Effect of Longitudinal Changes in Visceral Fat Area and Other Anthropometric Indices to the Changes in Metabolic Risk Factors in Japanese Men

The Hitachi Health Study

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OBJECTIVE—The effects of longitudinal changes in the visceral fat area (VFA), and other anthropometric indices, on the risk factors of metabolic syndrome were not studied. We calculated the changes in metabolic risk factors in relation to changes in certain anthropometric indices in a large-scale study of Japanese men.

RESEARCH DESIGN AND METHODS—The subjects were 1,106 men participating in the Hitachi Health Study who received a computed tomography examination in both 2004 and 2007. VFA, subcutaneous fat area (SFA), and waist circumference were measured using the computed tomography. We examined how longitudinal changes in each anthropometric index over a 3-year period influenced the value of each metabolic risk factor.

RESULTS—Changes (Δ) over a 3-year period in body weight, SFA, and waist circumference strongly correlated, while the changes in body weight and VFA were weakly correlated. Changes in the VFA were associated with changes in metabolic risk factors, especially changes in triglyceride and HDL; we found these changes to be independent of the Δbody weight and Δwaist circumference.

CONCLUSIONS—Change in body weight is not a precise surrogate marker of ΔVFA, and repeated VFA measurements over time are useful. Adopting a lifestyle that does not increase the VFA is important in preventing metabolic syndrome.

Cardiovascular disease (CVD) is one of the leading causes of morbidity and mortality in the world (1). Previous reports have shown that obesity plays a significant role in increasing cardiovascular risk (2). Certain indicators of obesity, such as the visceral fat area (VFA), or visceral adipose tissue, are more strongly associated with the risk of CVD than other indicators of obesity, such as waist circumference, BMI (3), or the subcutaneous fat area (SFA) (2). A large VFA is strongly related to a higher prevalence of impaired fasting glucose levels (4,5), diabetes (4,6,7), insulin resistance (4,8–10), hypertension (11,12), abnormality of lipid metabolism (13–16), and metabolic risk factors (14,17,18). Previous studies have examined the relationship between baseline VFA and metabolic risk factors. In a previous intervention study of 54 postmenopausal women, an increase in VFA strongly correlated with changes in triglyceride and HDL cholesterol levels compared with changes in the blood pressure and fasting blood glucose levels (19). In the current study, we examined the relationships between changes in the VFA, SFA, body weight, and waist circumference and changes in CVD risk factors to determine the relative contributions of the longitudinal changes in these anthropometric indices to the changes in metabolic risk factors over a 3-year period. Determining the relationships between the anthropometric indices and metabolic risk factors would be useful for preventing CVD in clinical settings.

RESEARCH DESIGN AND METHODS

Overall, a total of 13,971 male employees and their spouses, after ≥12 h of fasting, underwent health check-ups during a baseline survey performed in 2004 and 2005 at the Hitachi Health Care Center in Ibaraki Prefecture. Of these, 2,655 men received a computed tomography scan. The final analysis involved 1,106 men from the initial study who participated in a 3-year follow-up survey performed in 2007 and 2008 (aged 30–72 years in the baseline survey). The mean age of the men for whom follow-up data were available was younger than that of the men for whom follow-up data were not available. In addition, the mean age of the men who received a computed tomography examination in the baseline survey was greater than the mean age of the men who did not receive the computed tomography examination. No significant differences were seen between the other characteristics when age-adjusted comparisons were performed. Self-reporting questionnaires were used to investigate whether the subjects were currently receiving medical treatment for hyperlipidemia, hypertension, or diabetes

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at the time of both surveys. Body height and weight were measured using an automated scale (BF-220; Tanita), and the BMI was defined as the weight in kilograms divided by the square of the height in meters. VFA, SFA, and waist circumference were measured using a computed tomography scanner and protocols previously described (20). In brief, single-slice imaging was performed at the umbilical level in a spine position using a Redix turbo CT machine (Hitachi Medico). The imaging conditions were 120 kV, 50 mA, and a slice thickness of 5 mm. VFA, SFA, and waist circumference were calculated using fatPointer software (Hitachi Medico). Triglyceride and HDL cholesterol levels were measured using the oxygen method with a Hitachi 7600 device (Sekisui Medical). Blood glucose levels were measured using the glucose electrode technique with an ADAMS glucose GA-1170 device (Arkrey). Blood pressure was measured using an oscillometric method with a Kentaro ADVANCE BP-203RV III A/B device (Colin) while the patient was in a sitting position and after the patient had rested for 3 min. Informed consent was obtained from each examinee regarding the use of his or her data for research purposes. The current study was approved by the ethics review committee of the National Center for Global Health and Medicine.

