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## Clinical significance of visceral adiposity assessed by computed tomography: A Japanese perspective

Miwa Ryo, Ken Kishida, Tadashi Nakamura, Tohru Yoshizumi, Tohru Funahashi, Iichiro Shimomura

Miwa Ryo, Ken Kishida, Tadashi Nakamura, Tohru Yoshizumi, Tohru Funahashi, Iichiro Shimomura, Department of Metabolic Medicine, Graduate School of Medicine, Osaka University, Suita, Osaka 565-0871, Japan

Miwa Ryo, Osaka Health Support Center, Sumitomo Mitsui Banking Corporation, Osaka 541-0041, Japan

Ken Kishida, Department of Hemodialysis, Kishida Clinic, Toyonaka, Osaka 560-0021, Japan

Tadashi Nakamura, Department of Internal Medicine, Kawasaki Hospital, Kobe, Hyogo 652-0042, Japan

Tohru Yoshizumi, Department of Radiology, Kawasaki Hospital, Kobe, Hyogo 652-0042, Japan

Tohru Funahashi, Department of Metabolism and Atherosclerosis, Graduate School of Medicine, Osaka University, Suita, Osaka 565-0871, Japan

Author contributions: Ryo M, Kishida K, Nakamura T, Yoshizumi T, Funahashi T and Shimomura I contributed to this work.

Correspondence to: Miwa Ryo, MD, PhD, Department of Metabolic Medicine, Graduate School of Medicine, Osaka University, 2-2 B-5, Yamada-oka, Suita, Osaka 565-0871, Japan. [ryomw@gaia.eonet.ne.jp](mailto:ryomw@gaia.eonet.ne.jp)

Telephone: +81-6-68793732 Fax: +81-6-68793739

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### Abstract

Abdominal obesity, rather than total amount of fat, is linked to obesity-related disorders. Visceral adiposity is an important component of obesity-related disorders in Japanese individuals with a mild degree of adiposity compared with Western subjects. In 1983, our group reported techniques for body fat analysis using computed tomography (CT) and established the concept of visceral fat obesity in which intra-abdominal fat accumulation is an important factor in the development of obesity-related complications, such as diabetes, lipid disorders, hypertension and atherosclerosis. Our group also established ideal imaging conditions for determining abdominal fat area at the umbilical level CT scan.

Visceral fat area (VFA) measured in a single slice at L4 level correlated significantly with the total abdominal visceral fat volume measured on multislice CT scan. In a large-scale study of a Japanese population, the mean number of obesity-related cardiovascular risk factors (hypertension, low high-density lipoprotein cholesterol-emia and/or hypertriglyceridemia, and hyperglycemia) was greater than 1.0 at 100 cm<sup>2</sup> of VFA, irrespective of gender, age and body mass index. Our group also demonstrated that reduction of visceral fat accumulation subsequent to voluntary lifestyle modification, "Hokenshido", correlated with a decrease in the number of obesity-related cardiovascular risk factors. It is important to select the most appropriate subjects from the general population (*e.g.*, non-obese subjects with a cluster of risk factors for the metabolic syndrome) that are most suitable for body weight reduction, with the goal of preventing atherosclerotic cardiovascular diseases.

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**Key words:** Visceral fat; Metabolic syndrome; Computed tomography; Atherosclerotic cardiovascular diseases

**Core tip:** Accumulation of intra-abdominal visceral fat correlates with atherogenic and metabolic abnormalities, collectively known as the metabolic syndrome. Visceral adiposity is an important component of the syndrome in Japanese individuals with mild adiposity compared with Western subjects. A computed tomography (CT) scan allows the separate analysis of subcutaneous fat and visceral fat, and the visceral fat area (VFA) from a single CT slice L4 level correlates with total visceral fat volume. A VFA cut-off value of 100 cm<sup>2</sup> is used for risk assessment of obesity-related disorders.

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## ABDOMINAL OBESITY RATHER THAN TOTAL AMOUNT OF FAT CORRELATES WITH OBESITY-RELATED DISORDERS

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Obesity is generally defined as excess storage of energy in the form of fat. Clinical evidence indicates that regional body fat distribution correlates with morbidity and mortality in obese subjects. In 1947, Vague<sup>[1]</sup> was the first to report a link between adipose tissue distribution and complications in obese subjects. Subsequent clinical studies demonstrated that abdominal obesity [increased waist to hip (W/H) ratio], rather than total amount of fat, is linked to obesity-related disorders<sup>[1-5]</sup>. A high W/H ratio (an expression of upper body or abdominal obesity) became an index used to predict risks associated with fat accumulation. In comparison, “waist” originally comprised both abdominal subcutaneous fat and intra abdominal visceral fat.

