produced abundantly by adipose tissue in normal individuals and circulates in the blood stream. In addition, adiponectin strongly binds with subendothelial collagens such as collagen I, III, V, thus strengthening the sclerotic tissue plaque composition.[38] A possible mechanism of the prevention of atherosclerosis and acute coronary syndrome by adiponectin is shown in Figure 11. Adiponectin, abundantly present in the blood stream, may enter injured vascular walls by binding to subendothelial collagens and protecting against a variety of atherosclerotic cell phenomena as mentioned above. Thus, adiponectin could be likened to firefighters who put out small fires (in vascular walls) before they become big fires.

## Conclusion

Using CT scan for fat analysis revealed that intra-abdominal visceral fat accumulation has been shown to play crucial roles in the development of metabolic and cardiovascular diseases. Given these clinical findings, the functions of adipocytes have been intensively investigated in the past 10 years and have been shown to act as endocrine cells that secrete various bioactive substances and also as energy-storing cells. Accumulation of visceral fat that links directly with the liver by portal circulation may induce hyperlipidemia and hyperglycemia through increased flux of FFA and glycerol to the liver. In addition, visceral fat accumulation may induce oversecretion of offensive adipocytokines, such as plasminogen activator inhibitor 1, TNF-α and herpin binding EGF-like growth factor (HB-EGF), and insufficient secretion of defensive adipocytokine, namely adiponectin (Figure 12). The complex of these mechanisms may be present in the background of a variety of metabolic and cardiovascular disorders of visceral obesity.

## Conflict of interest

The author has declared no conflict of interest.

