Table 3. Odds Ratios of Prevalence of Abnormal Values for the Metabolic Parameters Classified by Fitness Level

Variable	Low-Fit	Mid-Fit OR	Mid-Fit 95% CI	High-Fit OR	High-Fit 95% CI
Hyperinsulinemia					
Model 1†		0.26	0.12-0.54*	0.20	0.09-0.44*
	Reference				
Model 2‡		0.35	0.16-0.78*	0.40	0.16-0.98*
High TC					
Model 1		1.42	0.71-2.84	0.89	0.44-1.79
	Reference				
Model 2		1.30	0.63-2.70	0.76	0.34-1.70
High TG					
Model 1		0.83	0.41-1.68	0.47	0.22-0.99*
	Reference				
Model 2		1.34	0.62-2.90	1.10	0.46-2.62
Low HDL-C					
Model 1		0.32	0.14-0.77*	0.17	0.06-0.48*
	Reference				
Model 2		0.35	0.14-0.86*	0.19	0.08-0.60*
Hypertension					
Model 1		0.56	0.28-1.14	0.31	0.15-0.66*
	Reference				
Model 2		0.79	0.37-1.69	0.56	0.24-1.34

NOTE. Values were derived from logistic regression model.
*$P < .05$
†Model 1 was adjusted for age.
‡Model 2 was adjusted for age and VFA.

groups. However, no significant differences were recognized in the prevalence of high TC and high TG among these groups.

Analysis for the Prevalence of Metabolic Abnormalities in Different Fitness Groups

In order to investigate the association between fitness level and the prevalence of any abnormality in the risk factors, either including or excluding the effect of VFA, multivariate logistic regression analysis using the following 2 models were performed; model 1 was adjusted for age, and model 2 was adjusted for age and VFA (Table 3).

The ORs for the prevalence of hyperinsulinemia calculated by model 1 were significantly lower both in the mid-fit group (OR = 0.26, 95% CI, 0.12 to 0.54) and in the high-fit group (OR = 0.20, 95% CI, 0.09 to 0.44) than in the low-fit group. After performing calculations using model 2, the ORs were also significantly lower in the mid-fit group (OR = 0.35, 95% CI, 0.16 to 0.78) and in the high-fit group (OR = 0.40, 95% CI, 0.16 to 0.98) than in the low-fit group. Regarding the prevalence of low HDL-C level, the ORs obtained from model 1 were significantly lower in the mid-fit group (OR = 0.32, 95% CI, 0.14 to 0.77) and in the high-fit group (OR = 0.17, 95% CI, 0.06 to 0.48) than in the low-fit group. The ORs obtained from model 2 were still significantly lower in the mid-fit group (OR = 0.35, 95% CI, 0.14 to 0.86) and in the high-fit group (OR = 0.19, 95% CI, 0.08 to 0.60) compared with that in the low-fit group. Regarding the prevalence of high TG and hypertension, the ORs obtained by model 1 were significantly lower (OR = 0.47, 95% CI, 0.22 to 0.99; OR = 0.31, 95% CI, 0.15 to 0.66, respectively) in the high-fit group compared with the low-fit group, whereas these significances disappeared after analyzing by model 2 (OR = 1.10, 95% CI, 0.46 to 2.62; OR = 0.56, 95% CI, 0.24 to 1.34, respectively). In contrast, ORs for the prevalence of high TC obtained by both models showed no significance in any groups.

A significant difference was observed in the rate of the patients with regular exercise among the 3 groups (Table 2); we therefore calculated the ORs for the prevalence of metabolic abnormality both in the exercise- and non-exercise groups using the same models. However, no significant difference was recognized in the ORs in the exercise group compared with that in the non-exercise group.

DISCUSSION

It has remained unclear whether cardiorespiratory fitness contributes to the risk factors independent of visceral fat, because most such studies tend to discuss these 2 predictors separately. Even in recent prospective studies investigating the effect of cardiorespiratory fitness to the risk factors and mortality,[13-15] neither VFA nor waist circumference was determined. Therefore, the first original point in the present study was that the cardiorespiratory fitness and VFA were simultaneously evaluated, and the contribution of cardiovascular fitness independent of VFA was investigated in each risk factor. The second original point in this study was that the investigation described above was performed in IGT and type 2 DM patients with a higher level of VFA, without any pharmacological therapy and any intervention. The mean VFA of the patients in this study was 161.9 ± 55.4 cm^2, which is 60% higher than the criteria for abdominal obesity (VFA ≥ 100 cm^2) used by the Japan Society for the Study of Obesity.[27] According to this criteria, 86.5% of the patients were diagnosed to have abdominal obesity. It is therefore of interest to clarify whether or not cardiorespiratory fitness is independent of VFA for the prevalence of metabolic abnormalities in such patients.

A middle and high level of fitness was found to be significantly associated with a low prevalence of hyperinsulinemia and low HDL-C without adjusting for VFA. A low prevalence of high TG and hypertension was also significantly associated with a high level of fitness. In addition, a remarkably low prevalence of hyperinsulinemia was still associated with the middle and high levels of fitness after adjusting for VFA. Especially in the prevalence of low HDL-C, the OR was linearly decreased as the fitness level increased. These results suggest that having more than a moderate level of fitness might be associated with a lower risk of both hyperinsulinemia and low HDL-C independent of VFA even in patients with a relatively higher VFA. However, it was speculated that the prevalence of hypertension might depend on VFA.

It should be pointed out that the subjects in this study had different pathological states such as IGT and type 2 DM. We confirmed the pathology-related difference in age and some metabolic variables between IGT and type 2 DM groups in each sex. However, as indicated in Table 2, the percentage of IGT/type 2 DM was not significantly different among the 3 groups classified by fitness level; we then interpreted that an adjustment for pathological state in the logistic regression model was not necessary.

Several reports support our results. Helmrich et al[28] confirmed in a prospective study that physical activity had a protective effect on the occurrence of type 2 DM adjusted for obesity, hypertension, and a parental history of diabetes. In addition, Lynch et al[29] indicated that moderately intense physical activities (5.5 metabolic units or greater) and cardiorespiratory fitness levels of greater than 31.0 mL/kg/min had a protective effect against type 2 DM in middle-aged men. These prospective studies similarly concluded that the effect of cardiorespiratory fitness was particularly strong in men who were at high risk for developing the disease.

Regarding the prevalence of hyperinsulinemia, some reports agree with our results. According to a prospective community study,[30] physical activity and cardiovascular fitness level were inversely associated with fasting insulin concentrations adjusted for waist circumference and the other confounders in nondiabetic men. In addition, an interventional study conducted by Poehlman et al[31] demonstrated that endurance training significantly enhanced glucose uptake without any change in VFA in non-obese women. Similar results in Japanese patients with type 2 DM were obtained in a study of aerobic and resistant programs, which found an improvement in insulin sensitivity without any significant change in BMI.[32] Considering these previous reports and our results, a strong association between fasting insulin level and cardiorespiratory fitness might thus exist independent of VFA.

However, the lipid profile results are more complicated. In cross-sectional studies, Hunter et al[33,34] showed that lipid profile was mainly associated with VFA, and slightly with physical activity. However, they did not determine cardiorespiratory fitness. Dvorak et al[35] indicated a significant association between lipid profile (TC, TG, TC to HDL-C ratio, and low-density lipoprotein cholesterol) and cardiorespiratory fitness rather than physical activity determined by a doubly labeled water method. Because this result was not adjusted for waist circumference, it might have included the effect of visceral fat or other factors. In interventional studies for obese subjects, Tremblay et al[36] reported that although the subjects remained obese after the intervention, cardiovascular exercise training caused favorable changes in their lipid profiles. Our results thus seem to be partially supported by the study because a significant contribution of fitness independent of VFA was only seen in the prevalence of low HDL-C among the lipid metabolism-related parameters. As the present study was cross-sectional study, a larger sample size and prospective and interventional studies are needed to confirm the effects of cardiovascular fitness on lipid metabolism independent of VFA.

We should mention some of the limitations of the present study. As cardiorespiratory fitness was indirectly determined, some errors in $\dot{V}o_{2max}$ could not be avoided. In addition, because the distribution of $\dot{V}o_{2max}$ was relatively narrow in the patients, the range of classification in this study became narrow and slightly shifted to a lower fitness level when compared to Japanese standard values.

In summary, it was suggested that a favorable cardiorespiratory fitness profile might be one of the predictors for a low prevalence of metabolic abnormalities (especially in hyperinsulinemia and low HDL-C) independent of VFA in Japanese patients with IGT and type 2 DM.

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REFERENCES

1. Fujioka S, Matsuzawa Y, Tokunaga K, et al: Contribution of intra-abdominal fat accumulation to the impairment of glucose and lipid metabolism in human obesity. Metabolism 36:54-59, 1987

2. DeNino WF, Tchernof A, Dionne IJ, et al: Contribution of abdominal adiposity to age-related differences in insulin sensitivity and plasma lipids in healthy nonobese women. Diabetes Care 24:925-932, 2001

3. Nagaretani H, Nakamura T, Funahashi T, et al: Visceral fat is a major contributor for multiple risk factor clustering in Japanese men with impaired glucose tolerance. Diabetes Care 24:2127-2133, 2001

4. Reaven GM: Banting Lecture 1988. Role of insulin resistance in human disease. Diabetes 37:1595-1607, 1988

5. Kaplan NM: The deadly quartet. Upper-body obesity, glucose intolerance, hypertriglyceridemia, and hypertension. Arch Intern Med 149:1514-1520, 1989

6. Alberti KGMM, Zimmet PZ, for the WHO Consultation: Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: Diagnosis and classification of diabetes mellitus, provisional report of a WHO consultation. Diabet Med 15: 539-553, 1998

7. Gautier JF, Mourier A, de Kerviler E, et al: Evaluation of abdominal fat distribution in noninsulin-dependent diabetes mellitus: Relationship to insulin resistance. J Clin Endocrinol Metab 83:1306-1311, 1998

8. Fujimoto WY, Bergstrom RW, Leonetti DL, et al: Metabolic and adipose risk factors for NIDDM and coronary disease in third-generation Japanese-American men and women with impaired glucose tolerance. Diabetologia 37:524-532, 1994

9. Boyko EJ, Fujimoto WY, Leonetti DL, et al: Visceral adiposity and risk of type 2 diabetes: A prospective study among Japanese Americans. Diabetes Care 23:465-471, 2000

10. Hayashi T, Boyko EJ, Leonetti DL, et al: Visceral adiposity and the risk of impaired glucose tolerance: A prospective study among Japanese Americans. Diabetes Care 26:650-655, 2003

11. Whaley MH, Kampert JB, Kohl HW 3rd, et al: Physical fitness and clustering of risk factors associated with the metabolic syndrome. Med Sci Sports Exerc 31:287-293, 1999

12. Carroll S, Cooke CB, Butterly RJ: Metabolic clustering, physical activity and fitness in nonsmoking, middle-aged men. Med Sci Sports Exerc 32:2079-2086, 2000

