

PAPER

Differences in the relationship between lipid CHD risk factors and body composition in Caucasians and Japanese

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OBJECTIVES: To examine differences in the relationship between fat distribution and lipid coronary risk factors in Caucasian and Japanese population and further to determine whether the cut-points for body mass index (BMI) and waist circumference (WC) proposed by WHO and NHLBI are applicable to Japanese population as a predictor of a lipid risk factor abnormality or not.

RESEARCH METHODS AND PROCEDURES: Subjects were 895 participants of the Baltimore Longitudinal Study of Aging in the US (BLSA) and 1705 participants of the Longitudinal Study of Aging by the National Institutes for Longevity Science in Japan (NILS-LSA). Subjects were divided into four demographic groups as younger (age < 65 y) men and women, and older (age ≥ 65 y) men and women. Blood total cholesterol, triglycerides, LDL- and HDL-cholesterol and anthropometry were measured. Regression coefficients of BMI and WC on risk factors, sensitivity and specificity of the BMI and WC cut-points for blood lipid abnormality, and mean values of blood lipids at BMI or WC cut-points were computed in both populations.

RESULTS: Height, weight, WC and BMI were significantly greater in the BLSA than those in the NILS-LSA subjects. Total cholesterol, HDL- and LDL-cholesterol were significantly greater in the NILS-LSA than in the BLSA subjects. Sensitivities of BMI and WC cut-points were much lower in the NILS-LSA than in the BLSA subjects. Specificities of BMI and WC cut-points were higher in the NILS-LSA than in the BLSA subjects. Mean values of triglycerides, total cholesterol, HDL- and LDL-cholesterol at BMI = 25 were significantly greater in the NILS-LSA than in the BLSA subjects. At the WC cut-point (94 cm for men, 80 cm for women), mean values of all lipids were significantly greater in the NILS-LSA than in the BLSA subjects with the exception of triglycerides in younger women.

CONCLUSIONS: The Japanese subjects have smaller BMI and WC, worse total and LDL-cholesterol levels and better HDL-cholesterol levels compared to Caucasians. Sensitivities of BMI and WC for predicting lipid risk factor abnormality are much lower in Japanese. The cut-points for BMI and WC proposed by WHO and NHLBI may be too high for predicting an abnormality in triglycerides, total and LDL-cholesterol in Japanese. For detecting an abnormal HDL-cholesterol level, the BMI and WC cut-points may not be as beneficial for the Japanese population as for Caucasians.

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Introduction

The prediction and prevention of coronary heart disease (CHD) are of great importance, especially in industrial countries. The National Cholesterol Education Program (NCEP)¹ recommended that a fasting lipoprotein profile (total cholesterol, LDL-cholesterol, HDL-cholesterol and triglyceride) should be obtained once every 5 y in all adults aged 20 y or older. LDL-cholesterol was defined as the primary target of cholesterol-lowering therapy. Therefore, detecting an abnormality in blood lipids and initiating early treatment is essential to decrease the incidence of CHD.

It has been established that obesity, especially central distribution of body fat, is associated with many chronic diseases.²⁻⁶ Although imaging techniques such as magnetic resonance imaging (MRI) and computerized tomography (CT) have been the 'gold standard' methods for quantification of visceral fat, these methods are inconvenient and costly for routine clinical use. Therefore, several surrogates of intra-abdominal fat measurement have been examined.⁷⁻⁹ The body mass index (BMI) has long been used as a convenient, useful index of overweight and obesity. Studies have shown that waist circumference (WC) could be used to predict risk factor abnormalities as a surrogate of body fat distribution.⁹⁻¹¹ Han *et al*¹² indicated the linear relationship between WC and intra-abdominal fat. The World Health Organization (WHO)⁶ and the National Heart, Lung, and Blood Institute (NHLBI)⁵ issued comprehensive recommendations for classifying abnormalities in body weight and body fat distribution. Both reports recommended the BMI and the WC as measures of obesity and fat distribution, and concluded that risk of disease increases at a BMI of 25 kg/m² in both men and women; the WHO report noted increased risk at a WC of 94 cm for men and 80 cm for women.

It has been well known that obesity and fat distribution are influenced by complex factors including social, behavioral, cultural, physiological, metabolic and genetic factors. Differences in the relationships among BMI, WC and waist-hip ratio (WHR) in 19 populations, including Beijing Chinese, were reported by Molarius *et al*.¹³ They concluded that the

optimal screening cutoff point of WC and BMI may be population specific. Also, Hu *et al*¹⁴ showed that a rural Chinese population in developing countries has a different relationship between BMI and CHD from Western populations. However, NHLBI and WHO reports did not propose population-specific cut-points for either BMI or WC. Although it was shown that the cut-points proposed by WHO and NHLBI for BMI and WC were useful predictors for coronary risk factors in Caucasian younger and older men and women in our previous studies,^{15,16} it is still not clear whether or not these cut-points are applicable to relatively short stature and lighter weight populations in an industrial country such as Japan.

The purposes of the present study are (1) to examine the relationship between plasma lipid coronary risk factors and indices of body composition (BMI and WC) in Caucasian and Japanese populations; (2) to test whether recently proposed cut-points of BMI and WC can be applied to the younger and older Japanese population as well as to Caucasians.

Methods

Subjects

The subjects of this study consisted of 566 men and 329 women who participated in the Baltimore Longitudinal Study of Aging (BLSA) in USA, and 868 men and 837 women who participated in the National Longevity Sciences-Longitudinal Study of Aging (NILS-LSA) in Japan. Subjects of both

Table 1 Characteristics of BLSA and NILS subjects

	Younger (40-64 y)				Older (65-80 y)			
	BLSA		NILS		BLSA		NILS	
	N	Mean	N	Mean	N	Mean	N	Mean
<i>Men</i>								
Height (cm)	318	178.6	598	166.8**	248	174.3	270	160.9**
Weight (kg)	318	84.7	598	64.0**	248	77.1	270	57.5**
BMI (kg/m ²)	318	26.5	598	23.0**	248	25.3	270	22.2**
WC (cm)	318	93.8	598	81.9**	248	92.8	270	80.6**
Total cholesterol (mg/dl)	316	191.7	594	212.8**	248	188.4	268	211.1**
Triglycerides (mg/dl)	316	135.8	587	133.5	248	115.0	259	122.0
HDL-cholesterol (mg/dl)	316	41.1	596	57.9**	248	44.0	269	57.3**
LDL-cholesterol (mg/dl)	316	123.3	582	128.6*	248	121.3	257	130.5**
<i>Women</i>								
Height (cm)	183	163.6	620	153.7**	146	159.4	217	147.3**
Weight (kg)	183	65.9	620	53.4**	146	64.2	217	49.4**
BMI (kg/m ²)	183	24.6	620	22.6**	146	25.2	217	22.6**
WC (cm)	183	76.3	620	73.4**	146	79.9	217	75.6**
Total cholesterol (mg/dl)	180	188.5	615	221.9**	145	204.0	216	234.6**
Triglycerides (mg/dl)	180	98.6	596	98.0	145	112.8	211	118.8
HDL-cholesterol (mg/dl)	180	52.9	616	67.9**	145	55.4	217	64.4**
LDL-cholesterol (mg/dl)	179	115.8	595	135.1**	145	126.0	210	147.3**

**P<0.01, significant difference in mean values between BLSA and NILS-LSA subjects. *P<0.05, significant difference in mean values between BLSA and NILS-LSA subjects.

Table 2 Regression coefficient and trend analysis for BMI and WC

	Men				Women			
	Younger		Older		Younger		Older	
	BLSA	NILS	BLSA	NILS	BLSA	NILS	BLSA	NILS
<i>(a) BMI</i>								
Total cholesterol	1.33	1.39	-0.44	0.36	1.98	0.68	0.01	0.07
Triglycerides	7.14	8.74	8.05	4.47	4.04	5.25	3.13	4.47
HDL-cholesterol	-0.61	-1.75**	-1.33	-1.49	-0.40	-1.65**	-1.02	-1.72
LDL-cholesterol	0.51	1.39	-0.75	0.93	1.58	1.21	0.40	1.09
<i>(b) WC</i>								
Total cholesterol	0.43	0.42	-0.03	0.28	1.30	0.49*	-0.01	0.24
Triglycerides	2.71	3.65	2.44	1.77	2.53	2.40	1.46	2.08
HDL-cholesterol	-0.24	-0.74**	-0.45	-0.49	-0.30	-0.72**	-0.42	-0.74*
LDL-cholesterol	0.08	0.42	-0.16	0.39*	1.10	0.69	0.12	0.56

***P* < 0.01, significant difference in the coefficient between BLSA and NILS-LSA subjects. **P* < 0.05, significant difference in the coefficient between BLSA and NILS-LSA subjects.

cohorts were aged between 40 and 80 y old. The populations were dichotomized at age 65 y into younger and older age groups for each sex. The BLSA subjects were Caucasian and the NILS-LSA subjects were Japanese. Details of the selection process and procedures of the baseline examination in the BLSA and the NILS-LSA have been published previously.^{17,18} The subjects in the NILS-LSA were randomly selected from resident registrations in cooperation with the local government. The subjects in the BLSA were self-recruited, community-dwelling volunteers. Table 1 shows some descriptive statistics of the population.

Subjects who were being treated for hyperlipidemia that could influence the level of the risk factors were excluded. Measurements from women who were pregnant at the visit or who had had a baby less than 1 y prior to the visit were also excluded from these analyses.

Anthropometry

Height and weight were measured after an overnight fast with subjects wearing a light-weight hospital gown and without shoes. As an index of obesity, BMI was calculated as weight (kg) divided by the square of the height (m).

WC was used as the index of the body fat distribution. The waist was defined as the minimal abdominal circumference between the lower edge of the rib cage and the iliac crests in the BLSA, and as the circumference at the middle point between the lower edge of the rib cage and the iliac crests in the NILS-LSA. The circumferences were obtained with a flexible, metal tape measure, while maintaining close contact with skin and without compressing the underlying tissues. Subjects were in a standing position and breathing normally. The same small group of trained personnel made these measurements for the entire study in both the BLSA and the NILS-LSA.