## References

1 Vague J. La differentiation sexuelle, facteur determinant des formes de l'obesite. *Press Med* 1947; **55**: 339–340.
2 Björntorp P. Regional patterns of fat distribution. *Ann Intern Med* 1985; **103**: 994–995.
3 Kissebah AH, Vydelingum N, Murray R, Evans DJ, Harz AJ, Kalkhoff RK *et al.* Relation of body fat distribution to metabolic complications of obesity. *J Clin Endocrinol Metab* 1982; **54**: 254–260.
4 Tokunaga K, Matsuzawa Y, Ishikawa K, Tarui S. Novel technique for the determination of body fat by computed tomography. *Int J Obes* 1983; **7**: 437–445.
5 Matsuzawa Y, Fujioka S, Tokunaga K, Tarui S. A novel classification: visceral fat obesity and subcutaneous obesity. In: Berry EM, Blondheim SH (eds). *Recent Advances in Obesity Research V*. John Libbey: London, 1987, pp 92–96.
6 Fujioka S, Matsuzawa Y, Tokunaga K, Tarui. Contribution of intra-abdominal fat accumulation to the impairment of glucose and lipid metabolism. *Metabolism* 1987; **3**: 54–59.
7 Kanai H, Matsuzawa Y, Kotani K, Keno Y, Kobatake T, Nagai Y *et al.* Close correlation of intraabdominal fat accumulation to hypertension in obese women. *Hypertension* 1990; **16**: 484–490.
8 Depres JP, Nadeau A, Tremblay A. Role of deep abdominal fat in the association between regional adipose tissue distribution and glucose tolerance in obese women. *Diabetes* 1989; **38**: 304–309.
9 Matsuzawa Y. Pathophysiology and molecular mechanism of visceral fat syndrome: the Japanese case. *Diabetes/Metab Rev* 1996; **13**: 3–13.
10 Nakamura T, Tokunaga K, Shimomura I, Nishida M, Yoshida S, Kotani K *et al.* Contribution of visceral fat accumulation to the development of coronary artery disease in non-obese men. *Atherosclerosis* 1994; **107**: 239–246.
11 Reaven GM. Role of insulin resistance in human disease. *Diabetes* 1988; **37**: 1595–1607.
12 Kaplan NM. The deadly quartet. *Arch Intern Med* 1989; **149**: 1514–1520.
13 Alberti KG, Zimmet P, Shaw J. Metabolic syndrome—a new world-wide definition. A Consensus Statement from the International Diabetes Federation. *Diab Med* 2006; **23**: 1385–1386.
14 Kotani K, Tokunaga K, Fujioka S, Kobatake T, Keno Y, Yoshida S *et al.* Sexual dimorphism of age-related changes in whole body fat distribution in the obese. *Int J Obes* 1994; **18**: 207–212.
15 Keno Y, Matsuzawa Y, Tokunaga K, Fujioka S, Kawamoto T, Kobatake T *et al.* High sucrose diet increases visceral fat accumulation in VMH-lesioned obese rats. *Int J Obes* 1991; **15**: 205–211.
16 Matsuzawa Y, Fujioka S, Tokunaga K, Tarui S. Classification of obesity with respect to morbidity. *Proc Soc Exp Biol Med* 1992; **200**: 197–201.
17 Clemens K, Vaisse C, Manning BSJ, Basdevant A, Guy-Grand B, Ruiz J *et al.* Genetic variation in the β3-adrenergic receptor and increased capacity to gain weight in patients with morbid obesity. *N Engl J Med* 1995; **333**: 352–354.
18 Kuriyama H, Yamashita S, Shimomura I, Funahashi T, Matsuzawa Y. Enhanced expression of hepatic acylCoA synthetase and microsomal triglyceride transfer protein mRNAs in the obese and hypertriglyceridemic rats with visceral fat accumulations. *Hepatology* 1998; **2**: 557–562.
19 Maeda K, Okubo K, Shimomura I, Mizuno K, Funahashi T, Matsuzawa Y *et al.* Analysis of expression profile of genes in the human adipose tissue. *Gene* 1997; **190**: 227–235.
20 Kishida K, Kuriyama H, Funahashi T, Shimomura I, Kihara S, Ouchi N *et al.* Aquaporin adipose, a putative glycerol channel in adipocytes. *J Biol Chem* 2000; **275**: 20896–20902.
21 Kishida K, Shimomura I, Kondo H, Kuriyama H, Makino Y, Nishizawa H *et al.* Genomic structure and insulin-mediated repression of the aquaporin adipose, adipose-specific glycerol channel. *J Biol Chem* 2001; **276**: 36251–36260.
22 Matsuzawa Y. Therapy insight: adipocytokines in metabolic syndrome and related cardiovascular disease. *Nat Clin Pract Cardiovasc Med* 2006; **3**: 35–42.
23 Shimomura I, Funahashi T, Takahashi M, Maeda K, Kotani K, Nakamura T *et al.* Enhanced expression of PAI-1 in visceral fat: possible contribution to vascular disease in obesity. *Nat Med* 1997; **2**: 1–5.
24 Maeda K, Okubo K, Shimomura I, Funahashi T, Matsuzawa Y, Matsubaa K. cDNA cloning and expression of a novel adipose specific collagen-like factor, apM1 (Adipose most Abundant Gene Transcript 1). *Biochem Biophys Res Commun* 1996; **22**: 286–289.
25 Matsuzawa Y. Adiponectin: identification, physiology and clinical relevance in metabolic and vascular disease. *Atherosclerosis* 2005; **6** (Suppl): 7–14.

