動機付け支援＋積極支援）（Support：S）群の3群に分類した。S群は危険因子の数により動機付け支援と積極支援に分けられ、それぞれ支援強度が異なるが、I群と比較する際に危険因子の数を同等とするため、両者を合わせて支援群として扱い、解析を行った。N群とI群、S群間で、身体計測値や血液検査、生活習慣、食習慣や栄養素を男女別に比較した。またN群とI群、S群間で有意差を認めた栄養素は、General linear regression modelを用いて交絡因子で調整後の結果も報告した。次に、ロジスティック回帰モデルを用いて、I群を参考群とした場合のS群の生活習慣上の特徴を交絡因子で調整した上で報告した。

統計解析は日本語Windows版Statistical Package for Social Science（SPSS, Chicago, IL）Ver.14を用いた。すべての解析は男女別に行い報告した。数値は平均値±標準偏差で示し、多群間の有意差の検定は、一元配置分散分析で群間の比較後Bonferroni's testを行い、有意水準はp<0.05とした。

本研究は、栗橋ライフスタイルコホート研究の一部

表2 Comparison of lifestyle behaviors, laboratory data and nutrient intakes between each group in women

	Normal	Information	Support	p for linear trend
Number of subjects	474	255	64	
Clinical and laboratory data				
Age (years)	50±7	53±7*	54±6*	<0.001
Body mass index (kg/m²)	21.1±1.9	21.4±1.9*##	26.6±2.6***	<0.001
Waist circumference (cm)	75.3±6.7	76.9±6.5***##	90.2±6.0***	<0.001
Systolic blood pressure (mmHg)	112±10	121±13***#	126±10***	<0.001
Diastolic blood pressure (mmHg)	66±8	71±9***#	74±9***	<0.001
Fasting plasma glucose (mg/dl)	86±6	92±10***#	95±9***	<0.001
HbA1c (%)	4.9±0.2	5.3±0.3***#	5.4±0.2***	<0.001
Triglyceride (mg/dl)	73±22	88±38***#	103±43***	<0.001
High-density lipoprotein cholesterol (mg/dl)	69±14	66±15***#	59±13***	<0.001
Physically active during their leisure time (%)	58.2	60.0	57.8	0.887
Physically active during work (%)	31.2	36.9	29.7	0.484
Current smoker (%)	7.2	39.2***	14.1	<0.001
Menopause (%)	50.1	55.0	59.4	0.089
Eating quickly (%)	34.2	36.5	40.6*	0.283
Supplement users (%)	39.0	42.4	29.7	0.595
Energy intake (kcal/day)	1850±483	1808±478	1925±534	0.197
Nutrient intake				
Carbohydrate (%energy)	56.8±7.0	56.5±7.2	57.2±6.6	0.728
Total fat (%energy)	27.0±4.9	26.0±5.0*	27.2±4.7	0.030
Alcohol (%energy)	1.9±4.3	3.4±7.0***#	1.3±2.8	<0.001
Saturated fatty acid (%energy)	6.9±1.6	6.6±1.6*	7.0±1.6	0.054
Monounsaturated fatty acid (%energy)	9.6±1.9	9.3±1.9*	9.8±1.8	0.051
Polyunsaturated fatty acid (%energy)	7.1±1.5	6.8±1.5*	7.0±1.5	0.055
Total dietary fiber (g/1000kcal)	7.0±2.0	6.7±1.8*	6.6±2.2	0.080
Vitamin C (mg/1000kcal)	67.4±29.3	63.8±27.0	63.5±29.6	0.203
Calcium (mg/1000kcal)	304.6±98.0	292.0±90.4	285.8±91.5	0.118

The values are means ± SD or percentages.
*: $p<0.05$, **: $p<0.01$, ***: $p<0.001$ vs. Normal
#: $p<0.05$, ##: $p<0.01$, ###: $p<0.001$ vs. Support

として埼玉県済生会栗橋病院の倫理審査委員会で承認され、参加者からインフォームドコンセントを得て施行された。

結 果

1．3群間の生活習慣、臨床検査、栄養素摂取量の比較

対象者3群における生活習慣、臨床検査所見、栄養素摂取量は表1並び2に示す。対象者の分布はN、I、S群の順にそれぞれ男性で252名（20.5%）、422名（34.3%）、300名（24.4%）、女性で474名（54.0%）、255名（29.1%）、64名（7.3%）であった。男女ともにN群に比べ、I、S群はいずれも高齢で、肥満度が高く、心血管危険因子は不良であった。また、S群ではI群と比較し肥満度が高く、心血管危険因子は不良であった。