13. Wei M, Kampert JB, Barlow CE, et al: Relationship between low cardiorespiratory fitness and mortality in normal-weight, overweight, and obese men. JAMA 27:1547-1553, 1999

14. Wei M, Gibbons LW, Mitchell TL, et al: The association between cardiorespiratory fitness and impaired fasting glucose and type 2 diabetes mellitus in men. Ann Intern Med 130:89-96, 1999

15. Wei M, Gibbons LW, Kampert JB, et al: Low cardiorespiratory fitness and physical inactivity as predictors of mortality in men with type 2 diabetes. Ann Intern Med 132:605-611, 2000

16. Kumagai S, Tanaka H, Kitajima H, et al: Relationships of lipid and glucose metabolism with waist-hip ratio and physical fitness in obese men. Int J Obesity 17:437-440, 1993

17. Brochu M, Tchernof A, Dionne IJ, et al: What are the physical

characteristics associated with a normal metabolic profile despite a high level of obesity in postmenopausal women? J Clin Endocrinol Metab 86:1020-1025, 2001

18. Delvaux K, Philippaerts R, Lysens R, et al: Evaluation of the influence of cardiorespiratory fitness on diverse health risk factors, independent of waist circumference, in 40-year-old Flemish males. Obes Res 8:553-558, 2000

19. Batty GD, Shipley MJ, Marmot M, et al: Physical activity and cause-specific mortality in men with type 2 diabetes/impaired glucose tolerance: Evidence from the Whitehall study. Diabet Med 19:580-588, 2002

20. Kuzuya T, Nakagawa S, Satoh J, et al: Report of the Committee on the Classification and Diagnostic Criteria of Diabetes Mellitus. Diabetes Res Clin Pract 55:65-85, 2002

21. Brozek J, Henschel A: Techniques for Measuring Body Composition. Washington, DC, National Academy of Science-National Research Council, 1961, p 300

22. Tokunaga K, Matsuzawa Y, Ishikawa K, et al: A novel technique for the determination of body fat by computed tomography. Int J Obesity 7:437-445, 1983

23. Åstrand PO, Rhyming I: A nomogram for calculation of the aerobic capacity (physical fitness) from pulse rate during submaximal work. J Appl Physiol 7:218-221, 1954

24. Hata Y, Mabuchi H, Saito Y, et al: Report of the Japan Atherosclerosis Society (JAS) Guidelines for Diagnosis and Treatment of Hyperlipidemia in Japanese Adults. J Atheroscler Thromb 9:1-27, 2002 (in Japanese)

25. Saruta T: The Japanese new guideline for the management of hypertension: Background of its preparation and characteristics of the new guideline. Nippon Rinsho 59:837-840, 2001 (in Japanese)

26. Tamakoshi K, Yatsuya H, Kondo T, et al: The metabolic syndrome is associated with elevated circulating C-reactive protein in healthy reference range, a systemic low-grade inflammatory state. Int J Obes Relat Metab Disord 27:443-449, 2003

27. Matsuzawa Y, Inoue S, Ikeda Y, et al: The new criteria for obesity and diagnostic criteria for syndrome of obesity. J Jpn Soc Study Obesity 6:18-28, 2000 (in Japanese)

28. Helmrich SP, Ragland DR, Leung RW, et al: Physical activity and reduced occurrence of non-insulin-dependent diabetes mellitus. N Engl J Med 325:147-152, 1991

29. Lynch J, Helmrich SP, Lakka TA, et al: Moderately intense physical activities and high levels of cardiorespiratory fitness reduce the risk of non-insulin-dependent diabetes mellitus in middle-aged men. Arch Intern Med 156:1307-1314, 1996

30. Kriska AM, Hanley AJ, Harris SB, et al: Physical activity, physical fitness, and insulin and glucose concentrations in an isolated native Canadian population experiencing rapid lifestyle change. Diabetes Care 24:1787-1792, 2001

31. Poehlman ET, Dvorak RV, DeNino WF, et al: Effects of resistance training and endurance training on insulin sensitivity in nonobese, young women: A controlled randomized trial. J Clin Endocrinol Metab 85:2463-2468, 2000

32. Taniguchi A, Fukushima M, Sakai M, et al: Effect of physical training on insulin sensitivity in Japanese type 2 diabetetic patients: Role of serum triglyceride levels. Diabetes Care 23:857-858, 2000

33. Hunter GR, Kekes-Szabo T, Treuth MS, et al: Intra-abdominal adipose tissue, physical activity and cardiovascular risk in pre- and post-menopausal women. Int J Obesity 20:860-865, 1996

34. Hunter GR, Kekes-Szabo T, Snyder SW, et al: Fat distribution, physical activity, and cardiovascular risk factors. Med Sci Sports Exerc 29:362-369, 1997

35. Dvorak RV, Tchernof A, Starling RD, et al: Respiratory fitness, free living physical activity, and cardiovascular disease risk in older individuals: A doubly labeled water study. J Clin Endocrinol Metab 85:957-963, 2000

36. Tremblay A, Doucet E, Imbeault P, et al: Metabolic fitness in active reduced-obese individuals. Obes Res 7:556-563, 1999

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Association between Relative Hypogonadism and Metabolic Syndrome in Newly Diagnosed Adult Male Patients with Impaired Glucose Tolerance or Type 2 Diabetes Mellitus

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ABSTRACT

Sex steroid hormones are known to be important regulators of the lipid and glucose metabolism. Lower levels of testosterone (T) or sex hormone-binding globulin (SHBG) have been reported in men with type 2 diabetes. On the other hand, the relationship between relative hypogonadism and metabolic syndrome has not yet to be thoroughly studied. Ninety-eight Japanese adult (age 20–64) male patients with impaired glucose tolerance (IGT) or type 2 diabetes mellitus were divided into either an metabolic syndrome group (n = 42) or a non–metabolic syndrome (n = 56) group according to the definition of metabolic syndrome from WHO, or into three tertiles according to their sex hormone index level. The metabolic syndrome group had a significantly lower T/estradiol (E_2) and SHBG level ($p < 0.01$). The age and subcutaneous fat surface area (SFA) were significantly different within the tertiles in SHBG and T/E_2. Logistic regression analyses were performed to investigate the association between the sex steroid hormone index level and the incidence of metabolic syndrome. Regarding the highest tertiles as a criterion, lower SHBG, T/E_2 or free T/E_2 had a higher odds ratio of prevalence of metabolic syndrome even after adjusting for age and SFA. Relative hypogonadism was strongly associated with the prevalence of metabolic syndrome in Japanese adult men who were newly diagnosed to have IGT or type 2 diabetes.

INTRODUCTION

VISCERAL FAT ACCUMULATION,[1,2] a low level of cardiorespiratory fitness,[3,4] and hypogonadism[5,6] have all been recognized as risk factors for males with coronary heart disease (CHD) and/or type 2 diabetes mellitus. We recently reported cardiorespiratory fitness to be associated with such factors as hyperinsulinemia and a low level of high-density lipoprotein–cholesterol (HDL-c),[7] or the clustering of these risk factors[8] in a group of newly diagnosed Japanese patients with impaired glucose tolerance (IGT) or type 2 diabetes independent of visceral fat accumulation. In the current study, we furthermore investigated the contribution of sex steroid hormones together with visceral fat and cardiorespiratory fitness in the same

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cohort but using only patients ranging in age from 20 to 64 years old.

These risk factors of metabolic impairment—such as "syndrome X"[9] and "the deadly quartet"[10]—have been described in numerous studies. In 1998, the World Health Organization (WHO) defined metabolic syndrome (MS)[11] as a concurrence of disturbed glucose and insulin metabolism, overweight and abdominal fat distribution, mild dyslipidemia, and hypertension, in order to promote the research and clinical application of this important syndrome. This syndrome also used to be called insulin resistance syndrome because insulin resistance was believed to be the most important pathogenesis and this syndrome is also associated with the subsequent development of type 2 diabetes mellitus as well as cardiovascular disease (CVD),[12,13] which has been reported to be the primary cause of mortality and morbidity in patients with type 2 diabetes.[14] We used the MS definition established by WHO in this study.

In addition to hypertension, hyperlipidemia, and smoking,[15,16] male sex is also an independent risk factor for CVD.[17] Sex steroid hormones were important regulators of the lipid and glucose metabolism and lower levels of testosterone (T) or sex hormone-binding globulin (SHBG), the major serum carrier protein for T, have been reported in men with type 2 diabetes.[18–21] In addition, a population-based prospective study of subjects above the age of 55 with an 8% prevalence of diabetes found an independent inverse association between the levels of T and aortic atherosclerosis in men.[22] Hyperinsulinemia, which is induced by insulin resistance and is a risk factor for CVD,[23] is associated with low concentrations of free and total T in men.[24,25] For any given level of generalized or regional adiposity, men with type 2 diabetes have a significantly higher degree of insulin resistance than non-diabetics.[26] Low plasma levels of free testosterone (FT) are also observed in obesity, particularly in abdominal obesity, a condition that is itself independently accompanied by insulin resistance and heightened risk for type 2 diabetes.[27,28] Compared to men with normal concentrations of T, men with low concentrations of T have a significantly higher body mass index (BMI), waist-to-hip ratio (W/H), as well as systolic blood pressure (SBP), fasting and postprandial plasma glucose concentrations, and fasting serum insulin and total cholesterol (TC) concentrations.[24] Furthermore, the administration of T to hypogonadal rats[29] or humans[30] has resulted in reductions of both abdominal obesity and insulin resistance.

Although the mechanisms underlying the association between hypogonadism and type 2 diabetes are still not entirely understood, it has been postulated that low plasma levels of both SHBG and T contribute to the development of obesity, which, in turn, predisposes such individuals to develop insulin resistance[25,31–37] and, through this effect, to the development of complex metabolic abnormalities that lead to type 2 diabetes in men.[38] On the other hand, the relationship between relative hypogonadism and MS, the cluster of abdominal obesity, glucose and lipid abnormalities, and hypertension, has yet to be thoroughly studied. To our knowledge, only Laaksonen et al.[39] recently reported lower T and SHBG levels in subjects with MS from a population-based study. The comparison of non-diabetic MS versus non-MS subjects in that study is thought to be an appropriate method to study the relationship between relative hypogonadism and MS. However, non-diabetics seldom meet the diagnostic criteria of MS. In addition, the relationship between relative hypogonadism and MS in subjects with abnormal glucose tolerance remains to be unclear. In view of these findings, in the current study, we cross-sectionally investigated 98 Japanese adult men who were newly diagnosed to have IGT or type 2 diabetes mellitus and had not previously received either any pharmaceutical treatment or behavior modifying intervention, in order to assess the contribution of relative hypogonadism on the prevalence of MS.

MATERIALS AND METHODS

Ninety-eight Japanese men, aged 20–64, who were newly diagnosed to have IGT or type 2 diabetes mellitus and had not previously received either any pharmaceutical treatment or behavior modifying intervention, were enrolled in this study, which was ap-

proved by the Ethics Committee at Kyushu University (Fukuoka, Japan). All of the patients were diagnosed as having IGT (n = 27) or type 2 diabetes mellitus (n = 71) by a 75-g oral glucose tolerance test (OGTT) in Chikushi Hospital, Fukuoka University (Fukuoka, Japan). None of them were taking any medications at the entry point to the study.