26 Maeda N, Shimomura I, Kishida K, Nishizawa H, Matsuda M, Nagaretani H *et al.* Diet-induced insulin resistance in mice lacking adiponectin/ACRP30. *Nat Med* 2002; **8**: 731–737.
27 Lindsay RS, Funahashi T, Hanson RL, Matsuzawa Y, Tanaka S, Tataranni PA *et al.* Adiponectin and development of type 2 diabetes in the Pima Indian population. *Lancet* 2002; **360**: 57–58.
28 Zoccali C, Mallamaci F, Tripepi G, Benedetto FA, Cutrupi S, Parlongo S *et al.* Adiponectin, metabolic risk factors, and cardiovascular disease. *J Am Soc Nephrol* 2002; **13**: 134–141.
29 Kumada M, Kihara, Sumitsuji S, Kawamoto T, Matsumoto, Ouchi N *et al.* Association of hypoadiponectinemia with coronary artery disease in men. *Arterioscler Thromb Vasc Biol* 2002; **23**: 85–89.
30 Kishida K, Nagaretani H, Kondo H, Kobayashi H, Tanaka S, Maeda N *et al.* Disturbed secretion of adiponectin of mutant adiponectin associated with the metabolic syndrome. *Biochem Biophys Res Commun* 2003; **306**: 286–292.
31 Kamada Y, Matsumoto H, Tamura S, Fukushima J, Kiso S, Fukui K *et al.* Hypoadiponectinemia accelerates hepatic tumor formation in a nonalcoholic steatohepatitis mouse model. *J Hepatol* 2007; **47**: 556–564.
32 Yokota T, Oritani K, Takahashi I, Ishikawa J, Matsuyama A, Ouchi N *et al.* Adiponectin, a new member of the family of soluble defense collagens, negatively regulates the growth of monocyte progenitors and the functions of macrophages. *Blood* 1999; **96**: 1727–1732.
33 Okamoto Y, Kihara S, Ouchi N, Nishida M, Arita Y, Kumada M *et al.* Adiponectin reduces atherosclerosis in apolipoprotein E-deficient mice. *Circulation* 2002; **26**: 2767–2770.
34 Ouchi N, Kihara S, Arita Y, Okamoto Y, Maeda K, Kuriyama H *et al.* Adiponectin, an adipocyte-derived plasma protein, inhibits endothelial NF-kappaB signaling through a cAMP-dependent pathway. *Circulation* 2000; **102**: 1296–1301.
35 Ouchi N, Kihara S, Funahashi T, Nakamura T, Nishida M, Kumada M *et al.* Reciprocal association of C-reactive protein with adiponectin in blood stream and adipose tissue. *Circulation* 2003; **107**: 671–674.
36 Matsuzawa Y. Adiponectin and inflammation. In: Fantuzzi G, Mazzone T (eds). *Nutrition and Health. Adipose and Adipokines in Health and Disease*. Human Press Inc.: Totowa, NJ, 2007, pp 111–117.
37 Kumada M, Kihara S, Ouchi N, Kobayashi H, Okamoto Y, Ohashi K *et al.* Adiponectin specifically increased tissue metalloproteinase 1 through interleukin expression in human macrophages. *Circulation* 2004; **109**: 2046–2049.
38 Okamoto Y, Arita Y, Nishida M, Muraguchi M, Ouchi N, Takahashi M *et al.* An adipocyte-derived protein, adiponectin, adheres to injured vascular walls. *Horm Metab Res* 2000; **32**: 47–50.

*Annals of Medicine*. 2007; 39: 482–494

informa
healthcare

REVIEW ARTICLE

# Metabolic syndrome: Clinical concept and molecular basis

TOHRU FUNAHASHI[1] & YUJI MATSUZAWA[2]

[1]*Department of Internal Medicine and Molecular Science, Graduate School of Medicine, Osaka University, Osaka, Japan, and* [2]*Sumitomo Hospital, Osaka, Japan*

**Abstract**

The metabolic syndrome is a cluster of insulin resistance, elevated blood pressure, and atherogenic dyslipidemia and is a common basis of cardiovascular diseases (CVD). Although the precise mechanism remains to be elucidated, a practical definition is needed. A worldwide definition that considers increased waist circumference as an essential component has been settled.

Visceral fat locates upstream of the liver. Free fatty acids and glycerol derived from visceral fat reach the liver and stimulate lipoprotein synthesis and gluconeogenesis, respectively. The adipose tissue produces a variety of bioactive substances conceptualized as 'adipocytokines'. Overproduction of plasminogen activator inhibitor-1 and tumor necrosis factor-α seems to relate to the thrombotic and inflammatory tendency. On the other hand, adiponectin, which has antiatherogenic and antidiabetic activities, is reduced in subjects with metabolic syndrome.

In Japan, the waist circumference criterion based on visceral fat accumulation has been adopted. The concept of this syndrome has been widely publicized, and health promotion programs based on the concept have commenced in various areas of the country. Such 'Adipo-Do-It' movement is an incentive to encourage physical exercise to reduce visceral fat and is a big challenge to prevent life-style-related diseases and CVD.

**Key words:** *Adipocytokines, adiponectin, aquaporin 7, metabolic syndrome, visceral fat*

## Introduction

Cardiovascular diseases (CVD) are the major causes of morbidity and mortality in the world. Numerous epidemiological and basic scientific studies have indicated that hypercholesterolemia and elevated serum levels of low-density lipoprotein (LDL) are major risk factors for CVD. Clinical trials have demonstrated that LDL-lowering therapy can reduce major cardiovascular events and mortality. The secondary target of CVD prevention is the multiple risk factor syndrome, representing clustering of mild dyslipidemia, hyperglycemia, and hypertension in individuals, which is increasing throughout the world.