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## SEPARATE ANALYSIS OF SUBCUTANEOUS FAT AND INTRA-ABDOMINAL VISCERAL FAT

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In 1983, our group introduced a new method for fat analysis using a computed tomography (CT) scan, which allowed the separate measurement of subcutaneous fat and intra-abdominal visceral fat<sup>[6]</sup>. We divided the human body into 11 cylindrical parts (head, forearm, upper arm, chest, abdomen, thigh, calf) for the measurement. Intra-peritoneal fat, with a density similar to the subcutaneous fat layer, is considered the visceral fat area (representing fat accumulation predominantly in the mesenteric and omental regions). These respective areas (cm<sup>2</sup>) are measured by tracing object contours on the films of each individual scan using the computerized planimetric method. CT scans at the level of the umbilicus show great variability in fat distribution. Two different types of fat distribution patterns are found among obese subjects with similar waist circumferences and body mass indices. In one group of subjects, subcutaneous fat is rather scanty; fat accumulates in the intraperitoneal compartment. In the other group of subjects, fat accumulates exclusively in the subcutaneous area. Lean body mass comprising muscles and bones did not increase with obesity, at least in the abdomen.

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## VISCERAL FAT OBESITY

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The average ratio of visceral fat to subcutaneous fat at

the level of the umbilicus (V/S ratio) in obese subjects is about 0.4. Accordingly, we defined obese subjects with V/S ratio of  $\geq 0.4$  as visceral fat obesity, whereas obese subjects with V/S ratio of  $< 0.4$  were considered subcutaneous fat obesity<sup>[7,8]</sup>. Comparison of the metabolic features of subjects with visceral fat obesity and those with subcutaneous fat obesity showed significantly higher or otherwise greater fasting plasma glucose level, area under the plasma glucose concentration curve after oral glucose loading, triglyceride level, and total cholesterol level in the former group, when either all or sex-matched obese subjects were examined, although BMI or the duration of obesity was not different between the two groups<sup>[7,8]</sup>.

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## STANDARD METHOD FOR MEASUREMENT OF VISCERAL FAT AND SUBCUTANEOUS FAT

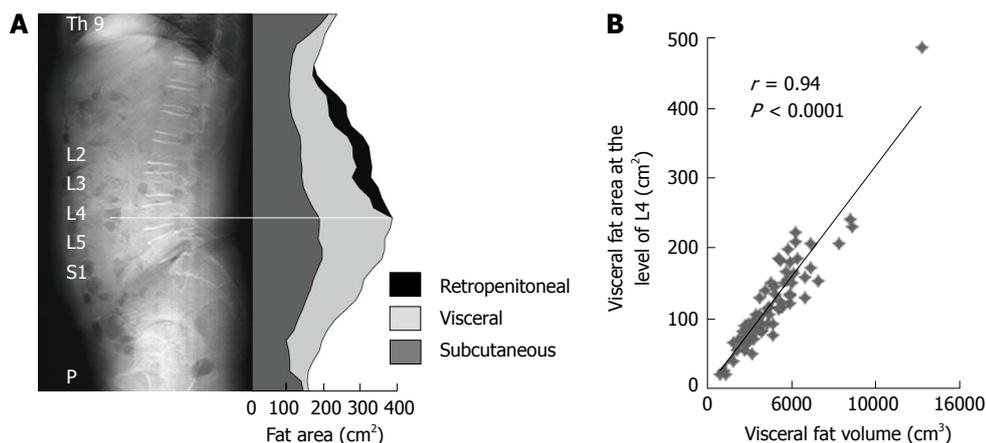
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A CT scan and magnetic resonance imaging (MRI) at the umbilical level are the standard techniques used for the assessment of visceral fat accumulation<sup>[6-12]</sup>. The MRI findings significantly correlate with those of a CT scan. MRI offers the advantage of lack of radiation exposure, although it is more expensive. Several studies have demonstrated that visceral fat area (VFA) measured in a single slice obtained at the level of the umbilicus (approximately the level of L4 and L5) correlates significantly with total visceral abdominal fat volume<sup>[6,9,10]</sup>.