Plasma lipids

After an overnight fast, an antecubital venous blood sample was drawn. The concentrations of plasma triglycerides and total cholesterol were determined by enzymatic method (Abbott Laboratories ABA-200 ATC Biochromatic Analyzer, Irving, TX 75015 for BLSA; Hitachi 7145 Automatic Analyzer, Hitachi Co., Ltd Japan for NILS-LSA). HDL-cholesterol was determined by dextran sulfate-magnesium precipitation procedure¹⁹ in the BLSA and enzymatic methods in NILS-LSA (Hitachi 7145 Automatic Analyzer, Hitachi Co., Ltd Japan). LDL-cholesterol concentrations were estimated by the Friedewald formula²⁰ in both BLSA and NILS-LSA.

Cut-points for abnormalities of BMI, WC and risk factors

Cut-points for BMI and WC abnormalities were determined according to NHLBI⁵ and WHO⁶ guidelines. The BMI and WC categories were dichotomized at the lower recommended cut-points due to the small number of subjects in the obese and high WC groups. In addition, the designation of the risk factor cut-points that define an abnormal level was derived from the 1994 recommendations of the National Cholesterol Education Program.²¹

BMI	25 kg/m ²
WC	80 cm for women, 94 cm for men
Total cholesterol	240 mg/dl
Triglyceride	200 mg/dl
HDL-cholesterol	35 mg/dl
LDL-cholesterol	160 mg/dl

Sensitivity and specificity of WC and BMI cut-points for risk factor abnormality

To examine the applicability of cut-points for WC and BMI proposed by WHO and NHLBI, the sensitivities and specificities of WC or BMI cut-points were calculated in the BLSA

and NILS-LSA subjects. By using cut-points both for risk factors and for BMI (or WC), subjects were divided into four groups as shown.

	Normal	Abnormal
Normal BMI (or WC)	A	B
Abnormal BMI (or WC)	C	D

Sensitivity is defined as D over the sum of B and D, and specificity is defined as A over the sum of A and C according to the general definition of these terms.¹³

Statistical methods

All data were analyzed using Statistical Analysis System (SAS) version 6. Standard methods were used to compute means and standard errors of the mean. *P*-values below 0.05 were regarded as indicating statistical significance. ANOVA was used to test for the presence of statistically significant differences in BMI, WC and risk factors between the BLSA and the NILS subjects. A test of whether or not the regression coefficients (slopes) of BMI (or WC) and the risk factors are consistent between the two populations was performed using general linear models. χ^2 analysis was performed for analyzing effects of population in the percentage of subjects with abnormal levels of BMI, WC and risk factors. Adjusted mean lipid values were computed using ANCOVA by setting the covariates (BMI or WC) to the appropriate cut-point value.

Results

Differences in BMI, WC and risk factors between the BLSA and NILS-LSA subjects

Height, weight, WC and BMI were significantly higher in the BLSA than those in the NILS-LSA subjects, regardless of the sex/age group (Table 1). The subjects in the NILS-LSA had significantly greater total and LDL-cholesterol in younger and older men and women. HDL-cholesterol was significantly greater in the NILS-LSA than that in the BLSA subjects for all demographic groups (younger and older men and women). There was no significant difference in triglycerides between BLSA and NILS-LSA.

Associations between BMI, WC and risk factors

The only lipid/anthropometric association that was consistently different between the two populations was that of HDL-cholesterol with both BMI and WC. In all cases, the regressions were negative, but the impact of the body composition variables was greater in the NILS population; in five of the eight regressions, these differences were statistically significant. These population differences were especially striking in the younger men and women.

There was also a consistent very large effect of both BMI and WC on the triglyceride levels, but there were no

Table 3 Percentage of subjects with an abnormal level in BMI, WC and lipid risk factors

	Men				Women			
	Younger		Older		Younger		Older	
	BLSA	NILS	BLSA	NILS	BLSA	NILS	BLSA	NILS
BMI	63.9	23.2**	48.8	17.9**	35.6	17.6**	44.1	21.8**
WC	49.4	5.2**	45.2	7.8**	31.7	19.0**	45.5	28.7**
Total cholesterol	8.2	20.5**	7.7	17.5**	12.2	30.9**	15.2	43.5**
Triglyceride	17.1	13.6	10.1	8.6	4.4	5.2	6.2	7.9
HDL-cholesterol	31.0	2.7**	23.4	2.2**	5.0	0.3**	6.2	0.0**
LDL-cholesterol	11.7	15.8*	10.1	11.2	11.7	20.8**	15.2	29.6**

***P*<0.01, significant difference between BLSA and NILS by χ^2 analysis.
**P*<0.05, significant difference between BLSA and NILS by χ^2 analysis.

significant differences in the slope between the two populations. The only other statistically significant slope differences were WC–total cholesterol in the younger women and WC–LDL-cholesterol in the older men, but these population differences were inconsistent in the other three demographic (age/sex) groups (Table 2).

Percentage of subjects with an abnormal risk factor status

Table 3 shows the percentages of subjects with an abnormal level of BMI, WC or risk factors for each age/sex group in the BLSA and NILS-LSA subjects. The percentage of subjects with an abnormal BMI as well as an abnormal WC was significantly greater in the BLSA than that in the NILS-LSA subjects in younger and older men and women. Consistent with these population differences, there was a significantly higher percentage of subjects with an abnormal HDL-cholesterol level in the BLSA than that in the NILS subjects in all age/sex groups. The percentage of subjects with an abnormal level of total and of LDL-cholesterol was significantly higher in NILS-LSA subjects than those in BLSA subjects with the exception of LDL-cholesterol in younger men. Abnormal triglyceride levels were similar in the two populations.

Sensitivity of BMI and WC

Table 4a shows the sensitivity of BMI cut-points proposed by WHO and NHLBI (BMI < 25 kg/m²) for predicting risk factor abnormality. Sensitivities of BMI were very much lower in the NILS-LSA than in the BLSA. Also, sensitivities of WC (Table 4b) were lower in the NILS-LSA than those in the BLSA subjects.

Specificity of BMI and WC

Specificity of BMI and WC is shown in Table 5a and b. Higher specificities of BMI were found in younger and older men

Table 4 Sensitivity of BMI and WC cut-point for lipid risk factor abnormality

	Men				Women			
	Younger		Older		Younger		Older	
	BLSA	NILS	BLSA	NILS	BLSA	NILS	BLSA	NILS
<i>(a) BMI</i>								
Total cholesterol	69.2	27.1**	63.2	17.0**	45.5	17.7**	31.8	20.7
Triglycerides	88.9	37.4**	84.0	29.2**	62.5	50.0	77.8	23.5**
HDL-cholesterol	78.4	12.5**	70.7	16.7**	75.0	—	75.0	—
LDL-cholesterol	70.3	33.0**	44.0	20.0**	42.9	16.4**	40.9	21.9
Mean	76.7	27.5	65.5	20.7	56.5	28.0	56.4	22.0
<i>(b) WC</i>								
Total cholesterol	50.0	8.2**	47.4	10.6**	45.5	24.1*	36.4	26.1
Triglycerides	75.9	14.5**	72.0	20.8**	62.5	59.4	66.7	41.2
HDL-cholesterol	65.0	6.3**	67.2	16.7**	75.0	50.0	75.0	—
LDL-cholesterol	46.0	9.6**	40.0	10.0**	42.9	23.4 (0.06)	40.9	31.6
Mean	59.2	9.6	56.7	14.5	56.5	39.2	54.7	33.0

***P*<0.01, significant difference in sensitivity between BLSA and NILS-LSA subjects. **P*<0.05, significant difference in sensitivity between BLSA and NILS-LSA subjects. —: there was no NIL-LSA subject in some categories that were used for calculation of sensitivity.

Table 5 Specificity of BMI and WC cut-point for lipid risk factor abnormality

	Men				Women			
	Younger		Older		Younger		Older	
	BLSA	NILS	BLSA	NILS	BLSA	NILS	BLSA	NILS
<i>(a) BMI</i>								
Total cholesterol	36.6	77.8**	52.4	81.9**	65.8	82.4**	53.7	76.3**
Triglycerides	41.2	79.2**	55.2	83.4**	65.7	84.2**	58.1	77.7**
HDL-cholesterol	42.5	76.6**	57.9	82.1**	66.3	82.3**	57.3	77.6**
LDL-cholesterol	36.9	78.7**	50.7	82.4**	65.4	82.0**	55.3	77.4**
Mean	39.3	78.1	54.0	82.5	65.8	82.7	56.1	77.3
<i>(b) WC</i>								
Total cholesterol	50.7	95.6**	55.0	92.8**	70.3	82.8**	52.9	67.8*
Triglycerides	56.1	96.2**	57.9	93.2**	69.8	83.0**	55.9	71.5**
HDL-cholesterol	58.0	94.8**	61.6	92.4**	70.4	80.8**	55.8	70.5**
LDL-cholesterol	50.5	95.5**	54.3	92.1**	69.8	81.8**	53.7	71.2**
Mean	53.8	95.5	57.2	92.6	70.0	82.1	54.5	70.3

***P*<0.01, significant difference in sensitivity between BLSA and NILS-LSA subjects. **P*<0.05, significant difference in sensitivity between BLSA and NILS-LSA subjects.

and women in the NILS-LSA subjects compared to the BLSA subjects. Specificities of WC were also higher in the NILS-LSA subjects than those in the BLSA subjects, especially in men.

Mean values of risk factors at cut-points of BMI and WC

At the cut-point of BMI, mean values of triglycerides, total and LDL-cholesterol were significantly greater (worse) in the NILS-LSA than those in the BLSA subjects regardless of demographic groups (Table 6a). Mean values of HDL-cholesterol in the NILS-LSA subjects were significantly higher (better) than in the BLSA subjects.

At the cut-points of WC, mean values of triglycerides, total and LDL-cholesterol were significantly greater (worse) in the NILS-LSA than those in the BLSA subjects in all groups with the exception of triglycerides in younger women (Table 6b). The mean values of HDL-cholesterol in younger and older men and women were greater (better) in the NILS-LSA than in the BLSA subjects.