Obesity is a well known major risk factor for hyperlipidemia, diabetes, and hypertension. However, not all obese subjects have such disorders and, on the other hand, mildly obese subjects sometimes have multiple comorbidities. Recent clinical research demonstrated that the distribution of body fat rather than the total amount of fat is related to obesity-linked disorders. Central obesity, especially accumulation of intra-abdominal visceral fat, has been identified as a common basis of dyslipidemia, hyperglycemia, hypertension, and CVD based on clustering of multiple risks. At present, there is recognition that people should distinguish body fat accumulation, especially visceral fat accumulation accompanied by various metabolic disorders, from simple obesity as a body status.

Recent progress in biological research has uncovered the mechanism of differentiation and functions of adipose tissue. The most striking finding in this field is that adipose tissue is not a simple energy storage organ but rather a large endocrine organ that produces and secretes various bioactive substances called 'adipocytokines'. Several experimental and clinical studies have demonstrated that the development of obesity-related comorbidities and CVD are

Correspondence: Dr Tohru Funahashi, Department of Internal Medicine and Molecular Science, Graduate School of Medicine, Osaka University, 2-2, Yamada-okaSuita, Osaka 565-0871, Japan. Fax: +81-6-6879-3739. E-mail: tohru@imed2.med.osaka-u.ac.jp

ISSN 0785-3890 print/ISSN 1365-2060 online 
DOI: 10.1080/07853890701491026

**Abbreviations**

| | |
|---|---|
| AMP | adenosine monophosphate |
| AMPK | AMP-activated protein kinase |
| apoB | apolipoprotein B |
| AQP | aquaporin |
| ARB | angiotensin receptor blocker |
| BMI | body mass index |
| CAD | coronary artery disease |
| COX | cyclooxygenase |
| CT | computed tomography |
| CVD | cardiovascular disease |
| EGF | epidermal growth factor |
| ERK | extracellular signal-regulated kinase |
| fat | ROS fat reactive oxygen species |
| FFA | free fatty acids |
| HB-EGF | heparin-binding EGF-like growth factor |
| HDL-C | high-density lipoprotein cholesterol |
| hs-CRP | high-sensitivity C-reactive protein |
| IDF | International Diabetes Federation |
| KO | knockout |
| LDL | low-density lipoprotein |
| MAP | mitogen-activated protein |
| MetS | the metabolic syndrome |
| NCEP | National Cholesterol Education Program |
| NF-κB | nuclear factor-kappa B |
| NO | nitric oxide |
| PAI-1 | type 1 plasminogen activator inhibitor |
| PPARγ | peroxisome proliferator-activated receptor-γ |
| SREBP | sterol-responsive element-binding protein |
| TIMP | tissue inhibitor of metalloproteinase |
| TNF | tumor necrosis factor |
| VCAM | vascular cell adhesion molecule |
| VLDL | very low-density lipoprotein |
| WHO | World Health Organization |
| WT | wild-type |

directly related to dysregulation of various adipocytokines associated with visceral obesity.

With the background of life-styles such as physical inactivity and overnutrition, the prevalence of the multiple risk factor syndrome is increasing explosively even in East Asia including China. From this world situation, together with a better clinical and scientific understanding of obesity, the International Diabetes Federation (IDF) published the definition of 'the metabolic syndrome' (MetS) on the basis of central obesity (visceral fat accumulation) that is associated with multiple comorbidities, to prevent CVD (1). Further scientific perception and appreciation of adipocytokines and obesitopathy may help people to change their life-styles and to reduce life-style-related comorbidities worldwide. Here, we review the clinical concepts and molecular mechanisms of MetS.

**Key messages**

- The metabolic syndrome is a common basis of cardiovascular diseases with multiple atherogenic risk factors, increasing in the countries where overeating and physical inactivity are common life-styles. A clinical definition of the metabolic syndrome is increased waist circumference plus two or more comorbidities (not simple obesity).
- Visceral fat locates upstream of the liver, and free fatty acids and glycerol derived from visceral fat reach the liver, resulting in stimulation of lipoprotein synthesis and gluconeogenesis, respectively. Dysregulation of adipocytokines, such as overproduction of PAI-1 and TNFα, and reduction of adiponectin, may be one of the molecular mechanisms of the metabolic syndrome.
- Risk factor-oriented (not simply obesity-oriented) and scientific health promotion programs based on the concept of the metabolic syndrome will encourage physical exercise to reduce visceral fat and will help to prevent life-style-related diseases and consequently to minimize the risk of cardiovascular diseases.