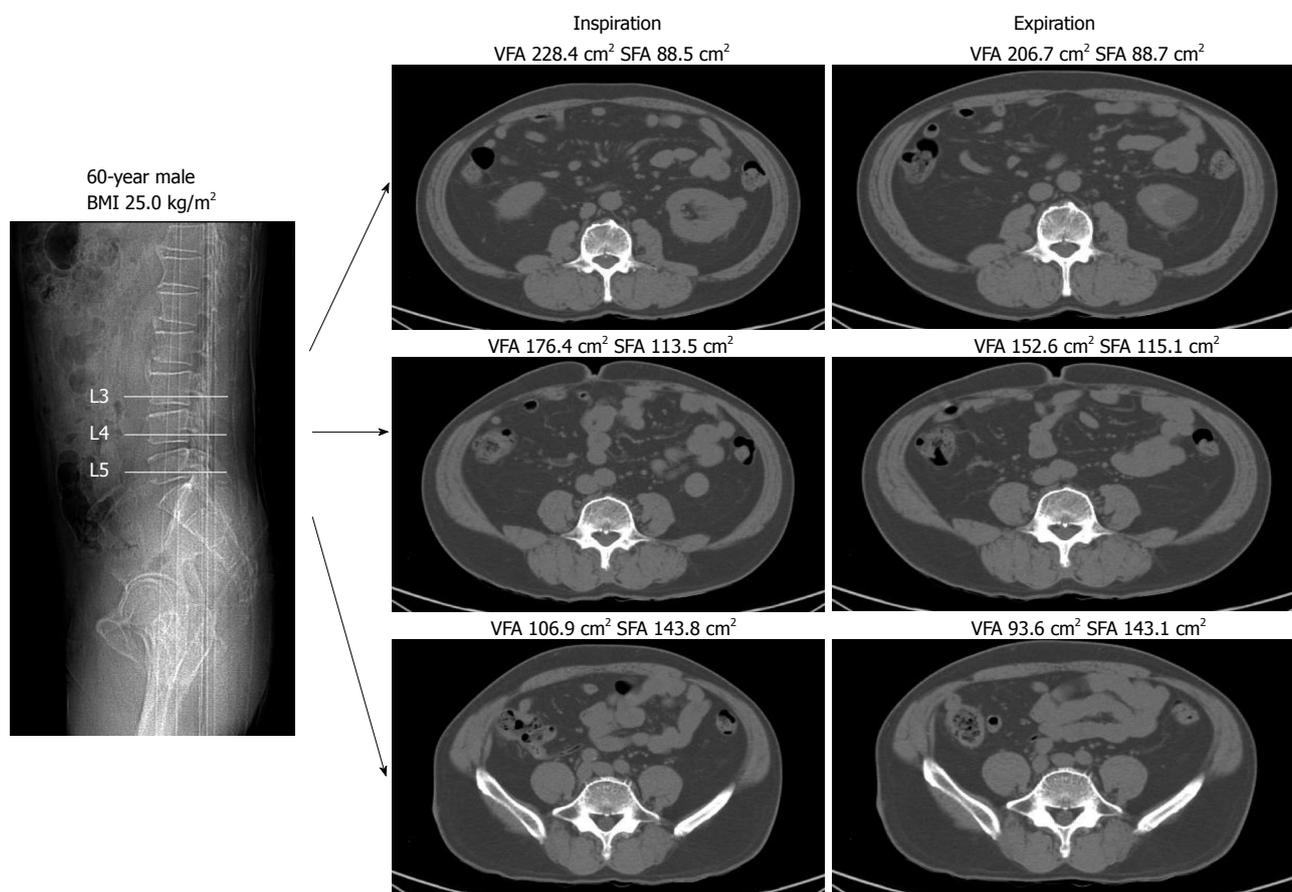
Accurate and standardized techniques are required to implement the use of CT in clinical practice for measurement of VFA. Our group established the imaging conditions necessary for measurement of abdominal fat area at the umbilical level from a CT scan taken in the supine position<sup>[11]</sup>. The VFA was measured by drawing a line within the muscle wall surrounding the abdominal cavity. The subcutaneous fat area (SFA) was calculated by subtracting the visceral fat area from the total fat area. Fat areas measured by this method correlated closely with those obtained by the computed planimetric method. Thus, VFA measured on a single CT slice at the L4 level correlated strongly with total abdominal visceral fat volume measured by multislice CT ( $r = 0.94$ ,  $P < 0.0001$ ) (Figure 1).