Discussion

Our previous reports on a Caucasian population^{15,16} showed that BMI and WC independently were significant predictors of coronary risk factors in the blood pressure, glucose-

Table 6 Mean lipid values

	Men				Women			
	Younger		Older		Younger		Older	
	BLSA	NILS	BLSA	NILS	BLSA	NILS	BLSA	NILS
<i>(a) BMI (25 kg/m²)</i>								
Total cholesterol (mg/dl)	189.6	215.6**	188.5	212.1**	189.2	223.5**	204.0	234.8**
Triglyceride (mg/dl)	124.8	151.3**	112.4	134.7**	100.0	110.4*	112.1	129.1*
HDL-cholesterol (mg/dl)	42.0	54.3**	44.4	53.2**	52.7	63.9**	55.6	60.4**
LDL-cholesterol (mg/dl)	122.5	131.4**	121.5	133.1**	116.4	138.0**	125.9	149.9**
<i>(b) WC (94 cm for men, 80 cm for women)</i>								
Total cholesterol (mg/dl)	191.8	217.9**	188.3	214.9**	193.3	225.1**	204.0	235.7**
Triglyceride (mg/dl)	136.4	177.8**	117.9	145.7**	108.0	113.7	112.9	127.7*
HDL-cholesterol (mg/dl)	41.0	49.0**	43.4	50.8**	51.8	63.1**	55.4	61.2**
LDL-cholesterol (mg/dl)	123.3	133.7**	121.2	135.7**	119.9	139.6**	126.0	149.7**

** $P < 0.01$, significant difference between the BLSA and NILS-LSA subjects. * $P < 0.05$, significant difference between the BLSA and NILS-LSA subjects.

insulin and plasma lipid domains. Furthermore, the gradation of BMI into normal, overweight and obese zones according to NHLBI⁵ and WHO⁶ recommendations was supported. Also, the sex-specific WHO cut-points for WC that provided three zones (NHLBI standards provided two zones) were also found to be applicable to the risk factors in the four age-sex categories in Caucasians. However, it was pointed out that the BMI and/or WC in Asian populations are much lower than those in Caucasians.²² Therefore, the important questions that remain are whether BMI and/or WC associated with coronary risk factors in relatively short and light-weight Asian populations as well as in Caucasians, and whether the BMI and WC cut-points proposed by NHLBI and WHO are applicable to Asian populations as a predictor of risk factor abnormality.

In the present study, in order to examine these questions, the relationship between BMI, WC and lipid risk factors (regression) and the applicability (sensitivity, specificity) of the BMI and WC cut-points for these risk factors were compared between the BLSA (Caucasian) and the NILS-LSA subjects (Japanese).

Height, weight and BMI were lower in the NILS-LSA than in the BLSA subjects regardless of the age/sex groups. There was a methodological difference in the measurement of WC between BLSA and NILS-LSA (see the Methods section). Although the minimal circumferences between the lower edge of the rib cage and the iliac crests were measured as WC in the BLSA subjects, the circumference at the middle point between the lower edge of the rib cage and the iliac crests was measured in the NILS-LSA subjects. Therefore, the measured WC in the NILS-LSA subjects may not be minimal as was the BLSA measurement. Despite this, WC in the NILS-LSA is still much smaller than that in the BLSA. In addition, WC of the NILS-LSA subjects was as highly correlated to BMI and to lipids as WC of the BLSA subjects (data not shown). Therefore, we compared the data of WC between the BLSA and the NILS-LSA directly.

It is well known that greater BMI or WC results in higher lipid risk factor levels. However, Japanese subjects (NILS-LSA) had higher levels in total cholesterol and LDL-cholesterol with smaller weight, BMI and WC, compared to Caucasians (BLSA). This result may indicate that associations between BMI, WC and lipid levels in Japanese differ from those in Caucasians. In the present study, the relationship (slope of regression) between BMI, WC and total cholesterol, triglycerides and LDL-cholesterol was similar, with the exception of the relationship between WC and LDL-cholesterol in older men, and between WC and total cholesterol in younger women. However, relationships between BMI, WC and HDL-cholesterol in most demographic groups were different in the two populations. Although relationships between BMI, WC and risk factors (triglycerides, total and LDL-cholesterol) were similar in the two populations, the mean values of total and LDL-cholesterol, and the percentages of subjects with an abnormal level of total and LDL-cholesterol in the NILS-LSA were higher than the levels of these variables in the BLSA subjects. In addition, the mean values at the BMI and WC cut-points in triglycerides, total and LDL-cholesterol were also higher (worse) in the NILS-LSA than those in the BLSA subjects. The mean plasma lipids are different between Japanese and Caucasians, although Japanese and Caucasians have similar relationships between BMI, WC and triglycerides, total and LDL-cholesterol. Because Japanese have higher levels of plasma lipids (excepting HDL-cholesterol) with a smaller BMI and WC, a normal BMI and WC defined by WHO and NHLBI does not indicate a lower risk in triglycerides, total and LDL-cholesterol in the Japanese population. The BMI and WC cutoff points seem to be too high as a predictor of risk abnormality to detect an abnormality in triglycerides, total and LDL-cholesterol for the Japanese population. Present data of very low sensitivities of the BMI and WC cut-points in the NILS-LSA support these results. For example, 83% of older men in the NILS-LSA who had an abnormal total cholesterol level had a normal

BMI, and 89.4% older men in the NILS-LSA with an abnormal total cholesterol had a normal WC.

Thus, the cut-points for BMI and WC proposed by WHO and NHLBI may not be ideal or even useful predictors of risk abnormality in the Japanese population. If these cutoff points of abnormality for BMI and WC are defined at lower levels, they may become a useful index for the Japanese population because BMI and WC still correlate with lipid risk factors in the Japanese subjects (data not shown). Further examinations are needed for the selection of the specific cutoff points for BMI and WC in the Japanese population.

In the present study, different relationships between BMI, WC and HDL-cholesterol in the two populations were found in most demographic groups. Although the magnitudes of the decrease in HDL-cholesterol with the increases of BMI and WC were greater in the NILS-LSA than in the BLSA subjects, mean values of HDL-cholesterol at the BMI and WC cut-points were still greater (better) in the NILS-LSA subjects. In the present study, there was a difference in the lipid methodologies between the two populations (see the Methods section). However, accuracy of both methods has been certified by the Center for Disease Control and Prevention (CDC). In addition, mean HDL-cholesterol levels were very similar in the BLSA and NHANES III,²³ and also in NILS-LSA and the National Nutrition Survey (Japan).²⁴ Therefore, we do not believe that these significant differences in HDL-cholesterol between BLSA and NILS-LSA subjects were caused by the methodological difference in HDL-cholesterol measurement. Thus, we compared HDL-cholesterol levels between BLSA and NILS-LSA subjects directly. Our result shows that the Japanese population with a normal BMI or WC has a remarkably higher level of HDL-cholesterol. NCEP noted that a high HDL-cholesterol level appears to be protective against CHD, and a level of ≥ 60 mg/dl can even be called 'a negative risk factor'. The mean values of HDL-cholesterol at the BMI cut-point in the Japanese population were 54, 53, 64 and 60 mg/dl in younger men, older men, younger women and older women, respectively. And the mean values of HDL-cholesterol at the WC cut-point were 49, 51, 63 and 61 mg/dl in these groups. Mean HDL-cholesterol levels in Japanese women were close to being 'a negative risk factor', even if their BMI levels exceeded 25 kg/m² or their WC levels exceeded 80 cm.

From our results, it may seem that the BMI and WC cut-points proposed by WHO and NHLBI are at levels too low for detecting HDL-cholesterol abnormality in the NILS-LSA subjects. However, it should be taken into account that most Japanese have relatively small BMI and WC (percentage of subjects with an abnormal BMI and WC in the four age/sex groups are only 5–29). If cut-points of BMI and WC are set at higher levels, almost no Japanese will have an 'abnormal' WC or BMI. In this Japanese population, lowering the cut-points for BMI or WC will provide very low specificity and rising the cut-points will yield very low sensitivity. The only other solution would be to redefine the level of HDL-cholesterol abnormality for the Japanese population.

Accumulation of intra-abdominal fat has been shown to be associated with risk factor abnormalities.^{3,25,26} Although we did not quantify intra-abdominal fat using CT scans in the present study, the distribution of intra-abdominal fat might well be different in the two populations. This may underlie the fact that the BMI and WC cut-points do not have the same level of applicability for predicting risk abnormality in Caucasian and Japanese populations. Therefore, further study is needed to better understand the relation between abdominal fat distribution (CT scan) and risk factor abnormality; it should however be noted that Takami *et al*²⁷ reported that BMI and WHR are better predictors of metabolic abnormalities than abdominal fat measured by CT.

Also, the reason for the differences in blood lipids between the Japanese and Caucasian populations was beyond the scope of the present study. Diet, exercise, body composition or genetics might be expected to contribute to these differences.^{28–32}

In the present study, there was an interesting finding that correlations between BMI, WC and lipids (total and LDL-cholesterol) in older people were weak or not significant regardless of populations, although BMI and WC were still highly correlated with triglycerides and HDL-cholesterol in older people. We have previously reported the effects of age on the relationship between body composition and risk factors in Caucasians^{15,16,33} and these effects are also seen in the Japanese population.

In conclusion, the Japanese subjects have higher total and LDL-cholesterol levels with smaller mean BMI and WC measurements compared to Caucasians. Although mean values in triglycerides, total and LDL-cholesterol at the recommended cut-points of BMI and WC (BMI = 25 kg/m², WC = 94 cm for men 80 cm for women) are obviously high (worse) in the Japanese, the mean HDL-cholesterol level at the cut-point is higher (ie, better) in Japanese. Thus, these cut-points for BMI and WC proposed by WHO and NHLBI may be too high for predicting an abnormality in triglycerides, total and LDL-cholesterol in Japanese. Predicting an abnormal HDL-cholesterol level using the cut-points for BMI and WC may not be as beneficial for the Japanese population as for Caucasians.

It must be noted that direct analyses of the predictive power of the cut-points for BMI and WC on the development of CHD itself in Japanese and Caucasian populations would be instructive, since the variables examined are risk factors for CHD in the present study. We must also note that direct examinations of the relationship among the characteristics in plasma lipids, nutrition intake, and morbidity and mortality of CHD in the Japanese and Caucasians are desirable in future studies.