After giving their written informed consent to participate, all subjects were examined for OGTT, sex steroid hormones, lipid metabolic indices, abdominal visceral (VFA) and subcutaneous fat surface areas (SFA) which were automatically calculated by a computer system connected to a computerized tomography (CT) scan (VIGOR LAU DATOR, Toshiba, Japan) as described by Tokunaga et al.,[40] and also underwent anthropometric measurements as well as a cardiorespiratory fitness test by a cycle ergometer. Weight to the nearest 0.1 kg, height to the nearest 0.1 cm, and waist and hip circumferences were measured at the umbilical level and the greatest protruberance of the buttocks, respectively. The resting SBP and diastolic blood pressure (DBP) were determined three times following a 30-min rest period using a mercury sphygmomanometer, and the lowest values were used as their resting blood pressure. Graded exercise tests using a cycle ergometer (Monark Co. Ltd., Stockholm, Sweden) were performed to evaluate the cardiorespiratory fitness by a skilled-identical examiner. The heart rate, electro-cardiograms and blood pressure were all monitored and recorded during the test. The exercise intensity increased three or four times every 4-min until their heart rate reached 70% of the heart rate max or above. The maximal oxygen uptake ($\dot{V}O_2$max) was predicted by an Åstrand and Rhyming nomogram,[41] a modality that is generally used to predict the $\dot{V}O_2$max, which is regarded as an index of cardiovascular fitness. The sex steroid hormones measured included T, FT, estradiol (E_2), dehydroepiandrosterone–sulfate (DHEA-S), and SHBG. Lipid profile was measured in TC, HDL-c, and triglyceride (TG). The concentrations of TC and TG were determined by the enzyme method. The HDL-c was quantitated using the heparinmanganese precipitation method. Fasting insulin (FIRI) was measured by a radioimmunoassay using IRI kits (Pharmasia, Uppsala, Sweden). E_2, T, FT, and DHEA-S were measured by a radioimmunoassay technique using commercial kits (DPC, Los Angeles, CA). SHBG was measured by an immunoradiometric assay technique using a SHBG [^{125}I] assay kit (Farmous Daiagnostica, Oulunsalo, Finland). HOMA-IR, the index for insulin resistance, was calculated from the fasting blood glucose and insulin concentrations by the formula: HOMA-IR = FIRI (μU/mL) × fasting blood glucose (FBG) (mmol/L)/22.5.[42,43]

Using the WHO diagnosis criterion[11] (FBG ≥ 110 mg/dL and at least two of the following: waist-hip ratio (W/H) > 0.90; TG ≥ 150 mg/dL or HDL-c < 35 mg/dL; blood pressure ≥ 140/90 mm Hg) for MS, the participators were divided into an MS group and a non-MS group. The difference between MS group and non-MS group was compared by the unpaired t-test. Differences in anthropometry, glucose or lipid metabolism, blood pressure, cardiorespiratory fitness were assessed by one-way ANOVA with *post hoc* comparisons made using Fisher's PLSD test, in equally divided three tertiles of each sex steroid hormone index. Regarding the MS diagnosis as the dependent variable, logistic regression was performed to assess the odds ratios (ORs) and confidence interval (CI) of every level in every sex steroid hormone index. Age and SFA—the parameters that show difference in ANOVA tests in most indices—were added into the model as adjustment factors.

As the calculated FT (CFT) using T and SHBG values was recently reported to be more accurate than a radioimmunoassay-measured FT, we duplicated the analyses concerning FT using the CFT.

All data are presented as the mean ± SE and all statistical analyses were performed using StatView 5.0 software (SAS Institute, Cary, NC). All p values were two-tailed, and statistical significance was defined as $p < 0.05$.

RESULTS

The subjects ranged in age from 20 to 64 years old. Teenagers and elderly men older than 64 were not enrolled in this study. The

anthropometric and metabolic characteristics of the 98 men are summarized in Table 1. According to the diagnosis criterion, 42 subjects were classified into the MS group, and 56 subjects were classified as non-MS. Compared with the non-MS group, the MS group had a significantly higher waist-to-hip ratio, resting blood pressure (both SBP and DBP), TC, TG, FBG, FIRI, HOMA-IR, VFA and SFA, but a significantly lower $\dot{V}O_2$max, HDL-C, SHBG, and T/E_2. The radioimmunoassay-measured FT (MS vs. non-MS: 16.23 ± 0.99 pg/mL vs. 16.10 ± 0.69 pg/mL) demonstrated different values than the CFT (MS vs. non-MS: 10.36 ± 0.43 ng/dL vs. 9.91 ± 0.38 ng/dL) in value. No significant difference was found in indices concerning FT or CFT between the two groups. Compared with the IGT group, the type 2 diabetes group had a significantly higher blood glucose indices, HOMA-IR, and the clustering of MS risk factors. No significant difference was found in age, W/H, blood pressure, $\dot{V}O_2$max, TC, HDL-C, TG, FIRI, VFA, SFA, or any sex steroid hormone indices.

Among sex steroid hormone indices, only E_2 ($r = 0.353$, $p = 0.0003$) and T/E_2 ($r = -0.241$, $p = 0.0165$), but not T ($r = -0.028$, $p = 0.7861$), FT ($r = 0.089$, $p = 0.3839$), CFT ($r = 0.154$, $p = 0.1305$), DHEA-S ($r = 0.082$, $p = 0.4226$), SHBG ($r = -0.188$, $p = 0.0636$), FT/E_2 ($r = -0.188$, $p = 0.0639$), or CFT/E_2 ($r = -0.196$, $p = 0.0533$), were significantly correlated with BMI.

Within each sex steroid hormone index, 98 patients were consecutively divided into three tertiles, high, medium or low, 31–34 patients in each tertile. Differences in anthropometry, glucose or lipid metabolism, blood pressure and cardiorespiratory fitness among tertiles of each index were assessed using one-way ANOVA tests. When ANOVA tests showed a significant difference, *post hoc* comparisons using Fisher's PLSD tests were additionally conducted. The comparison results are shown in Table 2. Age was significantly different among tertiles of SHBG or T/E_2. FIRI was different among tertiles of T/E_2. SFA was significantly different among tertiles of SHBG, T/E_2 or FT/E_2. No difference was found among tertiles of E_2 or T, and within FT and DHEA-S, only age showed a difference among the three tertiles (data not show).

In order to investigate the association between the sex steroid hormone index level and the prevalence of MS, multivariate logistic re-

TABLE 1. ANTHROPOMETRIC AND METABOLIC CHARACTERISTICS IN THE METABOLIC SYNDROME (MS) AND NON–METABOLIC SYNDROME (NON–MS) GROUPS

	MS (n = 42)	*non-MS (n = 56)*	*p*
Age (years)	49.21 ± 1.23	51.14 ± 1.13	0.2545
W/H	0.96 ± 0.01	0.93 ± 0.01	0.0101[a]
$\dot{V}O_2$max (mL/kg/min)	32.14 ± 0.69	35.92 ± 0.68	0.0002[a]
SBP (mm Hg)	135.31 ± 2.82	126.36 ± 1.89	0.0075[a]
DBP (mm Hg)	87.50 ± 1.82	80.04 ± 1.11	0.0004[a]
TC (mg/dL)	224.19 ± 5.52	209.16 ± 4.69	0.0401[a]
HDL-C (mg/dL)	45.19 ± 1.83	52.68 ± 1.70	0.0038[a]
TG (mg/dL)	200.86 ± 12.95	122.38 ± 10.18	<0.0001[a]
FBG (mg/dL)	151.81 ± 5.45	131.50 ± 4.33	0.0040[a]
FIRI (μU/mL)	8.19 ± 1.09	5.29 ± 0.35	0.0056[a]
HOMA-IR	3.21 ± 0.51	1.67 ± 0.10	0.0011[a]
VFA (cm^2)	185.68 ± 7.07	143.898 ± 6.863	<0.0001[a]
SFA (cm^2)	158.94 ± 10.93	132.27 ± 8.95	0.0600
E_2 (pg/mL)	26.33 ± 1.51	22.55 ± 1.47	0.0810
T (ng/dL)	437.88 ± 17.95	471.50 ± 17.40	0.1889
FT (pg/mL); CFT(ng/dL)	16.23 ± 0.99; 10.36 ± 0.43	16.10 ± 0.69; 9.91 ± 0.38	0.9126; 0.4314
DHEA-S (ng/mL)	1914.31 ± 142.13	1905.41 ± 117.13	0.9613
SHBG (nmol/L)	26.62 ± 1.78	34.20 ± 1.98	0.0071[a]
T/E_2	18.78 ± 1.25	25.92 ± 1.91	0.0045[a]
FT/E_2; CFT/E_2	0.69 ± 0.06; 0.45 ± 0.03	0.88 ± 0.07; 0.54 ± 0.04	0.0562; 0.0959

Values are the mean ± SE.
[a]Significantly different between MS and non-MS, $p < 0.05$.

TABLE 2. DIFFERENCE AMONG THE TERTILES OF EACH SEX STEROID HORMONE INDEX

	SHBG			*T/E₂*			*FT/E₂*		
	High	*Medium*	*Low*	*High*	*Medium*	*Low*	*High*	*Medium*	*Low*
Age	54.0 ± 1.2	52.0 ± 1.2	45.1 ± 1.4[a,b]	52.9 ± 1.1	51.2 ± 1.3	46.7 ± 1.7[a,b]	50.9 ± 1.4	49.8 ± 1.4	50.2 ± 1.6
W/H	0.9 ± 0.0	0.9 ± 0.0	0.9 ± 0.0	0.9 ± 0.0	0.9 ± 0.0	1.0 ± 0.0	0.9 ± 0.0	0.9 ± 0.0	0.9 ± 0.0
$\dot{V}O_2$max	35.0 ± 0.9	34.9 ± 1.1	33.1 ± 0.7	35.0 ± 0.9	35.1 ± 1.0	32.8 ± 0.8	36.0 ± 0.9	33.2 ± 0.9	33.6 ± 0.9
SBP	127.4 ± 2.7	131.7 ± 3.1	131.5 ± 3.0	125.9 ± 2.6	132.1 ± 2.9	132.9 ± 3.1	123.4 ± 2.4	136.3 ± 2.9[a]	130.9 ± 3.0
DBP	80.8 ± 1.5	83.0 ± 1.8	85.8 ± 2.1	81.3 ± 1.5	82.9 ± 1.8	85.6 ± 2.2	80.2 ± 1.7	86.8 ± 1.7[a]	82.8 ± 2.0
TC	204.9 ± 6.9	216.4 ± 6.4	225.2 ± 5.1	204.2 ± 6.1	230.9 ± 6.2[a]	212.4 ± 5.8[b]	208.1 ± 5.9	226.8 ± 5.5	211.8 ± 7.1
HDL-C	52.3 ± 2.6	46.8 ± 2.2	49.1 ± 2.0	52.2 ± 2.7	46.6 ± 1.9	49.5 ± 1.9	52.8 ± 2.5	46.9 ± 2.2	48.8 ± 2.0
TG	130.0 ± 14.7	159.3 ± 15.6	178.3 ± 15.3	148.5 ± 16.1	163.2 ± 15.0	156.8 ± 15.5	154.2 ± 15.9	167.2 ± 15.7	146.3 ± 14.9
FBG	132.6 ± 4.9	133.0 ± 5.2	154.1 ± 7.2[a,b]	141.0 ± 6.0	140.4 ± 6.2	139.1 ± 6.4	144.5 ± 7.9	142.6 ± 4.7	133.3 ± 5.2
FIRI	5.4 ± 1.1	6.4 ± 0.7	7.7 ± 0.8	5.9 ± 1.1	5.3 ± 0.4	8.3 ± 0.9[b]	5.7 ± 0.8	7.6 ± 1.2	6.3 ± 0.6
VFA	147.5 ± 10.6	165.0 ± 10.0	172.8 ± 6.7	151.5 ± 10.1	156.1 ± 7.0	178.5 ± 9.9	148.9 ± 8.6	168.9 ± 9.5	167.8 ± 9.5
SFA	129.3 ± 12.7	133.0 ± 9.0	167.4 ± 13.1[a,b]	122.7 ± 12.1	133.7 ± 7.4	176.0 ± 14.2[a,b]	117.8 ± 6.8	162.6 ± 16.3[a]	150.9 ± 10.2

