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Perspective

Rationale Diagnostic Criteria of the Metabolic Syndrome

Makiko Nakade[1], Akemi Morita[2], Shaw Watanabe[3], Naomi Aiba[4] and Motohiko Miyachi[5]*

[1]Department of Food Science and Nutrition, University of Hyogo, Japan

[2]Department of Public Health, Mie National University, Mie, Japan

[3]Lifescience Promoting Association, Tokyo, Japan

[4]Kanagawa University of Technology, Kanagawa, Japan

[5]National Institute of Health and Nutrition, Tokyo, Japan

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Conflicting Diagnostic Criteria of Metabolic Syndrome

The increase in obesity over the past 30 years has been fueled by a complex interplay of unhealthy diet and physical inactivity, environmental, social, economic, and behavioral factors, acting on a background of genetic susceptibility [1-3]. Obesity is a common risk factor for diabetes, hypertension, dyslipidemia and other lifestyle related diseases, and the preclinical condition has been summarized under the diagnosis of metabolic syndrome. The concept of metabolic syndrome was proposed by several committees, although there had been a considerable disagreement over the definition and diagnostic criteria. The use of definitions in conducting research into the metabolic syndrome resulted in wide-ranging prevalence rates, inconsistencies and confusion, and spurred on the vigorous debate regarding how the metabolic syndrome should be defined [4-6].

Excess abdominal fat is an important and independent risk factor for metabolic syndrome. Research has shown that waist circumference is directly associated with abdominal fat and can be used in the assessment of risks associated with excess weight and obesity [7,8]. Men with a waist circumference (WC) of more than 85 cm and women with a WC of more than 90 cm have more health risks than people with smaller WC measurements. In recent years, abdominal computed tomography has become available to determine the amount of abdominal fat directly and accurately (7).

Fortunately, people who have a BMI of 30 or greater can improve their health by losing weight. A loss of 5% to 10% of initial body weight can do much to improve health by lowering blood pressure and other risk factors for obesity-related diseases [9]. In addition, research showed that a goal of at least 7% weight loss from initial body weight brought by moderate diet and exercise could delay or possibly prevent type 2 diabetes in non-diabetic people [10].

Evidence-based Approach: Saku Control Obesity Program (SCOP)

We have carried out a series of epidemiological and clinical studies in Saku, Nagano prefecture in Japan [11-15]. Since 1990 a population-based Japan Public Health Center cohort study, consisting of 40- to 59-year-old residents, has been conducted in Saku. In Saku Health Dock Center each year about 7,000 examinees came to the center for health checkups, including an oral glucose tolerance test (OGTT) by 75 g glucose intake, endoscopy, and recently abdominal CT, in addition to the routine laboratory test and physical check-up. The Saku Health Dock Center database contains approximately 196,000 records connecting to the hospital database.

The purpose of the cohort study was to identify cancer and cardiovascular disease risks, and it represented a novel approach that incorporated biological markers as health screening data, blood, urine, and gene storage for future analyses. We selected this area because of a long collaborative history for primary prevention of chronic diseases [16].

The Saku Control Obesity Program (SCOP), the details of which have been described previously [11]. The SCOP study protocol included 235 Japanese obese subjects (116 men and 119 women) recruited from the database of medical health check-up of Saku Central Hospital Human Dock Center. The study participants were selected from medical records since 2000 and were aged 40-64 years old with a body mass index (BMI: kg/m^2) greater than 28.3 (the upper 5 percentile of all examinees). They were asked to participate in an intervention program for weight loss, Saku Control Obesity Program (SCOP).

The number of participants was 116 males and 119 females, aged 52.9 ± 6.6 and 54.4 ± 6.5 years, respectively. Basal metabolic rate, measured in one-tenth of the participants, was 1659 ± 226 kcal in males and 1477 ± 210 kcal in females, and physical activity energy expenditure (PAEE) was 271 ± 127 kcal in males and 246 ± 102 kcal in females.

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***Corresponding author:** Shaw Watanabe, Lifescience Promoting Association, Tokyo, Japan, E-mail: watashaw@lifescience.or.jp

Average body weight was 86.4 ± 11.8 kg in males and 75.2 ± 9.5 kg in females. Average BMI was 30.4 ± 3.5 kg/m^2 in males and 31.1 ± 3.1 kg/m^2 in females.