Acknowledgements

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References

- 1 National Cholesterol Education Program. Third report of the National Cholesterol Education Program (NCEP) Expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III) final report. *Circulation* 2002; 106: 3143–3421.
- 2 Fujioka S, Matsuzawa Y, Tokunaga K, Tarui S. Contribution of intra-abdominal fat accumulation to the impairment of glucose and lipid metabolism in human obesity. *Metabolism* 1987; 36: 54–59.
- 3 Bjorntorp P. Metabolic implications of body fat distribution. *Diabetes Care* 1991; 14: 1132–1143.
- 4 Bjorntorp P. Abdominal fat distribution and disease: an overview of epidemiological data. *Ann Med* 1992; 24: 15–18.
- 5 NHLBI Obesity Education Initiative Expert Panel. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults. *Obes Res* 1998; 6: 51S–209S.
- 6 WHO Consultation on Obesity. Obesity. In: WHO (ed). *Preventing and managing the global epidemic*. Division of Noncommunicable Diseases, Programme of Nutrition, Family and Reproductive Health, World Health Organization: Geneva, Switzerland; 1998.
- 7 Molarius A, Seidell J. Selection of anthropometric indicators for classification of abdominal fatness—a critical review. *Int J Obes Relat Metab Disord* 1998; 22: 719–727.
- 8 Poulriot M, Despres J, Lemieux S, Moorjani S, Bouchard C, Tremblar A, Nadeau A, Lupien P. Waist circumference and abdominal sagittal diameter: best simple anthropometric indexes of abdominal visceral adipose tissue accumulation and related cardiovascular risk in men and women. *Am J Cardiol* 1994; 73: 460–467.
- 9 Turcato E, Bosello O, Harris T, Zoico E, Bissoli L, Fracassi E, Zamboni M. Waist circumference and abdominal sagittal diameter as surrogates of body fat distribution in the elderly: their relation with cardiovascular risk factors. *Int J Obes Relat Metab Disord* 2000; 24: 1005–1010.
- 10 Lean M, Han T, Seidell J. Impairment of health and quality of life in people with large waist circumference. *Lancet* 1998; 351: 853–856.
- 11 VanItallie T. Waist circumference: a useful index in clinical care and health promotion. *Nutr Rev* 1998; 56: 300–313.
- 12 Han T, McNeill G, Seidell J, Lean M. Predicting intra-abdominal fatness from anthropometric measures: the influence of stature. *Int J Obes Relat Metab Disord* 1997; 21: 587–593.
- 13 Molarius A, Seidell J, Sans S, Tuomilehto J, Knulasmaa K. Varying sensitivity of waist action Levels to identify subjects with overweight or obesity in 19 populations of the WHO MONICA project. *J Clin Epidemiol* 1999; 52: 1213–1224.
- 14 Hu F, Wang B, Chen C, Jin Y, Yang J, Stampfer M, Xu X. Body mass index and cardiovascular risk factors in a rural Chinese population. *Am J Epidemiol* 2000; 151: 88–97.
- 15 Iwao S, Iwao N, Muller D, Elahi D, Shimokata H, Andres R. Effects of aging on the relationship between multiple risk factors and waist circumference. *J Am Geriatr Soc* 2000; 48: 788–794.
- 16 Iwao N, Iwao S, Muller D, Elahi D, Shimokata H, Andres R. A test of recently proposed BMI standards with respect to old age. *Aging: Clin Exp Res J* 2000; 12: 461–469.
- 17 Shock N, Greulich R, Andres R, Arenberg D, Costa PJ, Lakatta E, Tobin J. *Normal human aging*. U.S. Department of Health and Human Services, U.S. Government Printing Office, National Institutes of Health Publication: Washington, DC, 1984. pp 84–2450.
- 18 Shimokata H, Ando F, Niino N. A new comprehensive study on aging—the National Institute for Longevity Sciences, Longitudinal Study of Aging (NILS-LSA). *J Epidemiol* 2000; 10: S1–S9.
- 19 Warnick G, Benderson J, Albers J. Dextran sulfate-Mg²⁺ precipitation procedure for quantification of high-density-lipoprotein cholesterol. *Clin Chem* 1982; 28: 1379–1388.
- 20 Friedewald W, Levy R, Fredrickson D. Estimation of the concentration of low-density-lipoprotein cholesterol in plasma without the use of the preparation ultracentrifuge. *Clin Chem* 1972; 18: 499–502.
- 21 National Cholesterol Education Program. Second report of the expert panel on detection, evaluation, and treatment of high blood cholesterol in adults. *Circulation* 1994; 89: 1333–1432.
- 22 Molarius A, Seidell J, Sans S, Tuomilehto J, Kuulasmaa K. Waist and hip circumferences, and waist–hip ratio in 19 populations of the WHO MONICA Project. *Int J Obes Relat Metab Disord* 1999; 23: 116–125.
- 23 Brown C, Higgins M, Donato K, Rohde F, Garrison R, Obarzanek E, Ernst N, Horan M. Body mass index and the prevalence of hypertension and dyslipidemia. *Obes Res* 2000; 8: 605–619.
- 24 The Ministry of Health and Welfare. *National nutrition in 1998*. Daiichi Public: Tokyo, 1999 (in Japanese).
- 25 Nakamura T, Tokunaga K, Shimomura I, Nishida M, Yoshida S, Kotani K, Islam A, Keno Y, Kobatake T, Nagay Y, Fujioka S, Tarui S, Matsuzawa Y. Contribution of visceral fat accumulation to the development of coronary artery disease in non-obese men. *Atherosclerosis* 1994; 107: 239–246.
- 26 Despres J. Abdominal obesity as important component of insulin-resistance syndrome. *Nutrition* 1993; 9: 452–459.
- 27 Takami R, Takeda N, Hayashi M, Sasaki A, Kawachi S, Yoshino K, Takami K, Nakashima K, Akai A, Yamakita N, Yasuda K. Body fatness and fat distribution as predictors of metabolic abnormalities and early carotid atherosclerosis. *Diabetes Care* 2001; 24: 1248–1252.
- 28 Kumagi S, Tanaka H, Kitajima H, Kono S, Ogawa K, Yamauchi M, Morita N, Inoue M, Shindo M. Relationships of lipid and glucose metabolism with waist–hip ratio and physical fitness in obese men. *Int J Obes Relat Metab Disord* 1993; 17: 437–440.
- 29 Rodriguez B, Sharp D, Abbott R, Burchfiel C, Masaki K, Chyou P, Huang B, Yano K, Curb J. Fish intake may limit the increase in risk of coronary heart disease morbidity and mortality among heavy smokers. The Honolulu Heart Program. *Circulation* 1996; 94: 952–956.
- 30 Nakamura K, Shimai S, Kikuchi S, Tanaka M. Correlation between a liking for fat-rich foods and body fatness in adult Japanese: a gender difference. *Appetite* 2001; 36: 1–7.
- 31 Pott J, Simmons D. Sex and ethnic group differences in fat distribution in young United Kingdom South Asians and Europids. *J Clin Epidemiol* 1994; 47: 837–841.
- 32 The Research Group on Serum Lipid Survey. Analysis of serum lipid levels in Japanese men and women according to body mass index. Increase in risk of atherosclerosis in postmenopausal women. *Atherosclerosis* 1999; 143: 55–73.
- 33 Iwao S, Iwao N, Muller D, Elahi D, Shimokata H, Andres R. Does waist circumference add to the predictive power of the body mass index for coronary risk? *Obes Res* 2001; 9: 658–695.

ORIGINAL ARTICLE

Relationships of muscle strength and power with leisure-time physical activity and adolescent exercise in middle-aged and elderly Japanese women

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Aim: The purpose of the present study is to assess the relationships of muscle strength and power with recent leisure-time physical activity and exercise during adolescence in middle-aged and elderly Japanese women.

Methods: The subjects consisted of 1128 community-dwelling women aged 40–79 years. They were interviewed about their physical activity habits during leisure time in the past 12 months and exercise they engaged in during adolescence. Muscle function was measured as grip strength, knee extension strength and leg extension power. Subjects were grouped into three intensity levels for leisure-time physical activity and as to whether or not they engaged in adolescent exercise. The relationships of muscle strength and power with leisure-time physical activity and adolescent exercise were assessed using analysis of covariance controlled for age, smoking status, annual income and education level.

Results: The proportion of subjects that participated in leisure-time physical activity was 67.1% (light, 33.7%; moderate or heavy, 33.4%). The subjects that engaged in adolescent exercise represented 41.9% of the total. There was a significant relationship between leisure-time physical activity and adolescent exercise. In the analysis of covariance controlled for age, smoking status, annual income and education level, leisure-time physical activity and adolescent exercise had significant main effects on all muscle strength and power measurements. However, there was no interaction effect between leisure-time physical activity and adolescent exercise.

Conclusion: The results suggest that current leisure-time physical activity and adolescent exercise benefit muscle function in middle-aged and elderly women.

Keywords: adolescent exercise, leisure-time physical activity, middle-aged and elderly, muscle power, muscle strength.

Introduction

Regular physical activity and exercise are closely associated with muscle function. Previous cross-sectional studies suggest that regular physical activity, such as leisure-time physical activity or playing sports, is positively

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associated with muscle strength and power,^{1,2} and some longitudinal studies showed that elderly women who were very physically active maintained their knee extensor strength at a higher level.^{3,4} Intervention studies also documented the effects of strength training on the improvement of muscle strength.⁵⁻¹¹ The stimuli of physical activity or exercise on skeletal muscle may help maintain or improve muscle function.

On the other hand, since muscle function develops rapidly during childhood and adolescence, reaching a peak during adulthood, the beneficial effects of exercise on muscle development seem to be greater during this period. Moreover, Malina noted that tracking of physical activity in youth was associated with physical performance in later life.¹² Therefore, it is important to pay attention not only to current physical activity but also to adolescent physical activity to prevent a decline of muscle strength and power in the elderly. However, little is known about the contribution of both current and adolescent physical activity on muscle function in middle-aged and elderly people.

The purpose of the present study was to assess the relationships of muscle strength and power with current leisure-time physical activity (LTPA) and past adolescent exercise (AEX) in middle-aged and elderly Japanese women. Although the age-associated changes in muscle strength and power were similar by gender, women are generally weaker than men across the adult life span.¹³⁻¹⁸ Since women have a longer period of dependency than men, in spite of women's longer life expectancy,^{19,20} poor muscle strength and power may be a more serious physical problem for elderly women, resulting in disability or difficulty in performing basic daily tasks. For these reasons, we focused on women in this study.