[a]Significantly different from the high tertile of the same index.
[b]Significantly different from the medium tertile of the same index.

gression analyses using the following two models were performed: model 1, adjusted for age; and model 2, adjusted for age and SFA, the two parameters that showed differences in more than two sex steroid hormone indices based on the ANOVA tests.

The odds-ratios for the prevalence of MS calculated by the model 1 were significantly higher both in the low tertile of SHBG (OR, 4.59; 95% CI, 1.44–14.63), T/E_2 (OR, 3.29; 95% CI, 1.13–9.57), FT/E_2 (OR, 3.10; 95% CI, 1.07–8.97) and in the medium tertile of FT/E_2 (OR, 3.69; 95% CI, 1.29–10.61) than that in the high tertile of each index. After additionally adjusting for SFA in the model 2 (Fig. 1), the odds-ratios continued to be significantly higher in the low tertile of SHBG (OR, 4.60; 95% CI, 1.43–14.86) and in the medium tertile of FT/E_2 (OR, 3.28; 95% CI, 1.10–9.73) than that in the high tertile of each index. The odds-ratios of the low tertiles of T/E_2 (OR, 2.94; 95% CI, 0.98–8.75; $p = 0.053$) and FT/E_2 (OR, 2.82; 95% CI, 0.95–8.32; $p = 0.061$) had a borderline significance. The 90% CI of odds-ratios for the prevalence of MS calculated by model 2 showed significantly for low tertiles of T/E_2 (OR, 2.94; 90% CI, 1.17–7.34) and FT/E_2 (OR, 2.82; 90% CI, 1.13–6.99). No similar results were observed in T, FT, E_2, or DHEA-S. The percentage of IGT/type 2 DM was not significantly different among the three groups classified by SHBG (high, medium, low—11/22, 8/23, 8/23), T/E_2 (high, medium, low—10/24, 8/24, 9/23), or FT/E_2 (high, medium, low—11/22, 7/26, 9/23) level.

DISCUSSION

In this epidemiological study, the relative hypogonadism seen in Japanese adult men who were newly diagnosed with IGT or type 2 diabetes mellitus, which had not yet been treated by either any pharmaceutical therapy or behavior modifying intervention, was found to be strongly associated with the prevalence of MS. We have reported that regardless of visceral fat accumulation, cardiorespiratory fitness was associated with such individual factors as hyperinsulinemia and low HDL-c,[7] or the clustering of MS risk factors[8] in the same cohort. Among three tertiles of different sex hormone indices, visceral adiposity and cardiorespiratory fitness were not different from each other. Relative hypogonadism was found to be associated with the prevalence of MS independent of age and SFA. MS has been reported to be associated

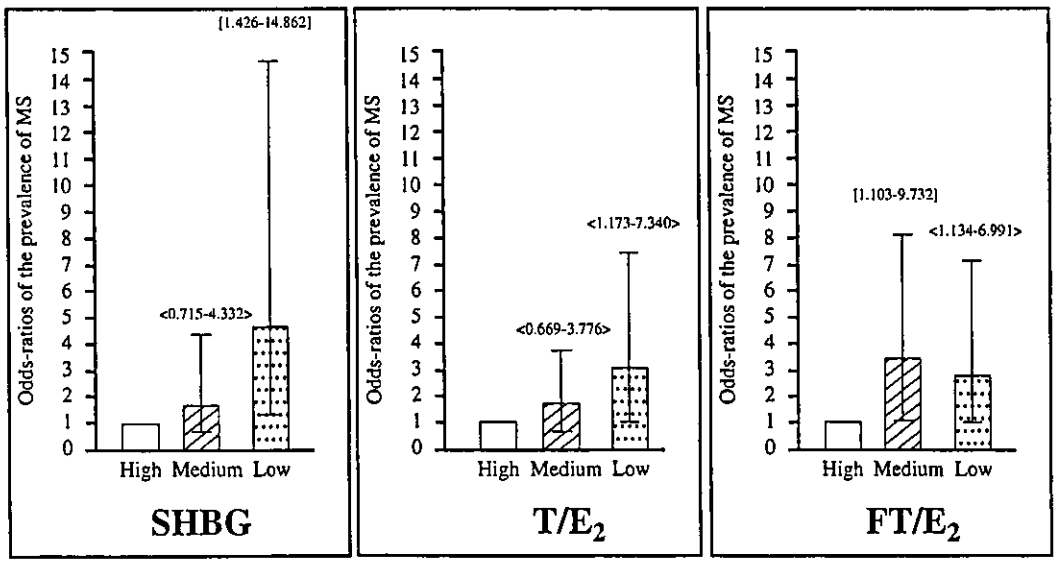

FIG. 1. Model 2. Odds-ratios of the prevalence of metabolic syndrome for each sex hormone tertile after adjusting for age and SFA. [#]; 95% CI; <#>: 90% CI.

with the development of type 2 diabetes[12,13] and relative hypogonadism was found in patients with type 2 diabetes.[18–21] The characteristic cohort here is ideal for verifying the contribution of the sex hormone index level to MS, and it also made it easier for us to investigate such interrelationships with less confounding. The subjects in this study had different pathological states such as IGT and type 2 diabetes. Compared with the IGT group, the type 2 diabetes group had a significantly higher blood glucose indices, HOMA-IR, and the clustering of MS risk factors. No significant difference was found in age, W/H, blood pressure, $\dot{V}O_2$max, TC, HDL-C, TG, FIRI, VFA, SFA, or any sex steroid hormone indices. The ratio of IGT/type 2 diabetes was not significantly different among the three groups classified by SHBG, T/E_2, or FT/E_2 level. We then interpreted that an adjustment for pathological state in the logistic regression model was not necessary.

Regarding the highest tertiles as criterion, lower SHBG, T/E_2 or FT/E_2 had a higher OR of prevalence of MS even after adjusting for age and SFA.

Sex steroid hormones have been reported to be important regulators of glucose and lipid metabolism. Lower levels of T or SHBG have been reported in men with type 2 diabetes.[18–21] Several prospective studies have shown that low levels of T and SHBG predict the development of type 2 diabetes in middle-aged men.[44,45] Hyperinsulinemia is associated with low concentrations of free and total T in men.[24,25]

Sex steroids modulate the action of insulin and influence body fat distribution by their effects on lipoprotein lipase (LPL) activity. The fasting adipose tissue LPL activity was found to correlate inversely with the plasma E_2 levels, consistent with E_2 being a negative regulator of adipose tissue LPL activity.[46] Such action of E_2 on the lipid metabolism therefore opposes that of insulin, whose effects on adipose tissue are anabolic, thus promoting energy storage. Androgens also play a role in the regulation of LPL activity. In a study by Iverius et al.,[46] the adipose tissue LPL activity positively correlated with the plasma FT levels, thus suggesting that T action is opposite that of E_2. A study of T substitution in hypogonadal male subjects showed a marked increase in LPL and the hepatic lipase activities.[47] This suggests that androgens play a physiological role in the regulation of triacylglycerol metabolism by maintaining the LPL activity and, like insulin, thus promoting anabolism.

Compared with lean controls, obesity in male patients is associated with relative hypogonadism.[25] Visceral obesity is believed to be associated more closely with insulin resistance than subcutaneous obesity does and abdominal obesity has been listed into the diagnosis criterion of MS. Visceral obesity is well recognized to be the characteristic for men as well as subcutaneous obesity for women. The administration of T in men reduced W/H[48] or visceral adiposity,[49,50] while it decreases the blood glucose level and improves insulin resistance,[48–50] thus suggesting that T plays a role in maintaining normal insulin resistance at physiological levels.[51] T replacement in men (or E_2 therapy in postmenopausal women) is known to decrease the visceral adipose tissue LPL activity.[50,52]

Relatively little is known regarding the influence of sex steroids on blood pressure. Both SBP and DBP significantly increase following the onset of menopause,[53–55] and the administration of E_2 to normotensive postmenopausal women tended to reduce the 24-h ambulatorily monitored blood pressure.[56–63] A lower level of circulating T has been reported in hypertensive men.[64–66] According to the data from Mårin et al.,[49,50] DBP decreased after T treatment in men. In view of the specific decrease of visceral fat mass in these studies, visceral adipose may mediate within the regulation of T on blood pressure. On the other hand, it was reported that T may elevate the blood pressure by altering the levels of endothelin-1[67] or catecholamines.[68]

MS is a syndrome consisting of a disturbed glucose and insulin metabolism, abdominal obesity, dyslipidemia, and hypertension. However, in the current study, rather than E_2, T or FT, which showed a relationship with individual component of MS, T/E_2 and FT/E_2, as well as SHBG, all showed a strong correlation with the incidence of MS, even after adjusting for age and SFA. Considering the fact that MS is a syndrome based on a disturbed glucose and

nsulin metabolism, the results in this study are in line with the finding that T/E_2 is associated with insulin in normal,[69,70] obese adult men,[35] or adult male patients with myocardial infarction[33] or coronary artery disease.[71] T/E_2 has also been reported to correlate more strongly than T with the insulin area, glucose area, and the ratio of insulin area-to-glucose area in the glucose tolerance test in non-obese men.[32] We duplicated the same statistical analyses used in the current study in a male cohort with normal glucose tolerance, SHBG but not FT/E_2 predicted the clustering of the MS risk factors (unpublished data). Therefore, in addition to SHBG, the balance of androgen and estrogen, rather than any individual sex hormones, plays an important role in the prevalence of abnormal glucose tolerance or MS in adult men.