Definition of the state of risk factor clustering

Subjects with two or more of the following four factors, defined by the National Cholesterol Education Program's Adult Treatment Panel III guidelines (21), with the exception of waist circumference, were defined to have clustering of metabolic risk factors: *1*) triglyceride ≥150 mg/dL (1.69 mmol/L), *2*) HDL cholesterol <40 mg/dL (1.03 mmol/L), *3*) systolic blood pressure (SBP) ≥130 mmHg or diastolic blood pressure (DBP) ≥85 mmHg, or *4*) fasting plasma glucose ≥110 mg/dL (6.11 mmol/L). Subjects currently receiving treatment for hyperlipidemia, hypertension, or diabetes were deemed as having the respective risk factor, regardless of the biochemical value.

Table 1—*Anthropometric and CVD risk variables at baseline and changes during the 3-year follow-up period* (n = 1,106)

	Baseline		Changes in 3-year period		
	Mean	SD	Mean	SD	P*
Height (cm)	169.0	6.1	0.3	0.5	<0.001
Weight (kg)	67.6	9.4	0.0	3.1	0.61
BMI (kg/m^2)	23.6	2.7	0.1	1.1	0.018
VFA (cm^2)	120.0	52.2	0.0	32.5	0.99
SFA (cm^2)	122.6	52.2	4.2	24.7	<0.001
VFA/SFA	1.03	0.54	−0.03	0.48	0.055
WC (cm)	85.6	8.1	−0.2	4.6	0.088
SBP (mmHg)	121.5	11.7	−1.1	10.8	0.001
DBP (mmHg)	76.9	8.2	−0.1	7.1	0.62
TG (mg/dL)	137.6	92.6	−9.0	80.0	<0.001
HDL cholesterol (mg/dL)	56.4	14.2	−1.8	7.9	<0.001
Fasting glucose (mg/dL)	105.2	13.0	−1.5	8.7	<0.001

TG, triglyceride; WC, waist circumference. *Paired *t* test between values at baseline and at the 3-year follow-up.

Statistical analyses

The baseline data and the 3-year changes (Δ) in CVD risk-related variables (i.e., BMI, VFA, SFA, VFA/SFA, waist circumference, SBP, DBP, triglyceride, HDL cholesterol, and glucose) were calculated for subjects who had not received a medical treatment in both surveys. The *P* value between baseline and the 3-year follow-up period was calculated using a paired *t* test. Pearson correlation coefficients for the changes in the anthropometric and CVD risk variables were calculated. To establish the independent contribution of each anthropometric variable, multiple linear regression analyses were used to obtain the standardized partial regression coefficients, where the change in the CVD risk variable was the dependent variable and the changes in the anthropometric indices were the independent variables; a stepwise procedure was used to select significant variables. All analyses were performed using SPSS (version 15.0; SPSS, Chicago, IL).

RESULTS—The anthropometric and CVD risk variables at the baseline survey and changes at the 3-year follow-up period are shown in Table 1. The mean (SD) age of the subjects was 52.7 (8.4)

Table 2—*Pearson correlations coefficients among changes in anthropometric and CVD risk variables* (n = 1,106)

	ΔVFA	ΔSFA	ΔBody weight	ΔWaist circumference	ΔBMI	ΔSBP	ΔDBP	ΔFasting glucose	ΔLog triglycerides	ΔHDL
ΔVFA	1	0.632	0.672	0.756	0.671	0.138	0.162	0.188	0.197	−0.234
ΔSFA	0.632	1	0.738	0.765	0.738	0.174	0.177	0.187	0.171	−0.238
ΔBody weight	0.672	0.738	1	0.722	0.989	0.155	0.210	0.203	0.222	−0.252
ΔWaist circumference	0.756	0.765	0.722	1	0.718	0.140	0.156	0.168	0.196	−0.233
ΔBMI	0.671	0.738	0.989	0.718	1	0.150	0.203	0.204	0.225	−0.253
ΔSBP	0.138	0.174	0.155	0.140	0.150	1	0.627	0.055	0.096	−0.003
ΔDBP	0.162	0.177	0.210	0.156	0.203	0.627	1	0.093	0.097	−0.004
ΔFasting glucose	0.188	0.187	0.203	0.168	0.204	0.055	0.093	1	0.039	0.041
ΔLog triglycerides	0.288	0.280	0.350	0.295	0.353	0.109	0.117	0.079	1	−0.288
ΔHDL cholesterol	−0.234	−0.238	−0.252	−0.233	−0.253	−0.003	−0.004	0.041	−0.250	1