Methods

Subjects

The data for the present study were derived from baseline data collected as part of the initial survey of the National Institute for Longevity Sciences-Longitudinal Study of Aging (NILS-LSA). In this project, the normal aging process has been assessed using detailed questionnaires and examinations including clinical evaluations, blood chemistries, anthropometrical measurements, physical fitness tests, nutritional analysis, and psychological tests. Details of the study are reported elsewhere.²¹ The initial survey of NILS-LSA involved 2267 men and women aged 40-79 years. They were gender- and decade age-stratified random samples living in Obu city and Higashiura-cho Aichi Prefecture, Japan. Written informed consent was obtained from all the participants. Out of these 2267 participants, 1128 women were used as subjects in this study.

Muscle function

Grip strength (GS): a handgrip dynamometer (Takei Co., Japan) was used to assess grip strength in kilograms. The subjects stood holding a handgrip dynamometer with their hands by their sides while squeezing with maximum force alternating the left and right hands. The average of two readings from each hand was used as the measurement result.

Knee extension strength (KES): the subjects were seated in an adjustable straight-back chair (Takei Co., Japan) with the pelvis, knee and ankle fixed at 90°. A strain gauge was attached to the distal leg by a strap just above the ankle. The subjects tried to extend their legs using maximum isometric force with the knee flexed at 90° while the amplified output from the strain gauge was recorded. The average of the maximum force that each leg attained after three attempts was used as the measurement result in kilograms.

Leg extension power (LEP): leg extension power was measured with the help of a sledge ergometer in a sitting position (Takei Co., Japan). The acceleration of the sledge was 0.73 m/s and the sledge stroke was 0.79 m. The subjects were fastened by a seat belt to the chair. In the starting position, the feet were placed on a footplate attached perpendicularly to a rail, and the knee angle was adjusted to 90°. The subjects were asked to extend their legs as quickly and powerfully as possible, so that the footplate started sliding horizontally on the rail. The highest result of eight attempts was taken as the measurement result in watts.

A medical doctor asked the subjects about their health condition before the muscle function tests. Subjects with serious pains, physical injuries or illness of the orthopedic or cardiovascular systems were excluded. All muscle function tests were performed on the same day.

Physical activity

Leisure-time physical activity (LTPA): trained interviewers using a questionnaire developed by the Japanese Lifestyle Monitoring Study Group asked subjects about the frequency and duration of their physical activity habits during leisure time for the past 12 months.²² This questionnaire was modified from the Minnesota Leisure-time Physical Activity Questionnaire, one of the most widely used physical activity questionnaires.²³ Activities that were performed at least once a week and for 10 min were defined as LTPA, and classified into three levels: light (approximate physical intensity; 2.5 METs [metabolic equivalents]); moderate (4.5 METs); heavy (> 6.5 METs) (Table 1). Sedentary activities in LTPA, for example, bonsai, were excluded.

Adolescent exercise (AEX): subjects were also interviewed in the same questionnaire about the frequency and duration of their participation in physical exercise

Table 1 The classification of leisure-time physical activity

Level	Approximate intensity (METs)	Description	Examples
Light	2.5	Activity such as walking	Walking, gymnastic exercise, gardening, etc.
Moderate	4.5	Sweating activity that one can do comfortably	Brisk walking, dancing, swimming for pleasure, etc.
Heavy	≥ 6.5	Vigorous exercise with heavy breathing	Several sports activities (swimming, tennis, badminton etc.)

METs, metabolic equivalents.

Table 2 Characteristics of the subjects

	<i>n</i>	Mean ± SD
Age (years)	1128	59.3 ± 10.9
Height (cm)	1128	151.3 ± 6.1
Weight (kg)	1128	52.4 ± 8.2
Body mass index (kg/m ²)	1128	22.9 ± 3.3
Body fat (%)	1120	31.5 ± 5.2
Grip strength (kg)	1106	23.8 ± 5.1
Knee extension strength (kg)	780	25.2 ± 6.8
Leg extension power (w)	1048	301.4 ± 107.1
Smoking status (%; currently)	1126	7.3
Annual income (%; ≥ ¥6 500 000)	1055	54.7
Education level (%; > high school)	1123	23.1

or sports, such as club activities, in addition to compulsory physical exercise at school from 12 to 20 years of age. Activities that were engaged in at least once a week over 1 year were defined as AEX.

Other parameters

Height and weight were measured using a digital scale. Body mass index was calculated by weight divided by height squared (BMI; kg/m²). Body fat mass was assessed by dual X-ray absorptiometry (DXA; QDR-4500A, Hologic, USA). Lifestyle factors including smoking status, annual income and education level were also determined by questionnaire.

Statistical analysis

The participation rate in physical activity was calculated as the percentage of subjects who reported such activities in a multiple response format. The subjects were divided into three groups according to the intensity of LTPA: no LTPA, LTPA (N); participation in only light activities, LTPA (L); participation in moderate or heavy activities, LTPA (H). Because there were only a few

Table 3 The participation rates in leisure-time physical activity (LTPA) and adolescent exercise (AEX)

	Levels	<i>n</i> (%)
LTPA	None	371 (32.9)
	Light	380 (33.7)
	Moderate or heavy	377 (33.4)
AEX		473 (41.9) [†]

[†]Total number of the subjects who participated in AEX.

subjects who participated in heavy LTPA, we combined the subjects who engaged in moderate LTPA and heavy LTPA together as LTPA (H). They were also divided into those who engaged in adolescent exercise, AEX (+), and those that did not, AEX (-). The Cochran-Mantel-Haenszel method was used to examine the relationship between LTPA and AEX. The relationship of muscle function with LTPA and AEX was analyzed using the analysis of covariance controlled for age, smoking status, annual income and education level. Statistical testing was performed using the Statistical Analysis System release.8.2 (SAS Institute Inc. NC, USA).²⁴ Significant probability levels were considered to be less than 0.05.

Results

The characteristics of the subjects are summarized in Table 2. The mean and standard deviation (SD) of age was 59.3 ± 10.9 years. The averages of the anthropometric parameters, height, weight, BMI and percent body fat, were 151.3 ± 6.1 cm, 52.4 ± 8.2 kg, 22.9 ± 3.3 kg/m² and 31.5 ± 5.2%, respectively. The averages for muscle strength and power, GS, KES and LEP, were 23.8 ± 5.1 kg, 25.2 ± 6.8 kg and 301.4 ± 107.1 w, respectively. The proportions of people who currently smoked, had an annual income of over 6 500 000 yen, and had an education beyond high school were 7.3, 54.7 and 23.1%, respectively.

Table 3 shows the participation rates in LTPA and AEX. Subjects who did not participated in leisure-time

Table 4 The relationship between leisure-time physical activity (LTPA) and adolescent exercise (AEX)

	LTPA (N)	LTPA (L)	LTPA (H)	P-value
AEX (-)	228 (34.8)	242 (37.0)	185 (28.2)	< 0.001
AEX (+)	143 (30.2)	138 (29.2)	192 (40.6)	

Numbers (%) are shown for those who participated in LTPA or AEX.
Cochran-Mantel-Haenszel test, $df = 1$.

Table 5 Covariance models for muscle functions

	Grip strength		Knee extension strength		Leg extension power	
	df	F-value	df	F-value	df	F-value
LTPA	2	5.6*	2	11.8*	2	13.8*
AEX	1	28.8*	1	17.3*	1	8.6*
LTPA \times AEX	2	0.2	2	0.1	2	0.9
Error	1023		718		972	
r^2		0.32		0.23		0.26

* $P < 0.05$.

Covariance models were controlled for age, smoking status, annual income and education level.
LTPA, leisure-time physical activity; AEX, adolescence exercise.

physical activity in the past 12 months accounted for 32.9%. Subjects who participated in light activities and in moderate or heavy activities were 33.7% and 33.4%, respectively. About 42% reported that they had participated in AEX. The most popular sports in adolescence were volleyball, table tennis and softball.

There is a significant difference in the participation rates of LTPA relative to the level of AEX (Table 4). The AEX (+) subjects were more likely to participate in higher levels of LTPA than the AEX (-) subjects ($P < 0.001$).

The relationships of muscle strength and power to both LTPA and AEX are shown in Table 5. As a result of analysis of covariance controlled for age, smoking status, annual income and education level, LTPA and AEX had significant main effects on GS, KES and LEP ($P < 0.05$). However, there was no interaction effect between LTPA and AEX, which indicated the subjects who participated in higher levels of LTPA or the subjects who participated in AEX independently have stronger muscle strength and power than those who did not participate (see Fig. 1).

Discussion

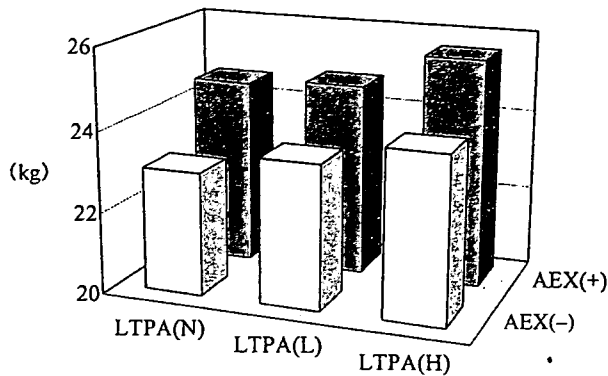
The aim of the present study was to examine the relationships of muscle strength and power with current leisure-time physical activity and past adolescent exercise in middle-aged and elderly women. We found that people who participated in higher levels of current leisure-time physical activity or adolescent exercise had stronger grip strength, knee extension

strength and leg extension power than those who did not participate.