A cognitive-behavioral treatment was employed in a randomized intervention trial by diet and physical activity [13]. All participants were randomly divided to two groups: group A received intervention in year 1 and will be followed-up in years 2 and 3; group B will receive intervention in year 2 and will be followed up in year 3. A diary to record body weight, body fat, number of steps, and success in achieving the established plan (e.g., not eating snacks, increase of 3,000 steps/day), as well as a dietary record, was given to each participant. The equipments for body weight and body fat scale and accelerometer (Lifecorder), were also provided.

The participants received individual counseling (30 minutes) by a registered dietician after physical examination and group sessions about effective exercise (20 minutes) by exercise instructors. Body composition parameters were measured at baseline and at 1, 3, 6 and 9 months during the intervention period.

At baseline, the prevalence rate of the risk factor of metabolic syndrome was as follows; hypertension; 27.2% and 42.7% for males and females, respectively, hyperglycemia; 39.5% and 40.2%, dyslipidemia; 57.9% and 35.9% for males and females, respectively (Table 1).

People who are obese could reverse an earlier metabolic syndrome by adopting a healthy lifestyle and losing weight.

In males, the number of risk factors decreased from 40.4% to 35.1% with one factor, 15.8% to 19.3% with two factors, and 14.0% to 7.0% with three factors. In females, 28.1% to 35.1% with one factor, 26.3% to 15.8% with two factors, 7.0% to 3.5% with three factors (Table 2).

A goal of 5% reduction of body weight attained more than half, and about one fourth achieved 10 kg reduction of body weight. Group A showed 4.5 ± 4.4 kg decrease by the one-year intervention, and group B decreased by 5.4 ± 6.1 kg body weight.

Anthropometric and Laboratory Data of SCOP

The waist circumference was measured twice at the umbilicus level while the subject was in a standing position using a fiberglass measuring tape; the average measurement was used for the analysis.

Total fat areas were assessed by a computed tomography scan at the level of the umbilicus, with the subjects in the supine position, and calculated using the software (Fat Scan; N2 System Corp, Osaka, Japan) (Figure 1).

Abdominal CT photo was taken annually and total fat, subcutaneous and visceral fat was separately measured by the computer software.

Body fat % was measured by In Body (body composition measurement by impedance) and change in fat measurements by 1-year intervention is shown in Table 3 [17].

The association between body weight, BMI, WC, and total fat, subcutaneous and visceral fat area (cm^2) by CT is shown in Table 4. BMI, WC and total fat area showed a significantly high association, and the visceral fat area only showed a mild association with total fat area and body weight. Visceral fat area had poor association with subcutaneous (SQ) fat area in female subjects.

Even though the WC increases, the increase of visceral fat area is the lowest compared to the subcutaneous fat area (Figure 2).

Table 1: Prevalence of each risk factor of metabolic syndrome at baseline.

	Males n=116	%	Females n=119	%
Hypertension	31	27.2	50	42.7
Hyperglycemia	45	39.5	47	40.2
Dyslipidemia	66	57.9	42	35.9

Table 2: Number of risk factors before and after the intervention.

	Baseline				After 1 yr intervention			
	Males		Females		Males		Females	
	n	%	n	%	n	%	n	%
No risk factor	17	29.8	22	38.6	22	38.6	26	45.6
1 risk factor	23	40.4	16	28.1	20	35.1	20	35.1
2 risk factor	9	15.8	15	26.3	11	19.3	9	15.8
3 risk factor	8	14.0	4	7.0	4	7.0	2	3.5
	57		57		57		57	

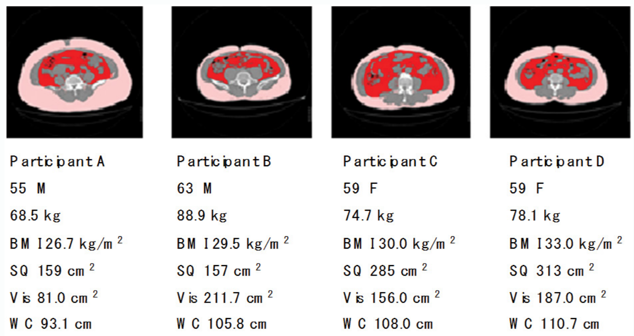

Figure 1: Abdominal computed tomography of visceral fat and subcutaneous fat. SQ: Subcutaneous fat area; Vis: Visceral fat area.

Table 3: Changes of fat volume and CT area by 1yr intervention.