VFA but not SFA value varies considerably (approximately 20%) with respiration and site of obtained CT scan (Figure 2). During inspiration, the downward movement of the diaphragm results in the compression of the abdominal cavity and extension of visceral fat. These changes cause overestimation of VFA and/or inclusion of the lower part of the kidney in the slice. For accurate measurement of VFA, it is important that measurement is made in late expiration. In subjects with a low position umbilicus, the umbilicus CT slices can also include the pelvic cavity. To avoid errors in measurements in such subjects, the slice position must be adjusted to a much higher level (L4 level).

To take VFA measurement from the research bench to daily clinical practice, our group also developed com-



**Figure 1 Correlation between visceral fat volume and visceral fat area measured by multislice computed tomography.** A: Abdominal fat distribution; B: Correlation between abdominal visceral fat volume and visceral fat area from a single slice at the level of L4. Number = 75 (males 55, females 20); age:  $53 \pm 1$  yr (range, 18-81 yr), body mass index:  $25.4 \pm 3.9$  kg/cm<sup>2</sup> (18.9-38.8 kg/cm<sup>2</sup>). Slice thickness was 10 mm, and images were obtained from Th 8/9 to the pubis. Fat area measurement application: Advanced area calculation, GE Healthcare Co.



**Figure 2 Measurement of visceral fat area varies with respiratory phase and level of computed tomography scan.** Fat area measurement application: Advanced area calculation, GE Healthcare Co. VFA: Visceral fat area; SFA: Subcutaneous fat area; BMI: Body mass index.

mercial software that measures both VFA and SFA from a single slice CT scan. These investigations were confirmed in the subsequent generation of CT scanners and the Japanese guidelines of obesity treatment 2011 (Japan Society for the Study of Obesity, in Japanese) defined the imaging conditions for assessment of abdominal fat in multislice CT scan (Table 1).

With regard to the radiation dose, the dose-length

product (mGy·cm) is determined by multiplying CT dose index volume (mGy) by scan length (cm)<sup>[13]</sup>. The effective dose (0.015 mSv/mGy·cm) is computed by multiplying the dose-length product by a conversion factor for the abdomen<sup>[13]</sup>. The mean  $\pm$  SD of the radiation dose used in the standard protocol for assessment of abdominal fat measured in 37 subjects (men 20, women 17) was  $26.6 \pm 4.4$  for men and  $25.6 \pm 4.2$  mGy/slice for women, while

**Table 1 Parameters used for computed tomography imaging of abdominal fat: Multislice computed tomography**

Scan position	Umbilicus. Scan around the level of L4 to avoid the kidney and/or the ilium in view. Take 3-5 slices in comparative scans after weight reduction
Tube voltage	120 kVp
Tube current	Preferred AEC. SD 8-10
Slice thickness	5-10 mm
FOV	Include whole circumference of the abdominal without deficiency
Respiratory phase	Late expiration
Reconstruction conditions	Displaying conditions common for plain CT scan of the abdomen

CT: Computed tomography; AEC: Automatic exposure control; FOV: Field of view.

the respective effective dose was  $0.42 \pm 0.07$  and  $0.41 \pm 0.06$  mSv/slice.

The above data indicate that radiation exposure for measurement of VFA and SFA is inevitable. Therefore, an alternative simple, rapid, noninvasive and convenient technique to evaluate visceral fat accumulation is desirable in routine clinical practice. To date, the abdominal bioelectrical impedance analysis (BIA) method represents a simple, rapid, noninvasive and convenient technique that can specifically measure VFA<sup>[14]</sup>. The voltage recorded at the flank to the flow of current between the umbilicus and the back correlates significantly with VFA and is unaffected by SFA. The VFA measured by abdominal BIA correlates significantly with VFA determined by CT scan. Routine measurement of VFA by the BIA method should provide more information on the importance of visceral fat.