There are some limitations in the current study. First, a part of the findings concerning FT in present study were based on the measurement of FT using a radioimmunoassay technique. This assay method of FT is still widely used in the worldwide[72] but has recently been reported to be inaccurate.[72–75] In view of this, we duplicated the same analysis using the CFT, an index calculated from T and SHBG concentrations which was reported to be reliable.[73] We duplicated the logistic regression analysis concerning FT/E_2 using the CFT. Unfortunately, although the CFT significantly correlated with the FT measured by direct assay ($r = 0.522$, $p < 0.0001$), and the odds-ratios calculated by the CFT showed a similar tendency (medium, 2.058; low, 1.456), the confidence interval of these odds-ratios (medium, 0.875–4.842; low, 0.614–3.454, 90%CI) were not statistically significant. Secondly, as cardiorespiratory fitness was indirectly determined, the accuracy of the determination might affect the result even in study made on such a scale. Thirdly, a cross-sectional model is not a powerful enough model to investigate the relationship between relative hypogonadism and the development of MS. We carried out a 1-year-last interventional to study the same relationship from a dynamic state. The results of the interventional study are expected to strengthen the findings reported herein.

In conclusion, in Japanese adult men who were newly diagnosed to have IGT or type 2 diabetes mellitus and had not accepted any pharmaceutical treatment or behavior rectifying intervention, lower T/E_2, FT/E_2, or SHBG, a relative hypogonadism status was found to be strongly associated with the prevalence of MS.

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REFERENCES

1. Lebovitz HE. The relationship of obesity to the metabolic syndrome. *Int J Clin Pract Suppl* 2003;134:18–27.
2. Nagaretani H, Nakamura T, Funahashi T, et al. Visceral fat is a major contributor for multiple risk factor clustering in Japanese men with impaired glucose tolerance. *Diabetes Care* 2001;24:2127–2133.
3. Whaley MH, Kampert JB, Kohl HW III, et al. Physical fitness and clustering of risk factors associated with the metabolic syndrome. *Med Sci Sports Exerc* 1999;31:287–293.
4. Carroll S, Cooke CB, Butterly RJ. Metabolic clustering, physical activity and fitness in nonsmoking, middle-aged men. *Med Sci Sports Exerc* 2000;32: 2079–2086.
5. Zhao SP, Li XP. The association of low plasma testosterone level with coronary artery disease in Chinese men. *Int J Cardiol* 1998;63:161–164.
6. Alexandersen P, Haarbo J, Christiansen C. The relationship of natural androgens to coronary heart disease in males: a review. *Atherosclerosis* 1996;125:1–13.
7. Nagano M, Kai Y, Zou B, et al. The contribution of cardiorespiratory fitness and visceral fat to the risk factors in the Japanese patients with impaired glucose tolerance and type 2 diabetes mellitus. *Metabolism* 2004;53:644–649.
8. KaiY, Nagano M, Zou B, et al. Relative contribution of fitness and fatness on metabolic syndrome in Japanese patients with type 2 diabetes mellitus. *Med Sci Sports Exerc* 2004;36:S84–S85.
9. Reaven GM. Banting lecture 1988. Role of insulin resistance in human disease. *Diabetes* 1988;37:1595–1607.
10. Kaplan NM. The deadly quartet. Upper-body obesity, glucose intolerance, hypertriglyceridemia, and hypertension. *Arch Intern Med* 1989;149:1514–1520.
11. Alberti KGMM, Zimmet PZ, for the WHO Consultation. Definition, diagnosis and classification of dia-

betes mellitus and its complications. Part 1: Diagnosis and classification of diabetes mellitus, provisional report of a WHO consultation. *Diabet Med* 1998;15:539–553.
12. Reaven GM. Role of insulin resistance in human disease. *Diabetes* 1988;37:1595–1607.
13. Liese AD, Mayer-Davis EJ, Haffner SM. Development of the multiple metabolic syndrome: an epidemiological perspective. *Epidemiol Rev* 1998;20:157–172.
14. Isomaa B, Almgren P, Tuomi T, et al. Cardiovascular morbidity and mortality associated with the metabolic syndrome. *Diabetes Care* 2001;24:683–689.
15. Multiple Risk Factor Intervention Trial Research Group. Multiple Risk Factor Intervention Trial: risk factor changes in mortality results. *JAMA* 1982;248: 1465–1470.
16. Castelli WP. Lipids, risk factors and ischemic heart disease. *Atherosclerosis* 1996;s124:S1–S9.
17. European Atherosclerosis Society Study Group. The recognition and management of hyperlipidaemia in adults: a policy statement of the European Atherosclerosis Society. *Eur Heart J* 1988;9:571–600.
18. Barrett-Connor E, Khaw KT, Yen SSC. Endogenous sex hormone levels in older adult men with diabetes mellitus. *Am J Epidemiol* 1990;132:895–901.
19. Barrett-Connor E. Lower enodgenous androgen levels and dyslipidemia in men with non-insulin-dependent diabetes mellitus. *Ann Intern Med* 1992;117:807–811.
20. Andersson B, Mårin P, Lissner L, et al. Testosterone concentrations in women and men with NIDDM. *Diabetes Care* 1994;17:405–411.
21. Haffner SM, Shaten J, Stern MP, et al. Low levels of sex hormone-binding globulin and testosterone predict the development of non-insulin-dependent diabetes mellitus in men. *Am J Epidemiol* 1996;143:889–897.
22. Hak AE, Witteman JC, de Jong FH, et al. Low levels of endogenous androgens increase the risk of atherosclerosis in elderly men: the Rotterdam Study. *J Clin Endocrinol Metab* 2002;87:3632–3639.
23. Ducimetiere P, Eschwege E, Papoz L, et al. Relationship of plasma insulin levels to the incidence of myocardial infarction and coronary heart disease mortality in a middle aged population. *Diabetologia* 1980;19:205–210.
24. Simon D, Charles MA, Nahoul K, et al. Association between plasma total testosterone and cardiovascular risk factors in healthy adult men: the Telecom Study. *J Clin Endocrinol Metab* 1997;82:682–685.
25. Haffner S, Karhapää P, Mykkänen L, et al. Insulin resistance, body fat distribution and sex hormones in men. *Diabetes* 1994;43:212–219.
26. Abate N, Garg A, Peshock RM, et al. Relationship of generalized and regional adiposity to insulin sensitivity in men with NIDDM. *Diabetes* 1996;45:1684–1693.
27. Abate N, Garg A, Peshock RM, et al. Relationships of generalized and regional adiposity to insulin sensitivity. *J Clin Invest* 1995;96:88–98.
28. Van Itallie TB. Health implications of overweight and obesity in the United States. *Ann Intern Med* 1985;103:983–988.
29. Holmäng A, Björntorp P. The effects of testosterone on insulin sensitivity in male rats. *Acta Physiol Scand* 1992;146:505–510.
30. Mårin P, Holmäng S, Jonsson L, et al. The effects of testosterone treatment on body composition and metabolism in middle-aged obese men. *Int J Obes Relat Metab Disord* 1992;16:991–997.
31. Phillis GB. Relationship between serum sex hormones and glucose, insulin and lipid abnormalities in men with myocardial infarction. *Proc Natl Acad Sci USA* 1977;74:1729–1733.
32. Birkeland K, Hanssen KF, Torjesen PA, et al. Level of sex hormone-binding globulin is positively correlated with insulin sensitivity in men with type 2 diabetes. *J Clin Endocrinol Metab* 1993;76:275–278.
33. Haffner S, Valdez RA, Mykkänen L, et al. Decreased testosterone and dehydroepiandrosterone sulfate concentrations are associated with increased insulin and glucose concentrations in nondiabetic men. *Metabolism* 1994;43:599–603.
34. Phillips GB. Relationship between serum sex hormones and the glucose-insulin-lipid defect in men with obesity. *Metabolism* 1993;42:116–120.
35. Simon D, Preziosi P, Barrett-Connor E, et al. Interrelation between plasma testosterone and plasma insulin in healthy adult men: the telecom study. *Diabetologia* 1992;35:173–177.
36. Pasquali R, Casimirri F, Cantebelli S, et al. Effect of obesity and body fat distribution on sex hormones and insulin in men. *Metabolism* 1991;40:101–104.
37. Fukui M, Koyama M, Nakagawa Y, et al. Castration and diabetes. *Diabetes Care* 2000;23:1032–1033.
38. Stellato RK, Feldman HA, Hamdy O, et al. Testosterone, sex hormone-binding globulin, and the development of type 2 diabetes in middle-aged men. *Diabetes Care* 2000;23:490–494.
39. Laaksonen DE, Niskanen L, Punnonen K, et al. Sex hormones, inflammation and the metabolic syndrome: a population-based study. *Eur J Endocrinol* 2003;149:601–608.
40. Tokunaga K, Matsuzawa Y, Ishikawa K, et al. A novel technique for the determination of body fat by computed tomography. *Int J Obesity* 1983;7:437–445.
41. Åstrand PO, Rhyming I. A nomogram for calculation of the aerobic capacity (physical fitness) from pulse rate during submaximal work. *J Appl Physiol* 1954;7: 218–221.
42. Howard G, Bergman R, Wagenknecht LE, et al. Ability of alternative indices of insulin sensitivity to predict cardiovascular risk: comparison with the "Minimal Model." *Ann Epidemiol* 1998;8:358–369.
43. Radziuk J. Insulin sensitivity and its measurement: structural commonalities among the methods. *J Clin Endocrinol Metab* 2000;85:4426–4433.
44. Haffner SM, Shaten J, Stern MP, et al. Low levels of sex hormone-binding globulin and testosterone predict the development of non-insulin-dependent diabetes mellitus in men: MRFIT Research Group Multiple Risk Factor Intervention Trial. *Am J Epidemiol* 1996;143: 889–897.