	Intervention group (Males (n=56))		Control group (M (n=49))		
Males	Baseline	After 1 yr	Baseline	After 1 yr	p
Age (years)	53.7 ± 6.7		53.9 ± 6.3		
Body fat (%)	28.5 ± 3.6	26.8 ± 4.4	29.2 ± 4.6	29.6 ± 5.1	**
Total fat area (cm2)	393 ± 82	333 ± 81	417 ± 137	397 ± 104	**
Subcutaneous fat area (cm2)	243 ± 66	207 ± 62	253 ± 114	238 ± 96	*
Viscera fat area (cm2)	150 ± 48	126 ± 46	164 ± 48	159 ± 48	**
	Intervention group (Females (n=52))		Control group (F (n=52))		
Females	Baseline	After 1 yr	Baseline	After 1 yr	p
Age (years)	55.0 ± 6.6		54.5 ± 6.2		
Body fat (%)	39.7 ± 5.2	37.8 ± 5.9	41.8 ± 5.4	41.8 ± 5.8	**
Total fat area (cm2)	467 ± 98	402 ± 93	468 ± 123	455 ± 108	**
Subcutaneous fat area (cm2)	343 ± 80	302 ± 76	335 ± 100	326 ± 88	
Viscera fat area (cm2)	125 ± 47	100 ± 38	133 ± 47	130 ± 45	**

Following an overnight fast, blood samples were collected for biological analyses at the time of each health check-up. HDL cholesterol (HDL-C), LDL cholesterol (LDL-C), triglyceride (TG) and HbA_{1c} levels were analyzed in the clinical laboratory of the Saku Central Hospital. High-molecular-weight form (HMW) adiponectin (μg/mL) and leptin (ng/mL) were measured by ELISA. Clinical and biological parameters were assessed at baseline (0 month), the end of intervention (12 months) and the end of follow-up (24 months).

Body weight, BMI, and other biological change are noted. Most of the biomarkers were significantly improved at the 12 and 24 months as compared with baseline (Table 5).

Changes in adiponectin and leptin were a good biomarker for the trend in body weight decrease and rebound (Figure 3).

Adiponectin is associated with insulin sensitivity and atherosclerosis. Despite adiponectin being secreted from adipose tissue, plasma levels are lower in individuals with obesity, insulin resistance and type 2 diabetes (T2D). Leptin continued to decrease throughout 24 months despite weight regain between follow-up periods (Table 5). HDL-C continued to increase from baseline to 24 months. At 24 months, HDL-C was significantly higher than at baseline for both men and women.

Different Prevalence of Metabolic Syndrome by Japanese, WHO and IDA Criteria

The first definition of criteria referring to abdominal obesity was proposed by the National Cholesterol Education Program Adult Treatment (ATPIII) in 2001. ATPIII adopted abdominal obesity estimated by the WC rather than by BMI in addition to

Table 4: Correlation between body weight, BMI, waist circumference and CT fat area.

M n=116		Weight	BMI	Waist	Total Fat	SQ fat	Visceral fat
F n=119	Weight		.863**	.890**	.837**	.798**	.539**
	BMI	.823**		.879**	.907**	.874**	.567**
	Waist	.798**	.769**		.917**	.877**	.585**
	Total Fat	.766**	.788**	.903**		.926**	.697**
	SQ fat	.739**	.719**	.857**	.906**		0.375**
	Visceral fat	.371**	.458**	.461**	.593**	.197**	
	*p<0.05	**p<0.01					

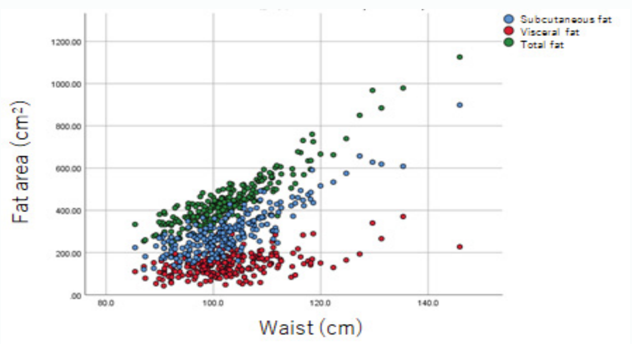

Figure 2: Relationship between waist circumference and CT estimated fat area. Total fat area= -908.991 × 13.16 WC (p<0.001); Subcutaneous fat area= -759.599 × 10.30 WC (p<0.001); Visceral fat area= -149.387 × 2.86 WC (p<0.001).