## Introduction of computed tomography scanning in obesity research and visceral fat obesity

Obese people with body mass index (BMI) greater than 30 kg/m$^2$ are rare (approximately 2% of the general population) in East Asia including Japan. However, this frequency provoked us to pay more attention to the pathological consequences of obesity. We identified a considerable number of people with plasma glucose, lipids, or blood pressure levels that were almost normal or abnormal but much milder than would be otherwise expected in extremely obese subjects. Even when these individuals had hyperglycemia, dyslipidemia, or hypertension,

these abnormalities improved markedly after only 3%–5% weight reduction despite persistence of obesity. Thus, it seemed that body weight itself does not simply determine the abnormalities in glucose, lipids, and blood pressure; i.e., body weight itself does not reflect the precise amount or properties of adipose tissue in the body. Our group introduced computed tomography (CT) scanning for precise evaluation of adipose tissue, because this imaging technique can detect adipose tissue. The amount of subcutaneous adipose tissue in the body was calculated from multi-slice CT images (2). In spite of these efforts, we found no significant difference in the relationship between clinical abnormalities and the amount of adipose tissue by CT, compared with the relationship between medical parameters and BMI. However, this method was critically distinct from other techniques used for evaluation of body fat, such as impedance method, in the point that CT scan can be used for assessment of the amount of fat in the body cavity. Some obese subjects possess significant amount of tissue in the abdominal cavity with CT values similar to subcutaneous fat (Figure 1), although there is considerable variation in abdominal fat distribution in the subjects. For example, some subjects have vast amounts of subcutaneous fat, while others have excess fat in the intra-abdominal region but little subcutaneous fat. Our group investigated the relationship between abdominal fat distribution and medical health problems and found that subjects with intra-abdominal fat had predominantly higher plasma glucose levels in glucose tolerance tests, higher plasma triglyceride levels, and higher blood pressure levels, compared with those with a predominant accumulation of subcutaneous fat (3,4). We designated such type of obesity, i.e. predominant accumulation of intra-abdominal fat, as 'visceral fat obesity' to discriminate it from 'subcutaneous fat obesity' (5).

## Syndrome X, deadly quartet, and visceral fat syndrome

In the late 1980s, a cluster of multiple risk factors in one individual, which was termed 'multiple risk factors syndrome', focused attention on beyond the