45. Stellato RK, Feldman HA, Hamdy O, et al. Testosterone, sex hormone-binding globulin, and the development of type 2 diabetes in middle-aged men: prospective results from the Massachusetts male aging study. *Diabetes Care* 2000;23:490–494.
46. Iverius PH, Brunzell JD. Relationship between lipoprotein lipase activity and plasma steroid level in obese women. *J Clin Invest* 1988;82:1106–1112.
47. Sorva R, Kuusi T, Taskinen MR, et al. Testosterone substitution increases the activity of lipoprotein lipase and hepatic lipase in hypogonadal males. *Atherosclerosis* 1988;69:191–197.
48. Mårin P, Krotkiewski M, Björntorp P. Androgen treatment of middle-aged, obese men: effects on metabolism, muscle and adipose tissues. *Eur J Med* 1992;1:329–336.
49. Mårin P, Holmäng S, Jonsson L, et al. The effects of testosterone treatment on body composition and metabolism in middle-aged obese men. *Int J Obes Relat Metab Disord* 1992;16:991–997.
50. Mårin P. Testosterone and regional fat distribution. *Obes Res* 1995;3:609S–612S.
51. Livingstone C, Collison M. Sex steroids and insulin resistance. *Clin Sci* 2002;102:151–166.
52. McCarty MF. Modulation of adipocyte lipoprotein lipase expression as a strategy for preventing or treating visceral obesity. *Med Hypoth* 2001;57:192–200.
53. Staessen J, Bulpitt CJ, Fagard R, et al. The influence of menopause on blood pressure. *J Hum Hypertens* 1989;3:427–433.
54. Weiss NS. Relationship of menopause to serum cholesterol and arterial pressure: The United States Health Examination Survey of Adults. *Am J Epidemiol* 1972;96:237–241.
55. Staessen JA, Ginnochio G, Thijs L, et al. Conventional and ambulatory blood pressure and menopause in a prospective population study. *J Hum Hypertens* 1997;11:507–514.
56. Regensteiner JG, Hiatt WR, Byyny RL, et al. Short-term effects of estrogen and progestin on blood pressure of normotensive postmenopausal women. *J Clin Pharmacol* 1991;31:543–548.
57. Szekacs B, Vajo Z, Acs N, et al. Hormone replacement therapy reduces mean 24-hour blood pressure and its variability in postmenopausal women with treated hypertension. *Menopause* 2000;7:31–35.
58. Pripp U, Hall G, Csemiczky G, et al. A randomized trial on effects of hormone replacement therapy on ambulatory blood pressure and lipoprotein levels in women with coronary artery disease. *J Hypertens* 1999;17:1379–1386.
59. Manwaring P, Morfis L, Diamond T, et al. Effects of hormone replacement therapy on ambulatory blood pressure responses in normotensive women. *Blood Press* 2000;9:22–27.
60. Akkad AA, Halligan AWF, Abrams K, et al. Differing responses in blood pressure over 24 hours in normotensive women receiving oral or transdermal estrogen replacement therapy. *Obstet Gynecol* 1997;89:97–103.
61. Seely EW, Walsh BW, Gerhard MD, et al. Estradiol with or without progesterone and ambulatory blood pressure in postmenopausal women. *Hypertension* 1999;33:1190–1194.
62. Manhem K, Ahlm H, Milsom I, et al. Transdermal oestrogen reduces daytime blood pressure in hypertensive women. *J Hum Hypertens* 1998;12:323–327.
63. Lind T, Cameron EC, Hunter WM, et al. A prospective, controlled trial of six forms of hormone replacement therapy given to postmenopausal women. *Br J Obstet Gynaecol* 1979;86:1–29.
64. Phillips GB, Jing TY, Resnick LM, et al. Sex hormones and hemostatic risk factors for coronary heart disease in men with hypertension. *J Hypertens* 1993;11:699–702.
65. Jaffe A, Chen Y, Kisch ES, et al. Erectile dysfunction in hypertensive subjects. Assessment of potential determinants. *Hypertension* 1996;28:859–862.
66. Hughes GS, Mathur RS, Margolius HS. Sex steroid hormones are altered in essential hypertension. *J Hypertens* 1989;7:181–187.
67. Giltay EJ, Hoogeveen EK, Elbers JM, et al. Effects of sex steroids on plasma total homocysteine levels: a study in transsexual males and females. *J Clin Endocrinol Metab* 1998;83:550–553.
68. Kumai T, Tanaka M, Watanabe M, et al. Possible involvement of androgen in increased norepinephrine synthesis in blood vessels of spontaneously hypertensive rats. *Jpn J Pharmacol* 1994;66:439–444.
69. Yang XC, Jing TY, Resnick LM, et al. Relation of hemostatic risk factors to other risk factors for coronary heart disease and to sex hormones in men. *Arterioscler Thromb* 1993;13:467–471.
70. Phillips GB, Jing T, Heymsfield SB. Relationships in men of sex hormones, insulin, adiposity, and risk factors for myocardial infarction. *Metabolism* 2003;52: 784–790.
71. Phillips GB, Pinkernell BH, Jing TY. The association of hypotestosteronemia with coronary artery disease in men. *Arterioscler Thromb* 1994;14:701–706.
72. Rosner W. An extraordinarily inaccurate assay for free testosterone is still with us. *J Clin Endocrinol Metab* 2001;86:2903.
73. Vermeulen A, Verdonck L, Kaufman JM. A critical evaluation of simple methods for the estimation of free testosterone in serum. *J Clin Endocrinol Metab* 1999;84:3666–3672.
74. Morley JE, Patrick P, Perry HM III. Evaluation of assays available to measure free testosterone. *Metabolism* 2002;51:554–559.
75. Matsumoto AM, Bremner WJ. Serum testosterone assays-accuracy matters. *J Clin Endocrinol Metab* 2004; 89:520–524.

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地域在住高齢者の転倒発生への身体的・精神的要因の関与に関する前向き研究

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A PROSPECTIVE STUDY OF THE RELATIONSHIP BETWEEN PHYSICAL DIFFICULTIES AND MENTAL PROBLEMS AND FALLS IN COMMUNITY-DWELLING ELDERLY.

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Abstract

The purposes of this prospective study were to investigate the incidence of falls or recurrent falls (more than 2 falls) and the falls-related risk factors, and to clarify the relationship between physical difficulties and mental problems and falls or recurrent falls in the elderly persons living independently in a local community in Japan. The participants were 775 elderly persons aged 60−79 years who participated in baseline assessment in 2002 by the questionnaire concerning the falls with injury during the past 5 years, and they had no injurious fall for 5 years before this survey. During prospective monitoring for 1 year, 173 falls were reported by 122 persons (15.7%), and recurrent falls were reported by 35 persons (4.5%). Significant gender difference was observed in falls for 1 year (Falls; men 11.3% vs female 20.0%, Recurrent falls; men 2.6% vs female 6.4%, $p<0.05$). Relationship between falls or recurrent falls and potential risk factors were identified in multiple logistic regression models. Physical difficulties (difficulties with standing from chair without their arms, balance on the one leg, and/or walking easily) was not associated with either falls. Mental problems (stressful, gloomy, less willingness, poor sleep, and/or forgetful) increased the risk of recurrent falls (Relative Ratio (RR) =3.50, 95% Confidence Interval (95%CI) =1.05-1.49). However, when physical difficulties were analyzed as a continuous variable, with each physical difficulty added, an relative ratio for recurrent falls increased by 1.5 times (95%CI=1.07-2.11) while mental problems did not show significant relation. When physical difficulties and mental problems were simultaneously analyzed, the risk of recurrent falls significantly increased in the category that had both physical difficulties and mental problems (RR=5.82, 95%CI= 1.25-27.04). These results suggest that mental treatments can be useful as a strategy for falls prevention in the elderly, as well as physical treatments.

Key Words: Falls, Elderly, Physical difficulties, Mental problems, Prospective study

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はじめに

高齢者の転倒は、寝たきりや転倒後症候群などを誘発することから、高齢期の身体的自立を脅かす要因であると考えられる。わが国における高齢者の年間転倒率は10-20%である[1-4]。これは欧米諸国に比べて低い発生率であるものの[5-7]、超高齢化に伴い転倒および転倒による諸問題は、本邦にあっても高齢者の深刻な健康問題として注目されている。転倒の予防には、まず転倒発生の要因を明らかにすることが重要である。欧米で行われた疫学研究によれば、転倒発生の危険因子として、高齢であること、女性であること、精神疾患薬の服用、身体の可動性の低下および認知障害などが報告されている[5-7]。特に身体能力の低下は転倒発生の重要な要因であることが示されている[8]。高齢期においては身体能力の低下だけでなく、抑うつなど精神心理的機能低下も生じる。地域高齢者を対象に抑うつと身体能力の低下との関連に焦点を当てた研究では、抑うつ症状または臨床的に診断された抑うつ双方は身体能力低下と密接に関連することが報告されている[9,10]。一方、身体能力低下が抑うつを増加させうるとの報告もあり[11]、両者には密接な関連性があることが示唆されている。

これまでに、身体能力の低下および抑うつは転倒発生の単独要因であることが報告されている[5-8,12]。すなわち、身体能力の低下と抑うつは相互に影響しあっていることから、両要因を併せ持つことは、単独要因に比べ相乗的もしくは相加的に転倒発生を高めることが予測される。しかしながら、先行研究において、この二要因の転倒発生に関する相互作用を検討した報告はない。我々[13]は、本研究に先立ち、ベースライン調査の横断的解析で、過去5年間の傷害を伴う転倒経験と身体的不自由および精神的不定愁訴との関連を検討した。その結果、二つの要因を併せ持つこと、さらにその数が増すほど転倒発生のオッズ比は有意に増加することを観察した。一般にある疾病や種々の健康事象の発生要因を証明しようとする場合、要因が結果に先行していること（関連の時間性）が要求される。すなわち、先述の我々の結果は、横断的調査における過去5年間の転倒経験の関連要因を明らかにしたに過ぎず、転倒の発生要因を明らかにしたとはいえない。そこで、本研究では地域在住の高齢者を対象として、転倒発生とその関連要因を明らかにし、転倒発生への身体的不自由および精神的不定愁訴の相互作用について、過去5年間に傷害を伴った転倒の未経験者を対象に1年間の前向き調査を実施したので報告する。

方法

1.対象者

本研究の対象者は、2002年に福岡県宗像郡津屋崎町在住の60歳以上の高齢者4,296名を対象として設定されたコホートの対象者である（Fig.1）。

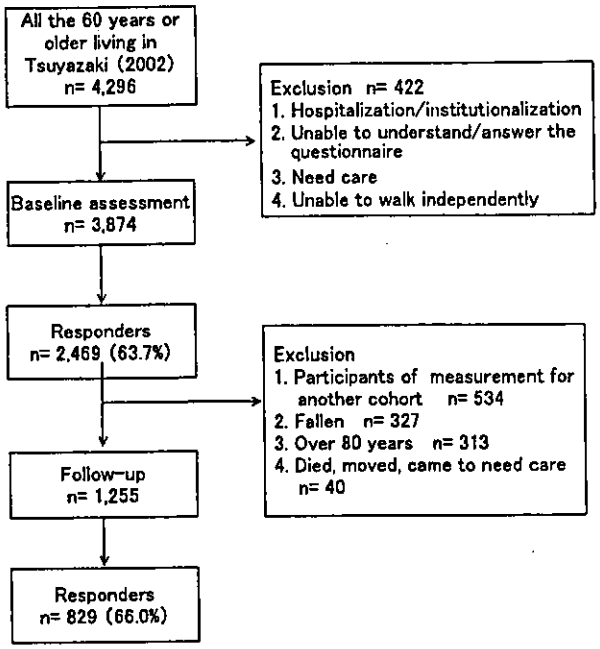

Fig.1 The flow chart of selection for participants in this study.