Table 5: Change of biomarkers at the baseline, after 1yr intervention, and 1 yr follow-up. Values are the mean ± SD. The serum level of both leptin and adiponectin are the median and range (25 percentile and 75 percentile), but the analyses were conducted by use of log-transformed data.

Males (n=56)	unit	Baseline	After 1 yr intervention	1 yr follow-up	p
Weight	kg	84.2 ± 8.5	79.3 ± 8.7	80.5 ± 1.2	**
BMI	kg/m²	29.8 ± 2.3	28.1 ± 2.5	28.5 ± 2.6	**
Systolic blood pressure	mmHg	131.9 ± 15.4	125.8 ± 14.3	128.3 ± 12.6	**
Diastolic blood pressure	mmHg	81.1 ± 14.2	79.3 ± 11.2	80.4 ± 10.1	
Waist circumference	cm	100.0 ± 6.5	96.0 ± 7.5	96.7 ± 7.3	**
Total fat area	cm²	393.3 ± 82.2	333.1 ± 80.7	350.3 ± 82.0	**
Total cholesterol	mg/dl	205.4 ± 29.3	203.3 ± 34.1	196.6 ± 29.9	**
HDL cholesterol	mg/dl	48.3 ± 10.8	50.3 ± 12.7	51.4 ± 14.6	**
LDL choloesterol	mg/dl	123.2 ± 28.9	124.4 ± 30.9	120.8 ± 31.2	
Triglyceride	mg/dl	169.7 ± 98.1	142.8 ± 74.4	146.4 ± 81.9	*
HbA1c	%	5.7 ± 1.1	5.5 ± 0.8	5.7 ± 0.7	**
Adiponectin	ug/ml	2.2(1.5-3.6)	3.2(2.1-5.9)	2.6(1.6-4.8)	**
Leptin	ng/ml	6.7(4.2-9.1)	5.7(3.8-8.8)	5.2(3.6-7.3)	**
Females (n=52)					
Weight	kg	74.5 ± 8.4	70.7 ± 9.3	71.9 ± 1.3	**
BMI	kg/m²	31.0 ± 2.9	29.4 ± 3.4	29.9 ± 3.3	**
Systolic blood pressure	mmHg	132.6 ± 16.1	126.8 ± 17.3	126.1 ± 17.4	**
Diastolic blood pressure	mmHg	81.3 ± 11.4	79.8 ± 11.7	78.9 ± 10.9	
Waist circumference	cm	103.2 ± 8.1	99.2 ± 9.6	100.7 ± 9.2	**
Total fat area	cm²	467.4 ± 97.6	402.0 ± 93.0	420.5 ± 90.8	**
Total cholesterol	mg/dl	210.3 ± 35.5	210.1 ± 26.8	206.4 ± 27.6	
HDL cholesterol	mg/dl	56.2 ± 11.8	57.2 ± 13.0	59.0 ± 13.4	*
LDL choloesterol	mg/dl	128.0 ± 31.8	129.2 ± 25.9	126.8 ± 25.0	
Triglyceride	mg/dl	130.8 ± 60.7	118.4 ± 57.9	112.9 ± 53.9	*
HbA1c	%	5.9 ± 1.2	5.6 ± 1.0	5.9 ± 1.0	*
Adiponectin	ug/ml	5.1(4.1-8.4)	6.8(5.1-10.2)	5.8(4.8-8.5)	**
Leptin	ng/ml	17.7(13.2-23.5)	15.7(10.7-20.7)	14.2(9.5-18.2)	**

hypertriglyceridemia, low HDL-cholesterol, high blood pressure, and hyperglycemia.

In 2005, the International Diabetes Foundation (IDF) reported a new diagnostic criterion of metabolic syndrome, making abdominal obesity an essential factor required in the diagnosis [4]. The representatives of the IDF, the International Atherosclerosis Society, and the American Heart Association/National Heart, Lung and Blood Institute agreed that abdominal obesity should not be a prerequisite for the diagnosis, requiring the present of any three of five factors. They also suggested that abdominal obesity should be defined based on the national cutoff point of each country [4]. Most countries accept the criteria of IDF.

Matsuzawa [5,18] accumulated data of abdominal CT scan in relationship to adiposity and diseases, and the Japanese committee adopted a cutoff point of 100 cm^2 of the visceral fat area for both men and women because the risk of metabolic syndrome increased over this point in both men and women simultaneously. WC that corresponded to visceral fat of 100 cm^2 was 85 cm in men and 90 cm in women.