The absolute value of a correlation coefficient >0.06 was statistically significant at $P < 0.05$. The correlation coefficients were essentially unchanged after adjustments for age (data not shown).

years at baseline. The mean BMI was 23.6 (2.7) kg/m^2, the mean VFA was 120.0 (52.2) cm^2, and the mean waist circumference was 85.6 (8.1) cm at baseline. The 3-year changes in each of these parameters were relatively small.

Pearson correlation coefficients for the changes in the anthropometric measurements and CVD risk variables are shown in Table 2. Strong correlations among the changes in the four adiposity indices were observed, with a colinearity observed among the indices. Correlations among the Δbody weight, ΔSFA, and Δwaist circumference were also strong, but the correlation between the Δbody weight and ΔVFA was weak. These findings suggested that the Δbody weight was not an exact surrogate marker of ΔVFA. We also analyzed correlations among the changes in anthropometric measurements and CVD risk variables. Significant correlations between the Δlog triglyceride and ΔVFA, the Δlog triglyceride and Δbody weight, the ΔSBP and ΔSFA, the ΔSBP and Δbody weight, and the Δglucose and Δbody weight were observed. The correlation coefficients were essentially unchanged after adjustments for age (data not shown).

Multiple linear regression analyses showed that the changes in VFA, SFA, body weight, and waist circumference were independently associated with the changes in CVD risk factors during the 3-year follow-up period (Table 3). The ΔDBP, Δglucose, Δlog triglyceride, and ΔHDL cholesterol were significantly affected by both the ΔVFA and ΔSFA. In contrast, the ΔSBP was only significantly affected by the ΔSFA. The Δlog triglyceride and ΔHDL cholesterol values were more strongly affected by the ΔVFA than by the ΔSFA. These results suggest that the ΔVFA and ΔSFA contribute differently to the ΔCVD risk variables. A multiple regression analysis showed that the ΔVFA were significantly related to the Δlog triglyceride and ΔHDL cholesterol and were independent of the Δbody weight and Δwaist circumference.

Table 3—*Independent associations of changes in VFA, SFA, body weight, and waist circumference with changes in the CVD risk factors during the 3-year follow-up period according to multiple linear regression analyses*

		Model 1		Model 2	
Dependent variable	Independent variables	Standardized partial β	*P*	Standardized partial β	*P*
ΔSBP	ΔVFA	0.056	0.115	—	—
	ΔSFA	0.161	<0.001	0.194	<0.001
	Age	0.034	0.216	—	—
ΔDBP	ΔVFA	0.093	0.008	0.093	0.008
	ΔSFA	0.135	<0.001	0.135	<0.001
	Age	−0.105	<0.001	−0.105	<0.001
ΔFasting glucose	ΔVFA	0.100	0.002	0.100	0.002
	ΔSFA	0.127	<0.001	0.127	<0.001
	Age	−0.071	0.005	−0.071	0.005
ΔLog triglycerides	ΔVFA	0.207	<0.001	0.206	<0.001
	ΔSFA	0.141	<0.001	0.143	<0.001
	Age	−0.026	0.295	—	—
ΔHDL cholesterol	ΔVFA	−0.154	<0.001	−0.154	<0.001
	ΔSFA	−0.134	<0.001	−0.134	<0.001
	Age	−0.082	0.001	0.082	0.001
ΔSBP	ΔVFA	0.031	0.480	—	—
	ΔSFA	0.121	0.011	0.128	0.002
	ΔBody weight	0.084	0.067	0.089	0.031
	ΔWaist	−0.009	0.866	—	—
	Age	0.041	0.142	—	—
ΔDBP	ΔVFA	0.055	0.203	—	—
	ΔSFA	0.070	0.139	—	—
	ΔBody weight	0.157	0.001	0.220	<0.001
	ΔWaist	−0.035	0.507	—	—
	Age	−0.092	0.001	−0.088	0.001
ΔFasting glucose	ΔVFA	0.080	0.040	—	—
	ΔSFA	0.085	0.045	—	—
	ΔBody weight	0.158	<0.001	0.223	<0.001
	ΔWaist	−0.082	0.070	—	—
	Age	−0.053	0.037	—	—
ΔLog triglycerides	ΔVFA	0.112	0.003	0.127	<0.001
	ΔSFA	0.008	0.846	—	—
	ΔBody weight	0.229	0.000	0.248	<0.001
	ΔWaist	0.031	0.483	—	—
	Age	−0.006	0.813	—	—
ΔHDL cholesterol	ΔVFA	−0.105	0.004	−0.112	0.001
	ΔSFA	−0.065	0.106	−0.073	0.043
	ΔBody weight	−0.116	0.003	—	—
	ΔWaist	−0.017	0.684	−0.119	0.002
	Age	−0.092	<0.001	−0.093	<0.001