津屋崎町は、九州の北端、福岡市、北九州市両政令都市のほぼ中間に位置した人口約14,000人、60歳以上の人口割合27.2%（2002年）の町である。ベースライン調査は、自立している在宅高齢者を対象とするため、対象除外条件として①入所あるいは入院中であること、②精神疾患または理解不十分な者、③既に介護認定者であること、④自立歩行できないこと、以上4項目に当てはまる422名を除く3,874名であった。なお、対象者の除外条件適合の判定は、津屋崎町に16年勤務する保健師1名によって行われた。

2002年2月に実施したベースライン調査のデータは、郵送法によるアンケート調査から得られた。送付対象であった3,874名のうち80歳以上の対象者（529名）には、民生委員による個別訪問調査を実施した。最終的に2,507名から返信があり、そのうち有効回答者数は転倒経験に関する項目に回答した2,469名（63.7%）であった。対象者の内訳は、男性1,060名、女性1,409名であり、年齢はそれぞれ71.6±7.7歳、71.8±8.2歳であった。

このうち、別コホートの設定で体力測定を受けた554名、過去5年間に傷害を伴う転倒を経験した者327名、80歳

以上の対象者313名およびこの一年間に死亡、転出、新たに介護認定を受けた40名を除く1,255名を対象として、2003年２月に郵送法による一年後の追跡調査を実施した。骨折や骨にひびが入るなど比較的大きなけがを経験した対象では身体能力の低下が生じる可能性が考えられ、本研究では転倒によって既にそのような状況に陥っている対象者ではなく、できるだけ既転倒による影響を除くために、既にけがを伴うような転倒をしたものは対象から除外した。また、80歳以上の対象者は、転倒が多発する80歳前に転倒の予防活動を展開することが望ましいとの判断から、転倒発生の要因を検討するための追跡調査からは除外した。体力測定群については、アンケート調査群と調査時期がずれており、追跡調査がアンケート調査群の解析時にはまだ追跡調査が終了していなかったため今回はアンケート調査群のみで解析を実施した。有効回答者数は829名（66.0%）であったが、ベースライン調査時に精神的不定愁訴5項目に全く回答していなかった54名を除外し、775名を本研究の解析対象者とした。

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2.ベースライン調査

ベースライン調査に用いたアンケートは、下記の項目から構成されている。

1）基本属性：年齢、性、婚姻、職業、家族構成

2）肥満度および疾患・服薬状況：自己申告の身長、体重からBody Mass Index（BMI:体重（kg）÷身長（m^2））を算出した。疾患状態は、高血圧、糖尿病、高脂血症、心臓病、脳血管疾患（脳卒中・脳梗塞）、骨折、運動に支障があるようなけがや病気の有無について調査した。慢性疾患は、高血圧、糖尿病、高脂血症、心臓病、脳血管疾患（脳卒中・脳梗塞）の罹患数を算出した。服薬状況に関しては、高血圧、糖尿病、高脂血症および心臓病について尋ね、脳血管疾患と骨折に関しては、現在生活に支障があるような障害の有無について調査した。脳血管疾患（脳卒中・脳梗塞）および骨折により生活に支障があると回答した者と運動に支障があるようなけがや病気を持つと回答した者は身体に「障害あり」とみなした。

3）身体活動：普段の活動範囲、週に一回以上の歩行や散歩、半年以上の運動実施状況について調査した。活動範囲については、通院以外は家にいがちであるかどうかを調べた。また、一日のうちで睡眠を除く座位または横になっている時間および立位時間についても調査した。さらに畑仕事の有無も調査した。

4）身体的不自由：本研究における身体的不自由は、対象者が次の３つの動作を支障なくできるかどうかによって判断した。①椅子から腕を使わずに立ち上がることができるか、②楽に歩行できるか、③30秒間片足で立っていることができるか、である。この３項目は、先行研究[5-8]において転倒の危険要因として指摘されている下肢筋力、歩行、およびバランス能力の低下などを反映している。これらの質問に対して、「できる」「できるが、やや困難である（30秒は立てない）」「できない」から最も当てはまる回答を選択させた。この３項目のうち１つでも「できる」以外の回答を選んだ場合に身体的に不自由があるとした。また、「できる」以外の回答数をカウントし0-3までの範囲でスコア化した。なお、歩行できないと回答した者は、除外条件④自立歩行できない者に該当するとして分析から除外した。

5）精神的不定愁訴：本研究における精神的要因は、臨床的抑うつではなく、精神的な不定愁訴に記憶力の低下を加えたオリジナル調査で評価した。すなわち、①ストレスを感じる、②憂鬱な日々が続く、③意欲がわかない、④不眠があるおよび⑤新しいことが覚えられない（以下、記憶力低下と称す）の５項目からなり、この一年間の状況について「はい」「いいえ」で回答させた。「はい」の回答が１つでもあった場合に精神的不定愁訴があるとした。また、「はい」の数をカウントし0-5の範囲でスコア化した。なお、このスコアは、別コホートの設定で同じ質問に回答した548名において、General Health Questionnaire 30 日本語版（GHQ30）の総得点およびGeriatric Depression scale 日本語短縮版（GDS）[14]の総得点と検討した結果、GHQ30と$r=0.39$、GDSとの間に$r=0.32$の有意な相関を認めた。５つの質問項目すべてに無回答であった者は、54名(6.5%)であった。

6）骨折・骨にひび・捻挫を伴う転倒経験：「過去５年間に骨折、骨にひびまたは捻挫を伴うような転倒をしたことがありますか」という問いに対して「はい」と回答したものを転倒者とし、転倒回数について回答を求めた。骨折や骨にひびなど比較的大きな傷害を伴う転倒経験者では、転倒経験による身体能力の低下が生じる可能性が高い。本研究では、過去の転倒歴に起因しない能力低下と転倒発生との関連を明らかにするため、ベースライン調査において、そのスクリーニングとして「過去５年間の傷害を伴う転倒歴」について調査した。

3.転倒の追跡調査

転倒要因と転倒との因果関係を明らかにするため、転倒発生に関する追跡調査を実施した。追跡調査は、ベースライン調査から1年後の2003年2月に郵送法を用い実施した。追跡調査の内容は、1年間の転倒の有無、転倒回数、転倒によるけがの有無であった。本研究における転倒の定義は「本人の意思とは関係なく、地面またはより低いところに膝や手など足底部以外の身体が接触すること」とした。転倒によるけがの内容は、最もひどいけがをした転倒での負傷内容について尋ねた。一般に、転倒発生調査には転倒日記やカレンダー、転倒時の葉書投函など転倒を随時モニターできるシステムが用いられるが、本研究では、1年間の思い出し法による調査を実施した。1年間の思い出し法による転倒発生調査は、本邦における高齢者の転倒調査として、その信頼性が報告されている[15]。

4.アウトカム

1年間に複数回転倒を経験する者は危険因子とより強固に関連することが示唆されている[6,8]ことから、本研究におけるアウトカムは、1年間の追跡期間中に少なくとも1回以上転倒を経験した「転倒」および2回以上転倒した「複数回転倒」とした。

5.解析

転倒者と非転倒者のベースライン時の特性比較には、連続変数には対応のないt検定を、名義変数にはχ^2検定を用いた。転倒発生と各要因との関連については、相対危険度（RR）と95%信頼区間（95%CI）を性、年齢で補正したロジスティック回帰分析で算出し、有意であった要因を用いて多重ロジスティック回帰分析を行った。

転倒発生と身体的不自由および精神的不定愁訴との関連を同時に検討するため以下のような手順を実施した。ベースラインの身体的不自由および精神的不定愁訴の有無を組み合わせて次の4つのカテゴリーに区分した（Fig. 2）。

		Physical difficulty	
		yes	no
Mental unspecified complaint	yes	Physical difficulty and mental unspecified complaint	Mental unspecified complaint
	no	Physical difficulty	No problem

Fig. 2　Categorization of physical difficulty and mental unspecified complaint for analysis.

身体的不自由および精神的不定愁訴がない場合を「問題なし」、精神的不定愁訴はないが身体的不自由がひとつ以上ある場合には「身体的不自由のみ」、身体的不自由はないが精神的不定愁訴がひとつ以上ある場合には「精神的不定愁訴のみ」、双方を持ち合わせる場合を「身体不自由・精神的不定愁訴あり」とした。「問題なし」を参照として、各カテゴリーにおける転倒発生の相対危険度と95%信頼区間を算出した。

各質問項目の欠損値の取り扱いについては、5%以上の欠損が確認された場合、「無回答」として独立したカテゴリーを設けた。疾患、職業、精神的不定愁訴の項目に5%以上の欠損が確認されたが、疾患および職業については電話調査において無回答は該当しないため記入しなかった者が多かったことから、無回答は「なし」とみなした。精神的不定愁訴の項目に一つ以上無回答がある場合は、回答しないということ自体が意味を有する可能性も考えられるため「無回答」のカテゴリーを独立させて解析した。統計処理にはStat view ver.5.0（SAS Institute Inc.）統計解析ソフトを用い、危険率5%未満をもって統計的に有意とした。

結果

本研究における対象者の性・年齢に有意差は認められなかった（p=0.46、Table 1）。1年間の転倒発生は122名（15.7%）であり、全転倒数は173件であった。このうち2回以上の複数回転倒者は35名（4.5%）であった。4名は転倒回数を回答しなかった。けがを伴う転倒者数は76名であり、骨折を伴う転倒者数は19名であった。また、転倒率は男性11.3%、女性20.0%、複数回転倒率は男性2.6%、女性6.4%であり（p<0.01）、有意に女性の転倒が多かった（p<0.05、Table 2）。

Table 1　Age, gender and faller distribution of participants

	Male		Female		
Age	n	faller	n	faller	total
60-64	102	(14)	106	(17)	208
65-69	95	(8)	116	(24)	211
70-74	112	(6)	100	(22)	212
75-79	71	(15)	73	(16)	144
total	380	(43)	395	(79)	775

p=0.46

Table 2　The number of fallers

	Faller			Recurrent faller		
	n	%		n	%	
Male	43	11.3%		10	2.6%	
Female	79	20.0%	**	25	6.4%	*
total	122			35		

* p<0.05, ** p<0.01
※4 persons didn't answer.
※Faller defined as those who fell once or more during follow-up.