When we compare the efficacy of intervention by Japanese criteria, the rate of metabolic syndrome-among men decreased from 100% to 97.3%, and among women 96.6% to 88.6% (Table 6). Three and 8% reduction in males and females occurred. However, when we applied the IDF criteria, metabolic syndrome rate decrease was found 9% in men, and none in women. Such unbalance is curious in biological response. It also suggests the prevalence of metabolic syndrome by IDF criteria is underdiagnosis in men and over diagnosis in women compared to the Japanese criteria.

Biological Rationale of the Japanese Criteria based upon the Abdominal fat Area by CT

Controversies on the significance and cutoff point of WC may have arisen from a misunderstanding of the purpose and the significance of the measurement of WC [18].

The adipose tissue had been considered as just an energy storage tissue, but recent studies reported that the tissue synthesizes and secretes various bioactive substances called adipocytokines, such as leptin, adiponectin, tumor necrosis factor-alpha (TNF-α), free fatty acids (FFAs), resist in and angiotensinogen [19]. Many studies have been investigated about adiponectin and leptin among various adipocyte-derived cytokines, and it is thought to be related in the process of metabolic syndrome to the disease [20,21].

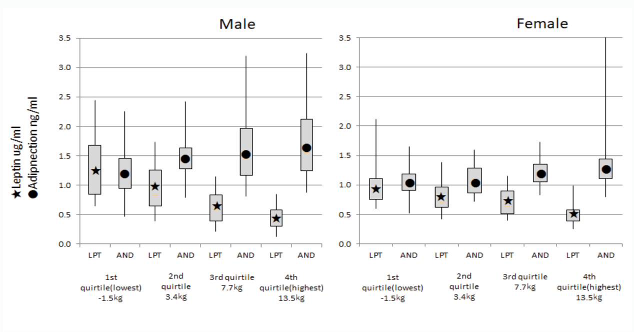

Figure 3: Leptin and adiponectin corresponding to the quartile of body weight decrease.

Table 6: Number of subjects by Japan and IDF criteria.

Baseline	Japan criteria				IDF criteria			
	M	%	F	%	M	%	F	%
MS -	0	0	4	3.4	3	2.6	0	0
MS +	116	100	115	96.6	113	97.4	119	100
total	116		119		116		119	
After 1yr intervention	Japan criteria				IDF criteria			
	M	%	F	%	M	%	F	%
MS -	3	2.7	13	11.4	13	11.5	0	0
MS +	110	97.3	101	88.6	100	88.5	114	100
total	113		114		113		114	

MS: Metabolic Syndrome; -: None; +: Present; M: Males; F: Females.

So far, visceral adiposity measured by CT scan is a golden standard, and it fits into the pathophysiology of metabolic syndrome.

The cutoff point in Japan was the only one that was based on the visceral fat area for the prevalence of diseases. The first nationwide lifestyle intervention program to improve the risk factors for metabolic syndrome in healthy adults was recently reported by Tushita et al. [22]. They used the registry of Specific Health Checkups and Specific Health Guidance focusing on metabolic syndrome in middle aged adults, 40 to 74 years of age, beginning in 2008 with follow-up period of 3 years. Number of participants to the program was 31,790 and non-participated controls were 189,726. Body weight reduction was 1.98 kg (participants) and 0.42 kg (non-participants) and WC reduction was 2.34 cm in men and 2.98 cm in women by the intervention, while among controls it was unchanged for 3 years.

So, the standardization of diagnostic criteria is important to compare the efficacy of intervention and prevention of diseases. It could be conclusive that the WC of Japanese criteria is appropriate avoiding both over-diagnosis and under-diagnosis. WC reflects both visceral fat and subcutaneous fat of the abdominal wall, women in middle age usually have more subcutaneous fat than visceral fat. A similar distribution is found among *sumou* wrestlers. The subcutaneous fat area did not show a high correlation with visceral fat.

As developing countries are simultaneously facing increasing obesity and lifestyle diseases, collaboration in research and programs is urgently needed to prevent disease through dietary and lifestyle intervention.

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Ethical Issue

The protocol of SCOP was approved by the National Institute of Health and Nutrition and the SAKU General Hospital. The Ministry of Health, Labour and Welfare supported the study by funding.

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