Model 1: All independent variables were entered into the model. Model 2: Significant variables were selected using the stepwise method. β, regression coefficient

CONCLUSIONS—This study investigated the change in metabolic risk factors between a baseline examination and a 3-year follow-up examination, measured using computed tomography. The changes in body weight, SFA, and waist circumference strongly correlated. The changes in body weight and VFA showed weak correlation, suggesting that changes in body weight are not an exact surrogate marker of changes in VFA. A multiple regression analysis showed that the ΔVFA was significantly related to Δtriglyceride and ΔHDL cholesterol independently of Δbody weight and Δwaist circumference, suggesting the importance of monitoring VFA over time.

In previous cross-sectional studies, positive correlations between VFA and SBP and between VFA and serum triglyceride were reported to be significant when VFA was measured by computed tomography (14). In previous longitudinal studies, the effects of changes in BMI (22), weight (23), and waist circumference (24,25) on metabolic risk factors were examined. One such report showed a strong linear trend between increasing BMI and a worsening of various variables of metabolic risk factors, including blood pressure and lipid

profiles (24). Likewise, another report showed that weight changes were linearly related to all measurements of each component of the metabolic risk factors (23). Other studies have shown that a reduction in the waist circumference and the VFA achieved through lifestyle modifications is closely linked to an improvement in metabolic risk factors (19,25). These studies suggest that the changes in BMI, weight, waist circumference, and VFA are related to risk factors for CVD. However, the impact of the change in the VFA (measured twice in the same person), which is regarded as the strongest indicator of CVD risk among the anthropometric variables, has remained uncertain. To our knowledge, this is the first study to analyze the relationships between changes in VFA and changes in metabolic risk factors, compared with other anthropometric variables, in a large population. Our findings clearly showed that the ΔVFA were significantly related to the Δlog triglyceride and ΔHDL cholesterol and were independent of the Δbody weight and Δwaist circumference.

In previous studies (22), the mean value of each component of metabolic risk factors or the prevalence of metabolic risk factors and its components were compared according to changes in BMI, body weight, and waist circumference. This is the first study that compared the strength of the association of metabolic risk factors with the change in VFA in a large population.

The current study has the following strengths: the study had a longitudinal design and examined the relationships between metabolic risk factors and the change in VFA using computed tomography scans performed twice on the same subject. The number of subjects was relatively large, with >1,000 subjects being followed over a 3-year period. Our study is thought to have a small measurement bias because VFA and SFA were measured using the same computed tomography machine, in the same region, and at the same state of expiration during both the baseline examination and the 3-year follow-up examination. A random measurement error could have diluted the relationship between ΔVFA and the metabolic risk factors. Thus, the real relationship may be stronger than the observed one. Nevertheless, the current study also has a limitation. The study subjects were limited to men, and further studies in women are needed.

In conclusion, the current study of Japanese men showed that changes in the VFA were associated with changes in metabolic risk factors. The ΔVFA was significantly related to Δlog triglyceride and ΔHDL cholesterol and was independent of Δbody weight and Δwaist circumference, suggesting the importance of measuring the VFA repeatedly over time. The adoption of a lifestyle that does not result in an increase in VFA is important in preventing metabolic syndrome.