生活習慣に関しては、男性ではN群と比べS群で余暇に運動する割合が低く、食事摂取速度が速い者の割合が高かった。またN群と比較し、I群では仕事の運動強度が高く、I、S群ではいずれも喫煙率が高かった。I群と比べS群では仕事の強度が高い者の割合が低く、食事摂取速度の速い者の割合が高かった。女性ではN群と比べS群で食事摂取速度が速い者の割合が高く、I群で喫煙する者の割合が高率であった。I群とS群間の有意差はみられなかった。

栄養素摂取量に関して、男性ではN群と比べI、S群いずれにおいても多価不飽和脂肪酸摂取量、食物繊

表3 Comparison of selected nutrient intakes between each groups after adjusting for confounding factors

	Men			Women		
	Normal	Information	Support	Normal	Information	Support
Total fat(%energy)	23.5	23.5	23.5	26.7	26.7	26.7
Alcohol(%energy)	6.0	6.8	7.3*	2.3	2.6	1.5
Monounsaturated fatty acid(%energy)	8.4	8.4	8.4	9.5	9.5	9.6
Saturated fatty acid(%energy)	5.9	5.9	5.9	6.8	6.8	6.8
Polyunsaturated fatty acid(%energy)	6.3	6.3	6.3	7.0	7.0	7.0
Calcium(mg/1000kcal)	246.7	250.9	251.2	258.1	238.6	243.2
Vitamin C(mg/1000kcal)	49.9	48.9	49.3	51.6	47.4	48.2
Total dietary fiber(g/1000kcal)	5.7	5.6	5.7	6.9	6.8	6.8

*：$p<0.05$ vs. Normal

Variables included in models were : age, eating quickly, physically active during leisure time, physically active during work, smoking status, total fat, monounsaturated fatty acid, saturated fatty acid, polyunsaturated fatty acid, alcohol, calcium, vitamin C, and total dietary fiber in men ; and age, eating quickly, smoking status, total fat, monounsaturated fatty acid, saturated fatty acid, polyunsaturated fatty acid, total dietary fiber, and alcohol in women

表4 Odds ratios of life style behavior with their 95%confidence interval for 'Support' group between 'Information' group

Variables	Odds ratios(95%confidence interval)	
	Men	Women
Physically active during leisure time(Yes vs. No)	1.02(0.73-1.41)	0.87(0.49-1.55)
Physically active during work(Yes vs. No)	0.54(0.39-0.74)	0.83(0.45-1.54)
Eating quickly(Yes vs. No)	1.59(1.16-2.16)	1.13(0.63-2.04)

Variables included in models were : age, smoking status, alcohol intake, physically active during leisure time, physically active during work, and eating quickly in men; and age, smoking status, alcohol intake, menopause status, and eating quickly in women

維摂取量が有意に少なく、アルコール摂取量が有意に多かった。さらに、I群では総脂質摂取量、飽和脂肪酸摂取量、一価不飽和脂肪酸摂取量、ビタミンC摂取量、カルシウム摂取量が有意に少なかった。女性ではN群と比べI群で総脂質、飽和脂肪酸、一価不飽和脂肪酸、多価不飽和脂肪酸の各摂取量、食物繊維摂取量が有意に少なく、アルコール摂取量が有意に多かった。一方、女性でのみ、I群はS群と比べアルコール摂取量が有意に多かった。

2．3群間の多因子調整後の栄養素摂取量の比較

男性では、年齢、食事摂取速度、余暇の運動量、仕事の強度、喫煙、総脂質、飽和脂肪酸、一価不飽和脂肪酸、多価不飽和脂肪酸の各摂取量、食物繊維、ビタミンC、カルシウムの各摂取量で調整後のアルコール摂取量はS群でN群に比べ有意に多かった（表3）。総脂質摂取量、飽和脂肪酸、一価不飽和脂肪酸、多価不飽和脂肪酸の各摂取量、食物繊維、ビタミンC、カルシウムの各摂取量で同様の解析を行ったが、有意な結果は得られなかった。