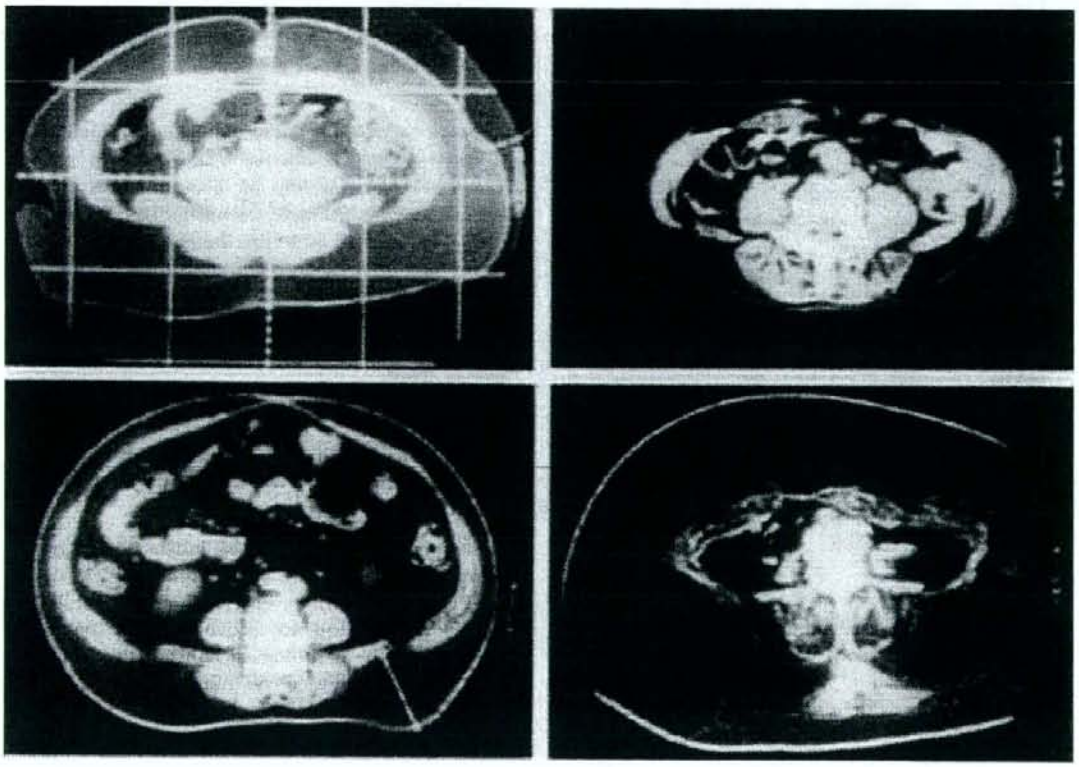

Figure 1. CT scanning images of obese subjects. Note the huge amount of subcutaneous fat in the lower right panel (D). Note also the relatively small amount of subcutaneous fat but massive intra-abdominal visceral fat in the lower left panel (C).

cholesterol point of view. Reaven (6) at Stanford University proposed 'syndrome X', and Kaplan (7) at Texas University proposed 'deadly quartet'. Subsequently, DeFronzo (8) at Texas University proposed a similar pathological entity as the 'insulin resistance syndrome'.

In the meantime, research on obesity revealed that the site of fat accumulation, rather than the grade of obesity, is a significant determinant of various morbid conditions. The link between specific body fat distribution and development of morbid conditions that could lead to CVD was first proposed by Vague at Marseille University. In 1947, Vague (9) stated that android obesity, which represents fat accumulation in the upper body, posed a higher risk for diabetes mellitus than gynoid-type obesity, which represents fat accumulation in the lower body. Subsequently in the 1980s, Kissebah (10) proposed upper body obesity based on the waist/hip ratio and reported its significance on the development of insulin resistance and lipid abnormality. Furthermore, Bjorntorp (11) described the concept of central obesity and stressed its significance for CVD.

Our group estimated the fat distribution in patients with coronary artery disease (CAD). We noted visceral fat accumulation even in people with within normal BMI. The area of visceral fat in approximately 40% of patients with CAD was greater than 100 $cm^2$ (Figure 2), although the subcutaneous fat was very thin in such patients. These individuals were positive for multiple coronary risk factors, such as hypertension, glucose intolerance, and dyslipoproteinemia (12). Thus, visceral fat accumulation is an attractive concept underlying CVD through the development of multiple risk factors. We thus proposed the concept of 'visceral fat syndrome' as a multiple risk factor clustering syndrome. Visceral fat syndrome is a condition compatible with 'syndrome X' or 'deadly quartet'.

## Characteristics of visceral fat

Adipose tissue provides free fatty acids (FFA) through lipolysis. Abnormality of FFA metabolism in upper body obesity is considered a cause of some metabolic defects such as dyslipidemia, insulin resistance, and vascular endothelial dysfunction. It has been reported that abdominal subcutaneous fat is lipolytically more active than lower-body subcutaneous fat, and the excess release of FFA from abdominal subcutaneous fat may contribute to the abnormalities described in MetS (13). The amount of intra-abdominal visceral fat is smaller than that of subcutaneous fat and thus the amount of FFA released by the visceral fat must contribute only a small percentage of systemic FFA delivery. However, clinical analyses of body fat distribution by CT scan revealed that glucose intolerance, plasma triglyceride level, and blood pressure level are closely related to the ratio of visceral fat area/abdominal fat area (3,4). Thus, the anatomical characteristics of visceral fat seem to relate to the development of these metabolic disorders. Visceral adipose tissue is located in the mesentery, where innumerable vessels run from the digestive tract to the liver and temporarily reserve excess energy as triglyceride. In response to energy demand, visceral adipose tissue quickly hydrolyzes triglyceride. FFA and glycerol released from visceral fat reach the liver via the portal vein (Figure 3). FFA is re-esterified to triglyceride and delivered to the systemic circulation as very low-density lipoprotein (VLDL). Glycerol is used for gluconeogenesis in the liver. FFA derived from VLDL and glucose are used in various tissues in the body. The above background indicates that visceral fat is a specially developed adipose tissue