## RELATIONSHIP BETWEEN VISCERAL FAT AND METABOLIC RISK ACCUMULATION AND CARDIOVASCULAR DISEASE

Analysis of abdominal fat on CT scan showed that body fat distribution, especially excess accumulation of visceral fat, rather than the amount of total fat, correlates with diabetogenic, atherogenic, prothrombotic and proinflammatory metabolic abnormalities or the “metabolic syndrome”, which is associated with increased risk of atherosclerotic cardiovascular diseases (ACVD)<sup>[15-17]</sup>.

Using a different approach, other investigators showed that ACVD can be predicted by measuring the carotid intima-media thickness (IMT) by ultrasonography (United States)<sup>[18]</sup>. Interestingly, however, the Multicultural Community Health Assessment Trial demonstrated that visceral adiposity measured by CT correlates with the ultrasound-measured carotid IMT, plaque area and total area (IMT area plus plaque area) after adjusting for demographics, family history, smoking and percent body fat<sup>[19]</sup>.

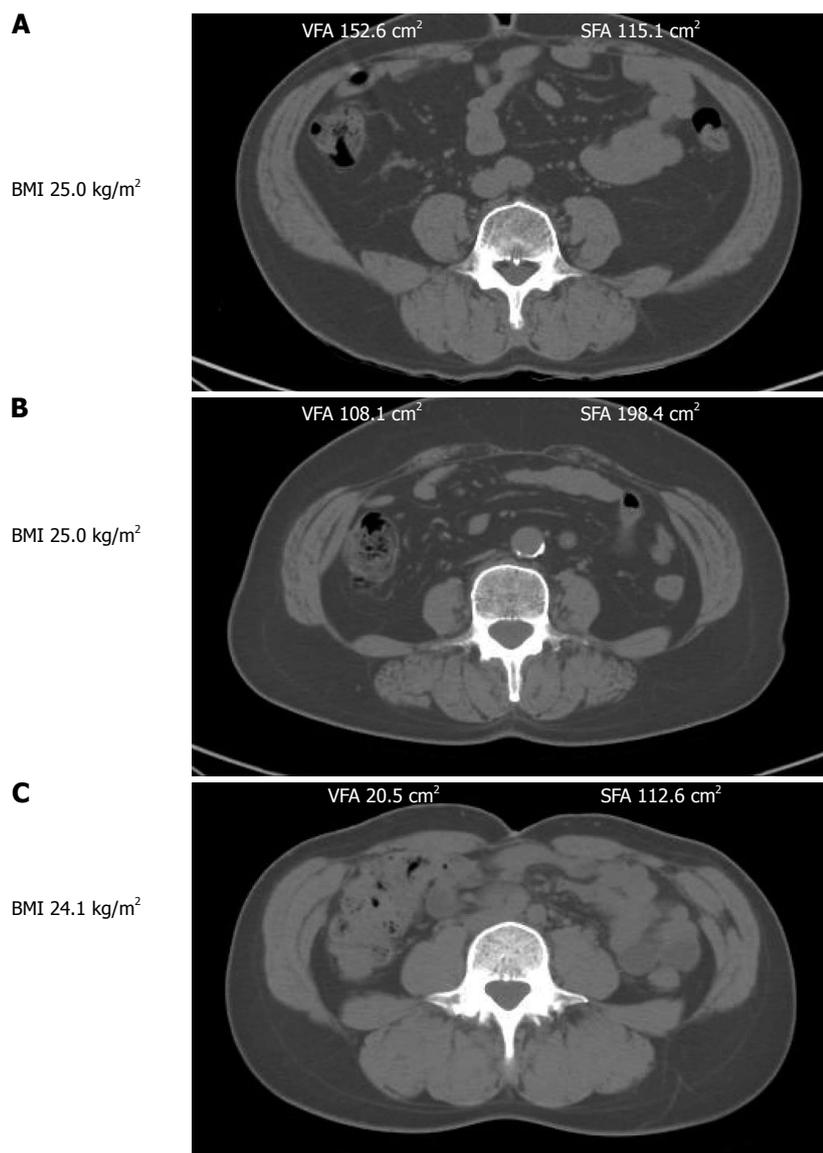
The importance of CT-based adiposity indexes in ACVD was further confirmed in the Framingham Heart study ( $n = 3086$ ; men = 1574, women = 1512; mean age 50.2 years; median follow-up 5.0 years), which showed a significant correlation between visceral adiposity and cardiovascular diseases (HR = 1.44; 95%CI: 1.08-1.92;  $P = 0.01$ ) and cancer (HR = 1.43; 95%CI: 1.12-1.84;  $P =$

0.005), even after adjustment for clinical risk factors and BMI. In contrast, the amount of subcutaneous adipose tissue did not correlate with ACVD<sup>[20]</sup>.