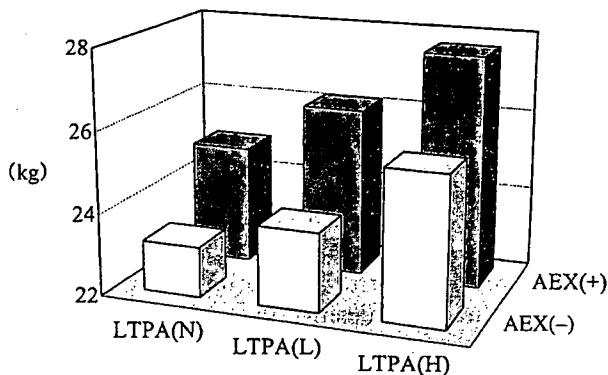
Our result that current leisure-time physical activity was associated with positive muscle functions is supported by previous studies. In a cross-sectional study, Hunter *et al.* reported that women who participated in recreational activity or exercise had stronger hand-grips and greater knee extensor strength across age groups (from the 20s through 80s) than those who did not participate in those activities.²⁵ Van Heuvelen *et al.* also reported that leisure-time physical activity is positively and age-independently associated with grip strength among a community-based sample aged 57 years and older.¹ As for muscle power, it was shown that current physical and sporting activities could contribute to muscular strength and power improvement among healthy subjects over 60 years old.²⁶ Current leisure-time physical activity may help preserve muscle strength and power. Improvements in muscle function due to training adaptation have been observed in several intervention studies.⁷⁻¹¹ Although strength training may increase muscle function, the results of our study suggest that stimuli from leisure-time physical activity, which does not necessarily include strength training, may also affect the development of muscle function.

Furthermore, although the data were not shown, we also analyzed the data excepted for the subjects who participated in heavy leisure-time physical activity from LTPA (H), and attained results similar to those we have presented here. Accordingly, the physical activity required to maintain or develop muscle function seems to be only moderate activity.

Grip strength



Knee extension strength



Leg extension power

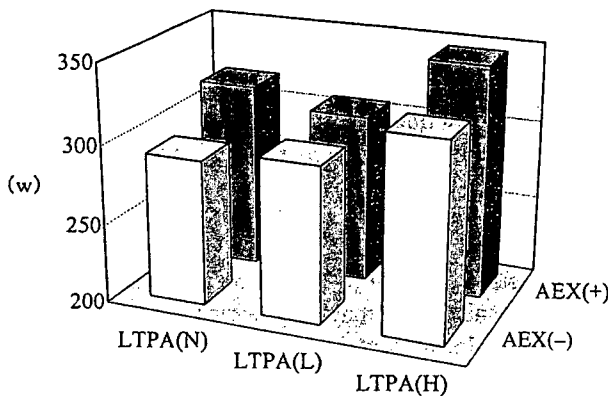


Figure 1 The relationships of leisure-time physical activity and adolescent exercise with grip strength, knee extension strength and leg extension power controlled for age, smoking status, annual income and education level. (AEX(-), without adolescent exercise; AEX(+), with adolescent exercise; LTPA(N), no leisure-time physical activity; LTPA(L), light leisure-time physical activity; LTPA(H), moderate and heavy leisure-time physical activity.)

The most interesting finding in our investigation was that adolescent exercise related positively to muscle function in middle-aged and elderly women.

It seems to contribute to strong muscle strength and power partly because the beneficial training effect of adolescent exercise remains in later life and partly because the continuation of physical activity from adolescence affects muscle function.

It is well known that resistance training increases muscle strength and power.⁷⁻¹¹ Therefore, training during adolescence may influence the build-up of muscle strength and power during the same period, although the positive benefit of training on muscle function decreases during a detraining period.²⁷⁻²⁹ Moreover, Connelly *et al.* suggested that long-term detraining effects on muscle function increased in elderly women because of aging and illness,³⁰ which makes it difficult to conclude that the adolescent training effect on muscle strength or power persisted for more than 20 years. It is unclear whether the effects of exercise or sport participation for longer than one year during adolescence are actually retained until middle and old age. Further studies are needed.

Since it has been suggested that past participation in regular exercise is highly predictive of exercise participation in current exercise in later life,^{31,32} which means that people who have participated in regular exercise tend to continue exercising, the continuation of physical activity may be the factor associated with positive muscle function. Hiraoka *et al.* reported that individuals examined at centers for health promotion who maintained the habit of regular exercise from school days to the present had a higher level of physical fitness than those who did not.³³ Although there were only 40 samples, Gauchard *et al.* also showed, that among the elderly aged over 60 years, individuals who participated in regular exercise for more than 40 years had stronger muscle strength and power compared to those who stopped physical activity at least 30 years before.²⁶ Frändin *et al.* reported that there was no association between activity level during the teenage years and muscle strength at age 76, but they also reported that the activity level throughout life was associated with walking speed among elderly women.³⁴ These results suggest that the continuation of exercise from early in life is associated with the prevention of declining muscle function in later life. Actually, our data indicated a relationship between current leisure-time physical activity and adolescent exercise as regards participation rates. It is possible that adolescent exercise is a predictor of participation in leisure-time physical activity later in life and the subjects who engaged in adolescent exercise continued exercising afterward.

It may be presumed that physical exercise or sports in youth are essential for the establishment of an exercise habit and the preference for an active lifestyle.

Participation in adolescent exercise may have not only direct effect on muscle functions but also indirect effect through increment of participation in leisure-time physical activity in later life.

There are some limitations in our study. First, because it was a cross-sectional study, cause and effect cannot be distinguished. For example, leisure-time physical activity can increase muscle function, but the level of muscle function may also contribute to participation in leisure-time physical activity. Secondly, the objective reliability of the results may be somewhat limited because the physical activity was based on self-rating, although previous study has already confirmed the reliability of the method,²² and trained interviewers conducted the questioning in order to maintain the validity of our data.

Finally, the criterion for acceptance of physical activity in the study was lower than the recommended criterion of exercise for improving physical fitness (i.e. two or more times per week). In addition, we assessed only the intensity of physical activity so that the effect of physical activity duration on muscle function could not be identified. Furthermore, it should be remembered that the habit of engaging in physical activity often includes a motivation to participate in a healthy and active lifestyle, which, in itself, might affect muscle function. Nevertheless, the results of this study afford some perspective for preventing the decline of muscle strength and power, and thus, maintaining the quality of life in the elderly.

In conclusion, women who participated in a higher level of leisure-time physical activity or those who participated in adolescent exercise have significantly stronger muscle strength and power than those who did not. These results suggest that current leisure-time physical activity and adolescent exercise are beneficial for maintaining muscle strength and power in middle-aged and elderly women.

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References

- 1 Van Heuvelen MJ, Kempen GI, Ormel J, Rispens P. Physical fitness related to age and physical activity in older persons. *Med Sci Sports Exerc* 1998; 30: 434-441.
- 2 Kostka T, Rahmani A, Berthouze SE, Lacour JR, Bonnefoy M. Quadriceps muscle function in relation to habitual physical activity and VO₂max in men and women aged more than 65 years. *J Gerontol A Biol Sci Med Sci* 2000; 55: B481-B488.
- 3 Rantanen T, Era P, Heikkinen E. Physical activity and the changes in maximal isometric strength in men and women from the age of 75-80 years. *JAGS* 1997; 45: 1439-1445.
- 4 Rantanen T, Heikkinen E. The role of habitual physical activity in preserving muscle strength from age 80-85 years. *JAPA* 1998; 6: 121-132.
- 5 Miszko TA, Cress ME, Slade JM, Covey CJ, Agrawal SK, Doerr CE. Effect of strength and power training on physical function in community-dwelling older adults. *J Gerontol A Biol Sci Med Sci* 2003; 58: 171-175.
- 6 Fiantarone MA, O'Neill EF, Ryan ND *et al.* Exercise training and nutritional supplementation for physical frailty in very elderly. *N Eng J Med* 1994; 23: 1769-1775.
- 7 Bishop D, Jenkins DG, Mackinnon LT, McEniery M, Carey MF. The effects of strength training on endurance performance and muscle characteristics. *Med Sci Sports Exerc* 1999; 31: 886-891.
- 8 Jozsi AC, Campbell WW, Joseph L, Davey SL, Evans WJ. Changes in power with resistance training in older and younger men and women. *J Gerontol A Biol Sci Med Sci* 1999; 54: M591-M596.
- 9 Humphries B, Newton RU, Bronks R *et al.* Effect of exercise intensity on bone density, strength, and calcium turnover in older women. *Med Sci Sports Exerc* 2000; 32: 1043-1050.
- 10 Bembem DA, Feters NL, Bembem MG, Nabavi N, Koh ET. Musculoskeletal responses to high- and low-intensity resistance training in early postmenopausal women. *Med Sci Sports Exerc* 2000; 32: 1949-1957.
- 11 Rhea MR, Alvar BA, Burkett LN, Ball SD. A meta-analysis to determine the dose-response for strength development. *Med Sci Sports Exerc* 2003; 35: 456-464.
- 12 Malina RM. Tracking of physical activity and physical fitness across the lifespan. *RQES* 1996; 67: S48-S57.
- 13 Metter EJ, Conwit R, Tobin J, Fozard JL. Age-associated loss of power and strength in the upper extremities in women and men. *J Gerontol A Biol Sci Med Sci* 1997; 52: B267-B276.
- 14 Samson MM, Meeuwse IB, Crowe A, Dessens JA, Duursma SA, Verhaar HJ. Relationships between physical performance measures, age, height and body weight in healthy adults. *Age Ageing* 2000; 29: 235-242.
- 15 Demura S, Minami M, Nagasawa Y, Tada N, Matsuzawa J, Sato S. Physical-fitness declines in older Japanese adults. *JAPA* 2003; 11: 112-122.
- 16 Lindle RS, Metter EJ, Lynch NA *et al.* Age and gender comparisons of muscle strength in 654 women and men aged 20-93 year. *J Appl Physiol* 1997; 83: 1581-1587.
- 17 Lynch NA, Metter EJ, Lindle RS *et al.* Muscle quality. I. Age-associated differences between arm and leg muscle groups. *J Appl Physiol* 1999; 86: 188-194.
- 18 Akima H, Kano Y, Enomoto Y *et al.* Muscle function in 164 men and women aged 20-84 year. *Med Sci Sports Exerc* 2001; 33: 220-226.
- 19 Katz S, Branch LG, Branson MH, Papsidero JA, Beck JC, Greer DS. Active life expectancy. *N Eng J Med* 1983; 309: 1218-1224.
- 20 Ministry of Health, Labour and Welfare. (*Annual Reports on Health and Welfare.*) Tokyo: Gyosei, 2000. [In Japanese.]
- 21 Shimokata H, Ando F, Niino N. A new comprehensive study on aging - the National Institute for Longevity Science, Longitudinal Study of Aging (NILS-LSA). *J Epidemiol* 2000; 10: S1-S9.
- 22 Iwai N, Yoshiike N, Saitoh S *et al.* Leisure-time physical activity and related lifestyle characteristics among middle-aged Japanese. *J Epidemiol* 2000; 10: 226-233.