女性では、年齢、食事摂取速度、喫煙、総脂質、飽和脂肪酸、一価不飽和脂肪酸、多価不飽和脂肪酸の各摂取量、食物繊維摂取量で調整後のアルコール摂取量には有意差を認めず、総脂肪、飽和脂肪酸、一価不飽和脂肪酸、多価不飽和脂肪酸の各摂取量、食物繊維摂取量も同様に有意差を認めなかった（表3）。一方、男女ともにI群とS群との間では栄養素摂取量に有意差は認められなかった。

3．情報提供群と比較した要支援群の生活習慣の特徴

男性では、I群と比較し食事摂取速度が速い、仕事の強度が低いことが、年齢、喫煙状況、食事摂取速度、

余暇の運動量、仕事の強度、アルコール摂取量から独立してS群であることに寄与していた（表4）。一方、同様の傾向は女性では認められなかった（表4）。

考察

本研究では特定健診における事後指導の有効性を予測する一手段として、既存の指導区分が、いかなる生活習慣の特徴を持つ集団を同定するかを調査した。その結果、男性では、要支援群は、肥満も心血管危険因子も持たない群と比べて、アルコール摂取量が多いこと、肥満はないが心血管危険因子を持つ群と比べると、食事摂取速度が速く、仕事の強度が低いことがその特徴として抽出された。しかし、これらの特徴は、女性では認められなかった。

生活習慣病やメタボリックシンドロームには食習慣が深く関係しており、健康日本21では脂肪エネルギー比率、塩分摂取量の目標が定められている[1]。本研究の集団では、総脂質摂取量は男性でいずれの群でも23%前後、女性で26%前後と、目標値とほぼ同程度と推定された。総脂質摂取量の上昇がインスリン抵抗性を上昇させるという報告[15]がある一方、脂質や炭水化物摂取量はメタボリックシンドロームと関係性が認められなかったとする報告[16]もある。特に脂質摂取量はBMIと正の相関があることが欧米の研究では示されている[17]が、中国の脂肪エネルギー比率が比較的低い集団（平均脂質摂取量は24.8%）においては同様の関係は認められず[18]、本研究において総脂質摂取量と支援強度の関係は認められなかった。また、各群間の肥満度に差があるにもかかわらず、総エネルギー摂取量に差は認められなかった。これは肥満度（BMI）が高い者ほど食事制限をしていること、肥満に対する社会の悪いイメージなどの要因により食事量を過小申告している[12-14]ことが影響している可能性があると考えられた。

栄養素に関して、総脂質、飽和脂肪酸、一価不飽和脂肪酸、多価不飽和脂肪酸の各摂取量、食物繊維、ビタミンC、カルシウム、アルコールの各摂取量において、心血管危険因子非合併非肥満情報提供群と心血管危険因子合併非肥満情報提供群あるいは要支援群との間の有意差が散見されたがいずれも心血管危険因子合併非肥満情報提供群、要支援群間で有意差は認められなかった。多因子補正後は、男性においてのみ要支援群において心血管危険因子非合併非肥満情報提供群と比べアルコール摂取量が高値であった。野菜や果物、未精製穀類、特にそれらの食品に含まれるビタミンC、ビタミンE、食物繊維等が抗酸化作用やインスリン抵抗性改善を介して、メタボリックシンドロームや心血管疾患、糖尿病のリスクを低下させることが多く報告されている[2][19]。本研究でも同様の食品や栄養素と心血管疾患危険因子との間の関係性を検討したが、期待した結果は得られなかった。

アルコール摂取量とメタボリックシンドロームや心血管疾患あるいはその危険因子との関係はJあるいはU型であり、少量から中等度の飲酒は有益であるとする報告が多くみられる[20]。そのメカニズムとしてHDLコレステロールの増加[21]、抗炎症作用[22]などが考えられている。逆に過量の飲酒では血清トリグリセライドの上昇[23]や血圧上昇[24]が示されており、有益な効果がみられる適正な飲酒量は各報告により様々である。アルコール摂取量と死亡率の関係を16のコホート研究と132の疫学研究のメタ解析で検討した報告では、男性は1日純アルコール10-19 g、女性で1日9 gまでで最も死亡率が低く、アルコール摂取量が増加するに従い死亡率が上昇することが示されている[25]。また、日本人の男性を対象とした同様の検討[26]から健康日本21では「節度ある適度な飲酒」として1日平均純アルコールで約20 g程度としている[27]。本研究では男性において要支援群でアルコール摂取量が多くなっていた。総摂取エネルギーを2000 kcal/日程度と仮定すると、純アルコールで1日当たり20 gを超過していると推定された。女性では男性と同様の推定を行うと、純アルコールで1日当たり4-7 g程度、といずれの群においても摂取量が少ないため、有意差が得られなかったのではないかと考えられた。