## DIAGNOSTIC CRITERIA OF VISCERAL FAT ACCUMULATION IN JAPAN

The Japanese Visceral Fat Syndrome (J-VFS) Study Committee of the Ministry of Health and Welfare of Japan was subsequently organized to establish the diagnostic criteria of obesity disease and the importance of visceral fat accumulation in obesity-related cardiovascular multiple risk factors<sup>[21]</sup>. Their study included 1193 subjects (men 775, women 418;  $55 \pm 12$  years of age, mean  $\pm$  SD). In that study, the mean number of obesity-related cardiovascular risk factors (hypertension, low high-density lipoprotein cholesterolemia and/or hypertriglyceridemia, and hyperglycemia) was greater than 1.0 at  $100 \text{ cm}^2$  of VFA in both men and women<sup>[21]</sup>. They also demonstrated that among the various anthropometric parameters measured in their study, waist circumference showed the closest relationship with VFA in both men and women. The regression line obtained from simple correlation analyses indicated that waist circumference that corresponds to  $100 \text{ cm}^2$  of VFA was 84.4 cm for men and 92.5 cm in women. The cut-off point of VFA of  $100 \text{ cm}^2$  as indicative of risk of obesity-related disorders in Japanese corresponds to waist circumferences of 85 cm in men and 90 cm in women<sup>[21]</sup>. The J-VFS study also reported a significant increase in the mean number of cardiovascular risk factors with increases in CT-measured VFA and was more than 1.0 at approximately  $100 \text{ cm}^2$  for VFA in both men and women. The area under the receiver-operating characteristic curve analysis indicated that VFA (men 0.741, women 0.763) was a significantly better indicator of clustering of risk factors ( $\geq 1$ ) than SFA (men 0.636, women 0.689). Furthermore, larger VFA values and smaller SFA values were recorded in men than in women at similar BMI categories<sup>[22]</sup> (Figure 3A and B).

The Visceral Fat Accumulation and Coronary Artery Disease Investigation in Japanese (VACATION-J) study was organized by the Ministry of Health, Labor and Welfare and included 12443 Japanese (men 10080, women 2363)<sup>[23-26]</sup>. The results showed that the mean number of obesity-related cardiovascular risk factors increased



**Figure 3** Differences in fat distribution based on sex and age. CT scans of the abdomen in three representative subjects. A: A 60-year-old male; B: A 60-year-old female; C: A 40-year-old female. Fat area measurement application: Advanced area calculation, GE Healthcare Co. CT: Computed tomography; BMI: Body mass index.

with increase in VFA but not with increase in SFA. VFA showed a normal distribution pattern in both men and old women, with a median value of 85-120 cm<sup>2</sup>. However, the VFA was markedly smaller (median: 59.8 cm<sup>2</sup>) (Figure 3C) and cardiovascular risk factors were fewer in younger women aged under 55 years<sup>[23]</sup>. The average number of cardiovascular risk factors exceeded 1.0 at VFA around 100 cm<sup>2</sup> for all groups in men and women, irrespective of age. Thus, VFA of approximately 100 cm<sup>2</sup> equates with the presence of more than 1.0 cardiovascular risk factors in Japanese, irrespective of gender, age and BMI<sup>[23]</sup>. In obese Japanese subjects, obesity-related risk factors did not increase with increase in SFA<sup>[23]</sup>, suggesting a protective effect for subcutaneous fat<sup>[27,28]</sup>. Considered together, the above studies suggest that “Hokenshido” designed to reduce visceral fat might target Japanese subjects with VFA  $\geq$  100 cm<sup>2</sup> (waist circumference of 85 cm for men and 90 cm for women) at risk of ACVD.