Table 3 Characteristics of participants who did and did not fall at baceline

Charateristic	Fallers		Reccurent fallers	
	non-fallers (%)	fallers (%)	non-fallers (%)	fallers (%)
Number	n=653	n =122	n=736	n=35
Demographic				
Age	68.6±5.4	69.7±5.8 p=0.06	68.8±5.5	69.1±5.8
Gender (% Female)	48.4	64.8 **	49.9	71.4 *
Spouse	81.2	74.4	80.8	65.6
Living alone	10.3	11.3	10.4	12.5
Medical problems and medication				
Chronic disease (≧3)	5.4	9.8 p=0.06	5.5	17.1 *
Medication (≧3)¶	1.1	0.8	1.1	-
Physical impairment	11.9	23.8 **	13.2	28.6 *
BMI	22.8±2.9	22.9±3.0	22.8±2.9	22.9±3.4
Physical activity				
Stay-at-home	8.3	11.6	8.9	8.8
Sedentary (sitting time per day ≧7h)	8.9	13.3	9.2	17.6
Weekly walking	48.3	46.2	48.6	32.4
Weekly exercise	19.2	21.5	19.2	22.9
Crops	34.2	36.7	34.3	39.4
Physical difficulty				
Chair stand	13.5	23.0 *	14.1	37.1 ***
Walking	13.8	20.5 p=0.07	14.2	31.4 *
Balance (One leg stand >30sec)	27.1	36.1 p=0.06	27.5	51.5 **
Mental unspecified complaint				
Stress§				
yes	66.3	50.0	65.2	34.3
no	15.0	23.0	15.5	34.3
missing	18.7	27.0	19.3	31.4
Gloominess**				
yes	71.4	57.4	70.5	42.9
no	8.1	9.8	8.2	14.3
missing	20.5	32.8	21.3	42.9
Lack of willingness**				
yes	64.5	50.8	63.5	40.0
no	16.8	17.2	16.7	20.0
missing	18.7	32.0	19.8	40.0
Poor sleep§				
yes	58.3	41.0	56.7	37.1
no	28.8	40.2	29.9	40.0
missing	12.9	18.8	13.4	22.9
Forgetfulness†				
yes	48.1	35.2	47.1	22.8
no	38.6	45.1	39.3	48.6
missing	13.3	19.7	13.6	28.6

BMI=body mass index; Age and BMI tested by t-test
* p<0.05, ** p<0.01, *** p<0.001
§p<0.01 for faller and p<0.001 for recurrent fallers, §§p<0.01 for fallers and p=0.06 for recurrent fallers, †p<0.05 for fallers and p<0.01 for recurrent fallers.
¶ There is no appropriate person in recurrent fallers.
§ Significant for fallers (≧1) only.
Missing is non-responders in mental unspecified complaint.

Table 3に転倒者の特性を示す。転倒者と非転倒者では、女性であること、日常生活や運動に支障のある障害を有すること、精神的不定愁訴を有する割合に有意差が認められた（p<0.05）。身体的不自由は、椅子からの立ち上がり困難者の割合にのみ有意差を認めた。複数回転倒者でも同様の結果を示したが、慢性疾患を3つ以上有すること、身体的不自由にも有意差を認めた（p<0.05）。身体活動の指標には、転倒者、複数回転倒者のいずれでも有意差は認められなかった。

Table 4 Relative risk (RR) and 95% confidence intervals (95%CI) for the variables was adjusted for age and gender

Variables	Fallers		Recurrent fallers	
	RR	95%CI	RR	95%CI
Demographic				
Age†	1.04	1.00 - 1.08	1.01	0.95 - 1.08
Gender(Female)‡	2.00	1.32 - 2.98 ***	2.51	1.19 - 5.31 *
Medical problems and medication				
Chronic disease (≧3)	2.07	1.03 - 4.17 *	3.97	1.53 - 10.3 **
Physical impairment	2.33	1.43 - 3.79 ***	2.69	1.24 - 5.81 *
Physical difficulty				
Chair stand	1.62	0.99 - 2.66 p=0.06	3.36	1.59 - 7.08 **
Walking	1.45	0.88 - 2.39	2.60	1.22 - 5.54 *
Balance (one leg stand >30sec)	1.30	0.84 - 2.00	2.69	1.28 - 5.64 **
Physical difficulty score♭	1.21	0.99 - 1.47 p=0.06	1.68	1.24 - 2.27 ***
Mental unspecified complaint#				
Stress	1.93	1.16 - 3.21 *	3.84	1.67 - 8.84 **
missing	1.70	1.05 - 2.76 *	2.94	1.24 - 6.97 *
Gloominess	1.53	0.77 - 3.02	2.88	1.01 - 8.25 *
missing	1.75	1.12 - 2.74 **	3.17	1.47 - 6.82 **
Lack of willingness	1.28	0.75 - 2.21	1.93	0.76 - 4.91
missing	1.95	1.23 - 3.09 **	3.00	1.38 - 6.56 **
Poor sleep	1.81	1.17 - 2.80 **	1.87	0.86 - 4.09
missing	1.89	1.08 - 3.30 *	2.47	0.98 - 6.22 p=0.06
Forgetfulness	1.49	0.99 - 2.23	2.51	1.06 - 5.96 *
missing	1.74	0.99 - 3.06 p=0.06	3.92	1.48 - 10.4 **
Mental unspecified complaint score♭	1.21	1.03 - 1.42 *	1.35	1.04 - 1.76 *

RR = Relative risk, 95%CI = 95% confedence interval
* p<0.05, ** p<0.01, *** p<0.001
† Adjusted for gender
‡ Adjusted for age
# Missing is Non-responsers who had unspecified complaints. The reference is those who answered "NO".
♭ The number of physical difficulties or mental unspecified complaints were counted, and it was treated as a continuous variable.

Table 4 に性・年齢を補正したロジスティック回帰分析の結果を示す。転倒・複数回転倒を問わず、女性であること、慢性疾患を3つ以上持つこと、日常生活や運動に支障のある障害を有していることが有意な相対危険度を示した（p<0.05）。転倒者では、身体的不自由に有意な相対危険度を示さず、ストレスを感じる（p<0.05）、不眠（p<0.01）の項目で転倒発生の危険度が有意に高かった。複数回転倒では、身体的不自由すべての項目に有意な危険度を認め（p<0.05）、精神的不定愁訴項目ではストレスを感じる（p<0.01）、憂鬱な日々が続く、記憶力低下（p<0.05）の項目で危険度が有意に高かった。多くの精神的不定愁訴項目における無回答カテゴリーで、転倒、複数回転倒のいずれも有意な危険度を認めた。

Table 5 Relative risk (RR) and 95% confidence intervals (95%CI) for the variables in multiple logistic regression

	Fallers		Recurrent fallers	
	RR	95%CI	RR	95%CI
Age	1.03	0.99 - 1.07	0.99	0.93 - 1.06
Gender (Female)	1.99	1.32 - 3.01 *	2.54	1.18 - 5.47 *
Chronic diseases	1.80	0.88 - 3.68	3.49	1.31 - 9.29 *
Physical impairment	2.21	1.31 - 3.73 **	1.94	0.84 - 4.49
Physical difficulty	0.96	0.62 - 1.50	1.39	0.65 - 2.97
Mental unspecified complaint	1.46	0.92 - 2.32	3.50	1.20 - 10.21 *

RR = Relative risk, 95%CI = 95% confedence interval
* p<0.05, ** p<0.01

Table 5 に多重ロジスティック回帰分析の結果を示す。転倒には女性であること（$p<0.05$）、日常生活や運動に支障のある障害を持つこと（$p<0.01$）が他の要因に独立して有意な相対危険度を示した。複数回転倒では、女性であること、慢性疾患を３つ以上持つこと、および精神的不定愁訴を有することが他の要因に独立して有意な相対危険度を示した（$p<0.05$）。身体的不自由を有することは、いずれの転倒でも有意な危険度を示さなかった。しかしながら、身体的不自由および精神的不定愁訴数を連続変数として投入した場合には、身体的不自由のみが複数回転倒の発生に有意な危険度を示し、身体的不自由が一つ増えるごとに複数回転倒の発生の危険度が1.51倍になることを示した（RR=1.51, 95%CI=1.06-2.15, データ非表示）。一方、精神的不定愁訴数との間には有意差は認められなかった。

Table 6 に身体的不自由および精神的不定愁訴と複数回転倒発生との関連を検討した結果を示す。身体的不自由と精神的不定愁訴を併せ持つ場合にのみ、性、年齢、疾患、日常生活や運動に支障のある障害ありで調整しても有意な相対危険度（RR=5.82, 95%CI=1.25-27.04）であった。

Table 6 Relative risk and 95% confidence intervals of physical difficulty and mental unspecified complaint interaction for recurrent falls

	RR	95%CI
No problem	1.00	
Physical difficulty	2.25	0.30 - 17.00
Mental unspecified complaint	4.46	1.00 - 19.90
Physical difficulty and mental unspecified complaint	5.82	1.25 - 27.04 *

RR = Relative risk, 95%CI = 95% confedence interval
Adjusted for age, gender, chronic disease, physical impairment.
* $p<0.05$

考察

本研究では、60歳以上の地域在住高齢者における１年間の転倒率は15.7%であった。この転倒率は、本邦において報告されている転倒発生率とほぼ同程度であった[1-3]。また、本研究では男性よりも女性の転倒発生率が有意に高かった。転倒発生に関する性差については、認められないとする報告[2]と有意に女性に多発するとする報告[1,4]があり成績の一致をみていない。Suzukiら[4]は、邦人を対象とした横断研究で、男性では四肢および認知に障害を持つこと、女性では尿失禁と背痛が転倒要因であることを示し、転倒要因が男女で異なることを報告している。背痛は骨粗鬆症の症状であり、骨粗鬆症による椎骨骨折は可動性に障害をもたらすことから転倒の危険度を高めると述べている。Campbellら[16]は、男性よりも女性が転倒しやすい状況にある原因として、女性に睡眠剤、精神安定剤を服薬するものが多いことや筋力低下など転倒しやすい身体的特徴があることを報告していることから、転倒発生の性差は、可動性や筋力の低下など身体能力の低下が女性に多いことに影響しているようである。

身体的不自由を有することは、複数回転倒発生の相対危険度を有意に高めた。特に腕を使わずに椅子から立ち上がることに困難がある群では、転倒発生の相対危険度が最も高かった。他の研究[17]でも椅子からの立ち上がりテストを含むバランスと歩行テストで、同様な成績が報告されている。Campbellら[7]は、椅子からの立ち上がりが不可能な男性で転倒の危険度が3.4倍になることを報告しており、本研究で示された結果とほぼ一致する。Nevitt[5]は椅子からの立ち上がり動作に２秒以上かかる者あるいは不可能な者では、その他の要因を調整したあとでも複数回転倒の危険度を３倍にすることから、複数回転倒の指標として有効であるとしている。また、身体的不自由度を連続変数として転倒発生との関連を検討したところ、性、年齢、および他の因子で調整しても身体的不自由がひとつ増えるごとに複数回転倒の危険度は1.5倍に高まった。Graafman[3]も前向き研究において身体能力の評価を含む移動障害が一つ増えるごとにオッズ比が1.5倍に高まることを報告している。これらの成績は、地域に自立して生活する高齢者における日常での身体的不自由度と複数回転倒発生との関連を示唆するものであった。

精神的不定愁訴をひとつでも有することは、その他の要因を調整しても複数回転倒の発生危険度を有意に高めた。しかし、不定愁訴数を連続変数として解析した際には、有意な関連を認めなかった。このことは、精神的不定愁訴に関してその数が増えることによって危険度が高まるというよりも、それを持つこと自体が複数回転倒発生に寄与していることを示唆している。先行研究では、抑うつと転倒との関連が報告されている[5,12]。本邦の疫学調査では地域の在宅高齢者のうつの発生率は５%程度であり[18]、抑うつの前段階として現れる抑うつ気分や憂鬱、