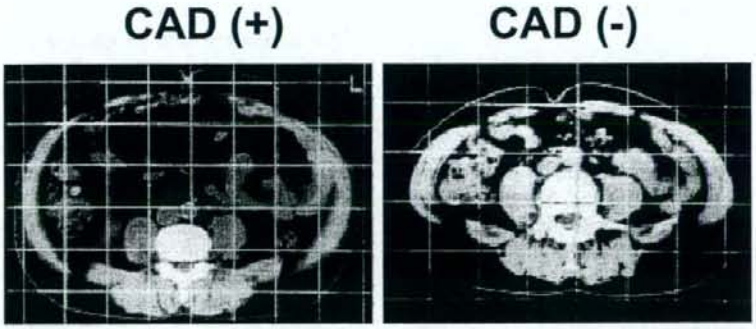


Figure 2. Visceral fat accumulation in a patient with coronary artery disease (CAD). Note accumulation of visceral fat and relatively thin subcutaneous fat in the CAD(+) versus the CAD(−) case.

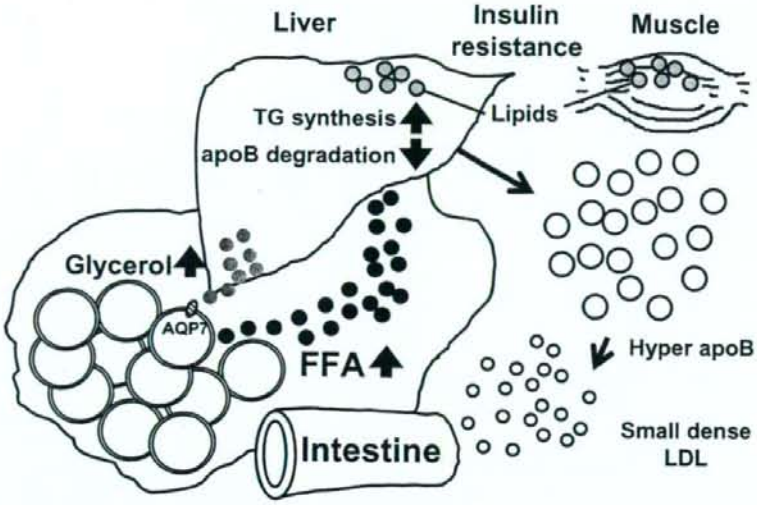


Figure 3. Visceral fat accumulation and hyperlipidemia. A large amount of FFA reaches the liver where it activates triglyceride (TG) synthesis. FFA inhibits intrahepatic degradation of apoB, resulting in overproduction of VLDL. Prolonged overnutrition causes lipid accumulation in visceral fat, liver, and muscle, resulting in insulin resistance.

and acts as a temporary energy reservoir to respond quickly to energy demand.

Overaccumulation of visceral fat and the large amounts of FFA result in acceleration of re-esterification of triglycerides. Acyl Coenzyme A (CoA) synthase, which activates FFA, is upregulated in a model of visceral fat accumulation (14). A large proportion of apolipoprotein B (apoB), a major apolipoprotein of VLDL, is degraded in hepatocytes after synthesis through the normal pathway. However, it is reported that some FFA, such as oleate, inhibit the degradation of apoB, with consequent overproduction of VLDL (15). Since one particle of VLDL contains one molecule of apoB and many triglycerides, the plasma level of apoB is elevated (hyperapobetalipoproteinemia), the resultant LDL becomes small and dense (small dense LDL) after lipolysis.

Glycerol released from visceral fat is delivered to the liver. The molecular mechanism of glycerol transport across the cell membrane is not clear at present. Aquaporin (AQP) adipose, which we identified in the human adipose cDNA project and later found to be human AQP7, belongs to the aquaglyceroporin subfamily, and its main function is the control of cell membrane permeability to glycerol as well as water. Disruption of AQP7 causes disturbance of the normal rise of plasma glycerol in human and profound hypoglycemia during prolonged fasting in mice because of impaired glycerol supply to the liver (16). AQP7 is overexpressed in visceral fat accumulation, accompanied by portal hyperglycerolemia and systemic hyperglycemia (17).