- 23 Taylor HL, Jacobs DR Jr, Schucker B, Knudsen J, Leon AS, Debacker G. A questionnaire for the assessment of leisure time physical activities. *J Chron Dis* 1978; 31: 741-755.
- 24 *SAS Procedures Guide*. Release 8.2 Edition. NC, USA: SAS Institute Inc, 2001.
- 25 Hunter SK, Thompson MW, Adams RD. Relationships among age-associated strength changes and physical activity level, limb dominance, and muscle group in women. *J Gerontol A Biol Sci Med Sci* 2000; 55: B264-B273.
- 26 Gauchard GC, Tessier A, Jeandel C, Perrin PP. Improved muscle strength and power in elderly exercising regularly. *Int J Sports Med* 2003; 24: 71-74.
- 27 Mujika I, Padilla S. Muscular characteristics of detraining in humans. *Med Sci Sports Exerc* 2001; 33: 1297-1303.
- 28 Winters KM, Snow CM. Detraining reverses positive effects of exercise on the musculoskeletal system in premenopausal women. *J Bone Miner Res* 2000; 15: 2495-2503.
- 29 Ivey FM, Tracy BL, Lemmer JT *et al.* Effects of strength training and detraining on muscle quality: age and gender comparisons. *J Gerontol A Biol Sci Med Sci* 2000; 55: B152-B157.
- 30 Connelly DM, Vandervoort AA. Effects of detraining on knee extensor strength and functional mobility in a group of elderly women. *J Orthop Sports Phys Ther* 1997; 26: 340-346.
- 31 Evenson KR, Wilcox S, Pettinger M, Brunner R, King AC, McTiernan A. Vigorous leisure activity through women's adult life: the Women's Health Initiative Observational Cohort Study. *Am J Epidemiol* 2002; 156: 945-953.
- 32 Hirvensalo M, Lintunen T, Rantanen T. The continuity of physical activity - a retrospective and prospective study among older people. *Scand J Med Sci Sports* 2000; 10: 37-41.
- 33 Hiraoka J, Ojima T, Nakamura Y, Yanagawa H. A comparative epidemiological study of the effects of regular exercise on health level. *J Epidemiol* 1998; 8: 15-23.
- 34 Frändin K, Mellström D, Sundh V, Grimby G. A life span perspective on patterns of physical activity and functional performance at the age of 76. *Gerontology* 1995; 41: 109-120.

Original Article

Serum total and free testosterone level of Japanese men: a population-based study

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Abstracts

Background: There has never been a large scale population-based study of serum levels of total testosterone (TT) and free testosterone (FT) in Japanese men.

Methods: We determined serum levels of TT and FT of 1120 Japanese men aged 40–79 years using radioimmunoassay (RIA), as a part of a population-based longitudinal study of aging. Of these, sex hormone binding protein (SHBG) was also measured by RIA in 471 men. For the latter group, the calculated free testosterone (cFT) was determined by a formula using serum level of albumin, TT and SHBG.

Results: The mean \pm 2 SD of TT, FT and cFT were 513 ± 326 ng/dL (187–839 ng/dL), 13.2 ± 7.8 pg/mL (5.4–21.0 pg/mL) and 77.0 ± 43.4 pg/mL (33.6–120.4 pg/mL), respectively. While TT did not relate to age, FT and cFT decreased with age. FT in the 40–49 years age group was 15.1 ± 8.4 pg/mL (6.7–23.5 pg/mL), in the 50–59 years age group was 13.9 ± 6.8 pg/mL (7.1–20.7 pg/mL), in the 60–69 years age group was 12.0 ± 6.6 pg/mL (5.4–18.6 pg/mL) and in the 70–79 years age group was 11.5 ± 7.0 pg/mL (4.5–18.5 pg/mL). FT significantly correlated with cFT (Spearman's $r = 0.803$). The correspondence rates were 92.3% at the mean -1 SD and 98.7% at the mean -2 SD level.

Conclusions: We determined the mean and standard deviation of TT, FT and cFT in Japanese men aged 40 years or older. It is supposed that FT determined by RIA would be useful for diagnosing partial androgen deficiency of aging males.

Key words elderly men, Japanese, population-based study, radioimmunoassay, testosterone.

Introduction

Partial androgen deficiency in aging males (PADAM) has recently been drawing great attention as populations age rapidly in developed countries.^{1–3} PADAM is defined as a biochemical syndrome associated with advancing age and characterized by a deficiency in serum androgen levels with or without a decreased genomic sensitivity to androgens.⁴

Therefore, it is apparently essential to measure serum testosterone (T) levels for diagnosing PADAM.^{3–5} Total

testosterone (TT) is the sum of free testosterone (FT), albumin-bound testosterone and sex hormone binding globulin (SHBG)-bound testosterone. Since only FT and albumin-bound T are bioavailable, serum TT level might not reflect the exact gonadal function. As the serum SHBG level increases with aging, it is probable that elderly men with a normal serum TT level might have PADAM.

The International Society for the Study of the Aging Male (ISSAM) described the methods for calculating FT and bioavailable T using serum levels of albumin, TT and SHBG.^{4,5} ISSAM suggested the lower reference value of TT and calculated FT (cFT) as 11 nmol/L (317.3 ng/dL) and 0.255 nmol/L (73.5 pg/mL), respectively.

In Japan, SHBG measurement is uncommon because it is not approved under the medical care system. At

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present. radioimmunoassay is the only available measurement for FT. In this population-based study, we present the serum levels of TT, FT and cFT of Japanese men aged 40 years or older.

Materials and methods

This study is just one part of the National Institute for Longevity Sciences – Longitudinal Study of Aging (NILS-LSA). The general protocol has been reported elsewhere.⁶ In summary, 2267 (94.5%) of 2400 residents randomly chosen in cooperation with the local administration of Obu city (population: 70 000) and Higashiura town (40 000) gave written informed consent and participated in the NILS-LSA between November 1997 and April 2000. The numbers of subjects in the 40–49 years, 50–59 years, 60–69 years and 70–79 years age groups were intended to be equal.

Blood samples were taken between 08:00 and 09:00 hours, separated immediately by centrifugation at 2000 g for 15 min, and sera were frozen and stored in a deep freezer (–80°C). They were transferred to the laboratory (SRL Inc., Tokyo, Japan) for TT, FT, and SHBG measurement.⁷ TT and FT were measured using commercial kits from Diagnostic Products Corporation (Los Angeles, CA, USA). The interassay coefficients of variation (CV) were less than 15% for both kits, according to the commercial information.

This study included 1139 men. After excluding men whose serum levels of TT and/or FT were not determined, we examined the distributions and averages of serum TT and FT levels according to age. In 471 men in this study, SHBG was also measured by radioimmunoassay using the commercial kit (Diagnostic Products Corporation, Los Angeles, USA). The CV was less than 8.5%, according to the commercial information.

The cFT was calculated from serum levels of albumin, TT and SHBG, using the following formula of Vermeulen *et al.*^{5,8}

$$cFT \text{ (mol/L)} = \{-b + \sqrt{(b^2 - 4ac)}\} / 2a$$

$$cFT \text{ (pg/mL)} = cFT \text{ (mol/L)} \times 28.84/10$$

Where

$$a = 10^9 \times \{0.52174 \times Alb(\text{mg/dL}) + 1\}$$

$$b = 10^9 \times \{SHBG(\text{nmol/L})/10^9 - TT(\text{ng/dL})/28.84 \times 10^9 + 0.52174 \times Alb(\text{mg/dL}) + 1\}$$

$$c = -10 \times TT \text{ (ng/dL)} / (28.84 \times 10^9)$$

The relationship between FT and cFT was investigated.

The data are presented as mean ± 2 standard deviation (SD). For statistics, *t*-test, Mann–Whitney test, Spearman test and ANOVA in SPSS Version 12.0 (SPSS, Cary, NC, USA) were used. *P*-values less than 0.05 were considered statistically significant.

Results

Of 1139 men, TT and/or FT were not measured in 19 (1.7%). Serum TT and FT levels were determined in 1120 men (59.2 ± 11.0 years old): 287 in their forties, 278 in their fifties, 276 in their sixties, and 279 in their seventies.

The mean ± 2 SD of serum TT level was 513 ± 326 ng/dL (187–839 ng/dL). Figure 1 demonstrates the distribution of serum TT level. Serum TT level did not decrease with increasing age.

The mean ± 2 SD of serum FT level was 13.2 ± 7.8 pg/mL (5.4–21.0 pg/mL). Figure 2 demonstrates the distribution of serum FT level. Serum FT levels gradually decreased with increasing age. However, there was no significant difference between those in their sixties and in their seventies.

The mean ± 2 SD of serum cFT level in 471 men was 77.0 ± 43.4 pg/mL (33.6–120.4 pg/mL). Figure 3 demonstrates the distribution of serum cFT level (127 men in their forties, 121 in their fifties, 102 in their sixties and 121 in their seventies). There was a gradual decrease in cFT according to age, but the difference between men in their sixties and in their seventies did not reach statistical significance either.

Figure 4 shows the relationship between FT and cFT. The lines represent the mean – 2 SD and the mean – 1 SD of FT and cFT. Table 1 shows the correspon-

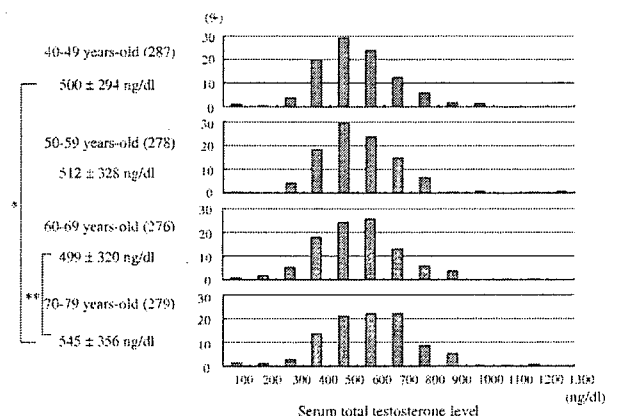


Fig. 1 Relationship between serum total testosterone level and age. **P* = 0.006; ***P* = 0.005.