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No potential conflicts of interest relevant to this article were reported.

Y.M. was the principal investigator, researched data, contributed to discussions, wrote the manuscript, and reviewed and edited the manuscript. T.N. researched data, contributed to discussions, and reviewed and edited the manuscript. S.Y. research data and reviewed and edited the manuscript. Y.T. contributed to discussions. T.Y., T.M., and M.N. contributed to discussions and reviewed and edited the manuscript. Y.M. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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成因

メタボリックシンドロームのリスク重積

2005年4月にメタボリックシンドロームの日本の診断基準が発表された。その基準を参考にして算出されたメタボリックシンドロームが強く疑われる者および予備群は，約1,960万人にも達するという。この診断基準の特徴は，内臓脂肪の蓄積の基準を最上位においたことである。しかし，内臓脂肪面積のカットオフ値が年齢別に異なるかは検討されていない。そこで，内臓脂肪面積のカットオフ値を性・年齢別に算出し，性・年齢別に異なる値が必要かどうかを明らかにすることを目的として本研究を行った。

2004年から2009年にかけて日立健康管理センタにて腹部CT検査（臍部normal slice）を行った11,561名を対象に，CTによる内臓脂肪面積の，メタボリックシンドロームのリスク重積を見出すための最適カットオフ値を，性・年齢別にROC解析により検討した。

解析対象者の平均年齢（標準偏差）は男性51.9（10.4）歳，女性55.8（9.8）歳であった。感度80%でメタボリックシンドロームのリスク重積者を拾い上げることのできる内臓脂肪面積は，40歳未満の若年層では小さく（40歳未満 vs. 40歳以上；男性86.4cm^2 vs. 103.9cm^2，女性36.5cm^2 vs. 69.2cm^2），また，ROC曲線の曲線下面積は男性に比べ女性で大きくなっており，いずれも年齢と共に小さくなる傾向が有意に認められた（男性；trend P=0.056，女性；trend P=0.020）。

以上が表題文献の内容であり，性・年齢別に異なる内臓脂肪面積のカットオフ値が実際には必要であることを明らかにしたものである（**表**）。すなわち，全体で感度が80%となる内臓脂肪面積を用いた場合，40歳未満では40歳以上と比べて感度が低く（男性70.0%，女性60.0%），40歳未満ではより小さい内臓脂肪面積のカットオフ値を採用すべきであることが示された。先行研究においてわれわれは，内臓脂肪蓄積の簡易代替指標として用いられているウエストは，内臓脂肪面積と比べて男性では7割，女性では5割のメタボリックシンドロームのリスク重積しか捉えられないことを明らかにしており[1]，今後は，内臓脂肪面積のより簡易な測定法を検討していく必要があるとも考えられる。

表．内臓脂肪面積とメタボリックシンドロームのリスク集積との関係

男性

内臓脂肪面積	感度80%の値	感度80%の特異度	感度＋特異度が最大の値	感度	特異度
40歳未満	86.4cm^2	49.2%	114.0cm^2	64.2%	72.9%
40代	103.6cm^2	52.6%	106.6cm^2	78.2%	55.4%
50代	104.5cm^2	47.3%	124.8cm^2	67.6%	62.6%
60代	102.1cm^2	44.2%	120.4cm^2	68.4%	57.6%
70代	109.4cm^2	50.4%	104.8cm^2	83.1%	49.3%
全年代	102.4cm^2	50.2%	115.6cm^2	72.1%	59.8%
40歳以上	103.9cm^2	48.8%	121.1cm^2	68.9%	61.3%

女性

内臓脂肪面積	感度80%の値	感度80%の特異度	感度＋特異度が最大の値	感度	特異度
40歳未満	36.5cm^2	51.2%	60.2cm^2	70.0%	80.5%
40代	66.4cm^2	67.7%	63.3cm^2	85.0%	66.1%
50代	68.3cm^2	53.2%	67.8cm^2	82.9%	53.0%
60代	75.7cm^2	43.0%	97.7cm^2	65.9%	65.7%
70代	77.3cm^2	43.1%	75.7cm^2	87.1%	43.1%
全年代	69.0cm^2	54.0%	67.8cm^2	82.9%	53.5%
40歳以上	69.2cm^2	50.9%	97.6cm^2	60.4%	74.5%

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