## HEALTH EDUCATION GUIDANCE “HOKENSHIDO” REDUCES METABOLIC SYNDROME

“Hokenshido”, a voluntary lifestyle modification, is a unique and original health education guidance used in Japan<sup>[26,29,30]</sup>. The Industrial Safety and Health Law of Japan stipulates that all workers must undergo annual health check-ups in the workplace. This includes anthropometry and laboratory measurements, testing visual acuity, audiometry, sphygmomanometry and chest X-ray. Other adult Japanese usually undergo annual public or private health check-ups. After the health check-up, physicians or public health nurses identify subjects at high risk of ACVD based on the presence of multiple risk factors, with and without visceral fat accumulation. Public health nurses and/or dietitians provide “Hokenshido” to subjects at high risk in a group setup and/or one-to-

one meetings. “Hokenshido” consists of education about the relationship between visceral fat accumulation and ACVD and interviews, including counseling, about eating habits, alcohol intake and physical activity. Through “Hokenshido”, the guided subjects image their own condition of vascular damage and identify problematic habits that need to be changed. “Hokenshido” allows subjects to understand the value of voluntary lifestyle modification with the aim of reducing visceral fat, consequently resulting in reduction of cardiovascular risks.

Using the health promotion program, we conducted a prospective cohort study (UMIN 00002391) of Amagasaki Visceral Fat Study based on visceral adiposity<sup>[29-40]</sup>. The study included 3174 employees [men 2440 (age 46 ± 11 years), women 734 (43 ± 10 years)] who underwent an annual health checkup. Application of “Hokenshido” resulted in reduction in the prevalence of the metabolic syndrome from 20.8% to 14.4% in men and from 3.0% to 1.9% in women in three consecutive years. Among subjects with the metabolic syndrome at baseline, the mean decrease in waist circumference was 2.5 cm in men and 3.9 cm in women after three consecutive years<sup>[29]</sup>. Furthermore, the decrease in visceral fat (measured by BIA) correlated with the decrease in the number of metabolic risk factors in men<sup>[31]</sup>.

## VISCERAL FAT REDUCTION EFFECTIVELY REDUCES CARDIOVASCULAR RISK

What is the pathological relationship between visceral fat and ACVD? Visceral fat comprises metabolically active adipose tissue. It provides fatty acids and glycerol to the liver *via* the portal vein and secretes adipocytokines and other vasoactive substances that can increase the likelihood of developing the metabolic syndrome. Excess visceral fat accumulation results in adipocyte dysfunction, *i.e.*, overproduction of plasminogen activator inhibitor type 1 and tumor necrosis factor alpha and underproduction of defensive adipocytokines, such as adiponectin<sup>[41-44]</sup>.

We have demonstrated through both the VACATION-J Study<sup>[23-26]</sup> and Amagasaki Visceral Fat Study<sup>[29-40]</sup> that a decrease in accumulated visceral fat (measured by CT or BIA) achieved within one year correlates with a decrease in the number of metabolic risk factors (hypertension, dyslipidemia and hyperglycemia)<sup>[24,31]</sup> and an increase in serum adiponectin level<sup>[32]</sup>. During 4 years follow-up of cardiovascular events in 3228 employees (men 2486, women 742), providing risk factor-oriented “Hokenshido” to subjects with visceral fat accumulation resulted in a significant decrease in the cumulative incidence of cardiovascular events in subjects who showed visceral fat reduction ( $-20.7 \pm 16.1 \text{ cm}^2$ ), compared to those who showed an increase in visceral fat ( $12.7 \pm 14.6 \text{ cm}^2$ ) ( $P = 0.0049$ )<sup>[39]</sup>.

Considered together, the above results suggest that reducing the amount of visceral fat is beneficial as it improves obesity-related disorders, possibly preventing ACVD. Based on this clinical and scientific background,

it is important to select the most appropriate subjects from the general population, including nonobese overweight subjects with a cluster of risk factors known as the metabolic syndrome, for body weight reduction in order to prevent ACVD. Health promotion programs should be useful in reducing visceral fat accumulation with subsequent improvement in cardiovascular risks (*e.g.*, glucose intolerance, dyslipidemia, hypertension, increased systemic oxidative stress and hypo adiponectinemia)<sup>[32]</sup>, as well as reducing the number of obesity-related cardiovascular risk factors<sup>[24,31]</sup> to prevent cardiovascular events<sup>[39]</sup>.

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