食事摂取速度については、男性において要支援群で心血管危険因子合併非肥満情報提供群と比較し摂取速度が速いことが独立因子であった。日本人における横断研究では、食事摂取速度とBMIの正の相関が示されているが[3][4]、本研究においてもそれに矛盾しない結果であった。食事摂取速度が速いと満腹感を感じる前に必要以上にエネルギーを摂取してしまう可能性が考

えられるが、本研究では摂取エネルギー量に有意差はみられず、肥満者における過小評価の影響が推察された。

仕事の強度に関して、男性の要支援群では心血管危険因子合併非肥満情報提供群と比較し強度が低いことが独立因子であった。精神的ストレスや仕事量増加は、肥満を引き起こす可能性が示唆されている[28]。一方、定期的な運動よりも労働や日常生活における身体活動量の方が健診成績や死亡率との関連が明らかであったとの報告がある[29]。今回使用した問診票では、定量的な活動量の把握が不可能であり、個人の主観に左右されるため、今後詳細な身体活動量の測定による検討が必要である。

特定健診・保健指導区分は、高リスク群を効率よく分類し、内臓脂肪型肥満に着目した早期介入、行動変容の指導を行うことで将来的な生活習慣病を予防しようとするものである。本研究では要支援群で心血管危険因子合併非肥満情報提供群と比較し、男性においてアルコール摂取量が多く、食事摂取速度が速く、仕事の強度が低かった。特に生活習慣の相違に関しては、肥満の有無を反映していると考えられ、要支援群では減量による保健指導の効果が期待できる可能性が高い者を鋭敏に抽出している可能性が示唆された。女性で有意差がみられなかったのは、要支援群に分類される者が少なく、男性と比べ1/5であったこと、生活習慣の性差が推察された。

今回使用した質問票BDHQは、食事記録法と比べて経済的・時間的負担が小さく、日間変動を考慮したつくりになっている等の長所がある反面、短所もある。摂取した内容に関する情報を直接得る方法でないため、妥当性研究を十分行う必要があるが、現時点では不十分である。そのため、得られた結果の解釈は慎重を期す必要がある。また、BDHQは、他の多くの食事アセスメント法と同様に全体的に過小申告を示す傾向があり[12]、この問題を考慮して、今回はエネルギー調整値を用いた。しかし、この方法にも問題が残されており、今回得られた結果の解釈には注意を要するものと考えられる。栄養素摂取量をいかに高い精度で推定できるかはこの種の研究の根幹であり、今後の課題である。

特定健診・保健指導区分が栄養摂取状況や運動習慣に与える影響を既存の人間ドック受診者のデータを用いて調査した。男性では、肥満があり心血管危険因子を持つ群、すなわち要支援群では肥満も心血管危険因子も持たない群と比べ平均アルコール摂取量が多かった。また、要支援群では、肥満がなく心血管危険因子を持つ群と比べると、食事摂取速度が速く、仕事の身体活動量が少なかった。本研究結果として示された保健指導区分間の食事・運動習慣の違いが、将来の動脈硬化性疾患発症にどう関与するのか、今後、追跡調査を行う予定である。

謝　辞

本研究に際し、データ管理等に尽力、協力くださった埼玉県済生会栗橋病院健診部・遠藤康弘先生、東京女子医科大学糖尿病センター・長谷川美彩氏に厚く御礼申し上げます。本研究の解析は、日本女医会、東京女子医科大学医師会、東京女子医科大学吉岡弥生研究奨励金、やずや食と健康研究所からの研究助成金の一部を使用して行われ、第51回日本糖尿病学会年次学術集会・東京において口演発表された。

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