Table 1 Correspondence between free testosterone and calculated free testosterone at the mean -1 SD and the mean -2 SD level

cFT (pg/mL)	Mean -1 SD level		Total	cFT (pg/mL)	Mean -2 SD level		Total
	<9.0	FT (pg/mL) ≥9.0			<4.5	FT (pg/mL) ≥4.5	
<55.4	46	19	65	<33.7	5	4	9
≥55.4	15	391	406	≥33.7	2	460	462
Total	61	410	471	Total	7	464	471

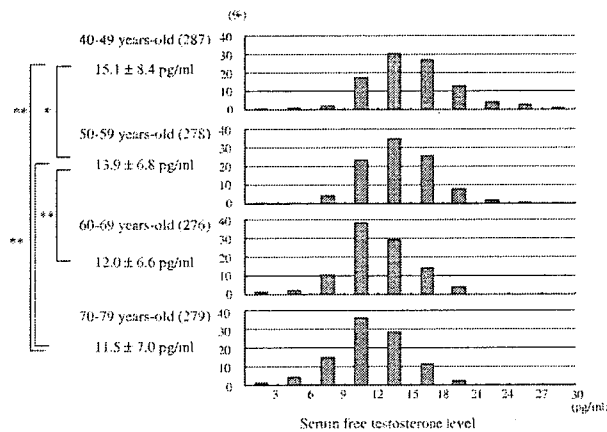


Fig. 2 Relationship between serum free testosterone level and age. * $P = 0.001$; ** $P < 0.001$.

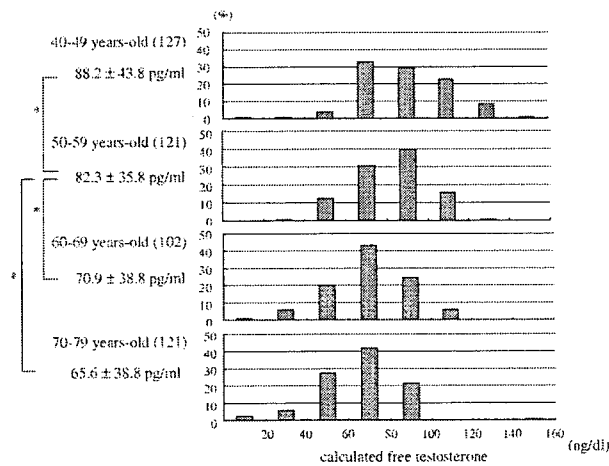


Fig. 3 Relationship between calculated free testosterone level and age. * $P < 0.001$.

dence between FT and cFT, using the limitation values of the mean -2 SD and the mean -1 SD. The correspondence rates were 92.3% ([46 + 391]/471) in the former and 98.7% ([5 + 460]/471) in the latter range.

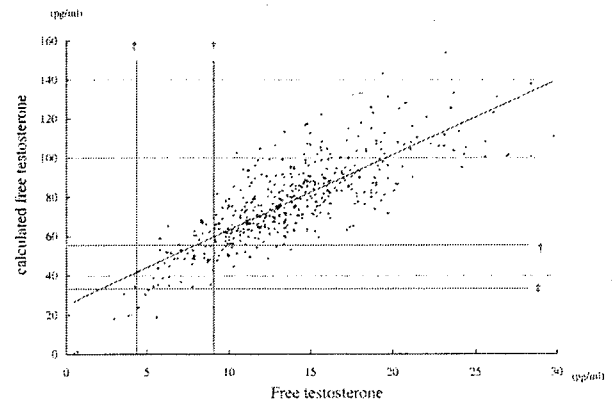


Fig. 4 Relationship between free testosterone (FT) and calculated free testosterone (cFT). $y = 3.8341x + 24.919$; Spearman's $\rho = 0.803$, $P < 0.001$. †mean \pm 1 SD level: cFT 55.4 pg/ml, FT 9.3 pg/ml; ‡mean \pm 2SD level: cFT 33.7 pg/ml, FT 5.4 pg/ml.

Discussion

We did not use the term 'reference ranges' in this study because we did not follow the formal procedures to determine reference ranges as proposed by NCCLS: National Committee for Clinical Laboratory Standards.⁹ This study did not attempt to determine the reference ranges of TT, FT, and cFT, and therefore a certain number of people with PADAM might have been included in this study.⁹ Unfortunately, NILS-LSA did not include any questionnaires for sexual problems such as the International Index of Erectile Function.¹⁰ Several reasons to avoid identifying the men with PADAM made us decide to only describe the average and standard deviation in this study.

Recently, the reference ranges of FT or TT in Japanese men have been reported by Iwamoto *et al.*¹¹ While the number of men aged 50 years or more in their study was smaller than ours, they reported reference ranges of FT or TT of men aged 20-39 years.

In this study, serum TT levels were equal among men in their forties and sixties, although the serum TT

level in men in their seventies was unexpectedly higher than those in their forties and sixties. The precise causes were unknown, but it is possible that, of the oldest men, only those with a good ability for daily living and of good cognitive ability could participate the NILS-LSA. Serum TT level did not decline with age, as Iwamoto *et al.* pointed out.¹¹ The range (mean -2 SD to mean $+2$ SD) of TT in our study was 187–839 ng/dL, while Iwamoto *et al.* indicated 201–750 ng/dL.

Although equilibrium dialysis is thought to be the best method for FT, ISSAM recommended cFT as a standard diagnostic indicator for PADAM because of the cost and time-consuming techniques of equilibrium dialysis.^{4,5,8,12} ISSAM also described that the values of FT using radioimmunoassay were much lower than that of cFT. In fact, serum FT levels appeared to be one-fifth to one-sixth of those of cFT in this study. Matsuda *et al.* reported that FT values were approximately one-eighth of cFT values.¹³ Interestingly, FT in their report seemed to be lower than in our report. This might have been caused by differences in the populations: randomly selected community-dwelling men versus patients visiting an 'andropause' clinic.

As shown in Figure 4, there was a significantly positive relationship between FT and cFT. Supposing that the lower reference value of hypogonadism is the mean -2 SD or -1 SD for cFT in men aged 40 or older, correspondence rates were 92.3% in the former level and 98.7% for the latter. The false positive rates were 0.4% (2/462) for the former and 3.7% (15/406) for the latter, and the false negative rates were 44.4% (4/9) and 29.2% (19/65), respectively. We believe that FT measurement using RIA might be valid to diagnose PADAM, although it is necessary to consider false negative cases. For patients who are suspected of having PADAM, multiple examinations of FT should be mandatory.

FT and cFT decreased with aging as anticipated. In this study, the FT range was 6.7–23.5 pg/mL among men in their forties, 7.1–20.7 pg/mL in the fifties, 5.4–18.6 pg/mL in the sixties and 4.5–18.5 pg/mL in the seventies. Iwamoto *et al.* demonstrated a higher mean -2 SD (7.7 pg/mL) of FT in the forties than our subjects but almost identical mean -2 SD level in their fifties to seventies.¹¹

We suspected that the cutoff values of TT, FT and cFT in Japanese men might be from the mean -2 SD to the mean -1 SD: 187–350 ng/dL, 5.4–9.3 pg/mL and 33.7–55.4 pg/mL, respectively. It was thought that 73.5 pg/mL of cFT suggested by ISSAM might be higher than estimated in Japanese men. Iwamoto *et al.* proposed 70% (10.9 pg/mL) for FT and 80% (12.4 pg/

mL) of the value of YAM: Young Adult Mean for the androgen replacement therapy (ART).¹¹ When these values are applied to our study, the former and latter values might indicate that 301 (27%) and 483 (43%) men are candidates for ART, respectively.

In summary, we demonstrated serum TT and FT levels of 1120 Japanese men aged 40 or older. Furthermore, we determined cFT from albumin, TT and SHBG in 471 men. FT and cFT decreased with aging and there was a good correlation between FT and cFT. We believe that FT determined by RIA would be useful for diagnosing PADAM.

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References

- 1 Morley JE, Charlton E, Patrick P. Validation of a screening questionnaire for androgen deficiency in aging males. *Metabolism* 2000; **49**: 1239–42.
- 2 Heineman LAJ, Zimmermann T, Vermeulen A *et al.* A new 'aging males' symptoms' rating scale. *Aging Male* 1999; **2**: 105–14.
- 3 Tsujimura A, Okuyama A. Concept and future view of partial androgen deficiency in the aging male. *Jpn J. Urol. Surg.* 2003; **16**: 819–24.
- 4 Morales A, Lunenfeld B. Investigation, treatment and monitoring of late-onset hypogonadism in males Official recommendations of ISSAM. *Aging Male* 2002; **5**: 74–86.
- 5 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**: 3666–72.
- 6 Shimokata H, Ando F, Niino N. A new comprehensive study on aging – the National Institute for Longevity Sciences, Longitudinal Study of Aging (NILS-LSA). *J. Epidemiol. Suppl.* 2000; **10**: S1–9.
- 7 Plymate SR, Tenover JS, Bremner WJ. Circadian variation in testosterone, sex hormone-binding globulin, and calculated non-sex hormone-binding globulin bound testosterone in healthy young and elderly men. *J. Androl.* 1989; **10**: 366–71.
- 8 Fiers T, Kaufman JM. *Free & Bioavailable Testosterone Calculator*. International Society for the Study of the Ageing Male, Prague. Available from: <http://www.issam.ch/freetesto.htm>
- 9 Sasse EA, Aziz KJ, Harris EK *et al.* How to define and determine reference intervals in the clinical laboratory; approved guideline. *NCCLS document C28-A*. 1995; **15**. NCCLS Wayne, PA.
- 10 Rosen RC, Riley A, Wagner G *et al.* The international index of erectile function (IIEF): a multidimensional

- scale for assessment of erectile dysfunction. *Urology* 1997; **49**: 822–30.
- 11 Iwamoto T, Yanase T, Koh E, Horie H, Baba K, Namiki M, Nawata H. Reference ranges of serum total and free testosterone in Japanese male adults. *Jpn J. Urol.* 2004; **75**: 1–60.
 - 12 Rosner W. Errors in the measurement of plasma free testosterone. *J. Clin. Endocrinol. Metab.* 1997; **82**: 2014–15.
 - 13 Matsuda T, Tatsumi M. Diagnosis and treatment of partial androgen deficiency in aging male. *Jpn J. Urol. Surg.* 2003; **16**: 831–7.