Subcutaneous fat is necessary for long-term storage of excess energy and for maintenance of insulin sensitivity. Genetic or acquired loss of normally developed subcutaneous fat causes lipodystrophic diabetes and accumulation of fat in the liver and muscle (18). Development of subcutaneous fat is an active process in infancy, adolescence, and pregnancy. Overeating at these ages results in massive obesity. After adolescence in men and in postmenopausal women, exposure to overnutrition does not result in effective storage of excess energy in subcutaneous fat. Visceral fat must play a role in storage of excess energy in these ages, though its capacity is somewhat limited because of the narrow intra-abdominal space. Normally, the liver and muscle quickly take up glucose and store energy as glycogen. Accumulation of visceral fat enhances VLDL synthesis. Prolonged hyperinsulinemia further activates a series of enzymes in FFA synthesis in the liver via upregulation of the transcriptional factor sterol-responsive element-binding protein (SREBP)-1c, resulting in fatty liver. Lipids also accumulate in skeletal muscles. In such circumstances, organs do not have enough capacity to take up plasma glucose in spite of very high levels of plasma insulin, subsequently resulting in insulin resistance. Genetic factor(s) will modify these processes to enhance the development of insulin resistance in individuals. To disrupt this scenario,

the capacity for glucose storage must be recovered by diet or exercise.

Substantial data have also accumulated in support of the roles of various adipocyte-derived factors in the development of insulin resistance in MetS.

## Systemic survey of genes expressed in adipose tissue and adipocytokines

In addition to the localization and functional properties of visceral fat, there is evidence linking certain molecules in visceral fat to human disorders, especially CVD. What is the profile of molecules or genes expressed in subcutaneous and visceral fat? To answer this question, our group in collaboration with the human body map project team investigated the gene expression profile in adipose depots during the early 1990s (19). Surprisingly, we found that adipose tissues, especially visceral fat, expressed a variety of genes for secretory proteins including complement factors in the immune system, growth factors, and cytokines (Figure 4). We found type 1 plasminogen activator inhibitor (PAI-1) and heparin-binding epidermal growth factor (EGF)-like growth factor (HB-EGF) in the visceral fat cDNA library. Accumulated visceral fat overproduces and secretes PAI-1, which in turn raises the risk for thrombotic disorders (20). Thus, it seems that visceral fat is directly linked with CVD. We named collectively these adipocyte-derived molecules as 'adipocytokines' (21). The 'visceral fat syndrome' may accelerate atherosclerosis through dysregulation of adipocytokines as well as clustering of coronary risk factors. The Harvard group of Spiegelman and coworkers (22) was the first to describe the contribution of adipocyte-derived factors to obesity-related disorders. The same group investigated changes in the cytokine profile during differentiation of adipocytes, and found overexpression of tumor necrosis factor (TNF)-α in the adipose tissue of insulin-resistant obese animals. They also demonstrated that blockade of TNFα improved insulin resistance. At Rockefeller University, the group led by Friedman (23) discovered a gene for congenital obesity in mice, leptin, which is a circulating factor derived from adipocytes and transmits a satiety signal.

Every type of cell produces and secretes a variety of bioactive substances to control the function of the cells themselves or the surrounding environment. A single adipocyte may secrete a small amount of adipocytokines, but the total amount of adipocytokines becomes a considerable amount because the adipose tissue is one of the largest organs in the body. In this regard, the production of adipocytokines varies in response to energy balance, and simple blood tests could provide important information on abnormal synthesis and production.

## Discovery of adiponectin and the concept of hypoadiponectinemia

Up to 70% of human genes had not been registered in the 'Genbank' database at the time of search for genes expressed in the adipose tissue. We tried to pull out unknown 'adipocytokines' related to the development of CVD. Through a systematic analysis of adipose-expressed genes, we discovered a novel gene for adipocyte-derived secretory protein, lately named 'adiponectin'. Adiponectin is specifically expressed in the adipose tissue (24). The molecule has two domains, namely a collagen-like fibrous domain and a C1q-like globular domain. The single molecules combine and form a high-ordered structure (25). Regarding its effects, adiponectin has

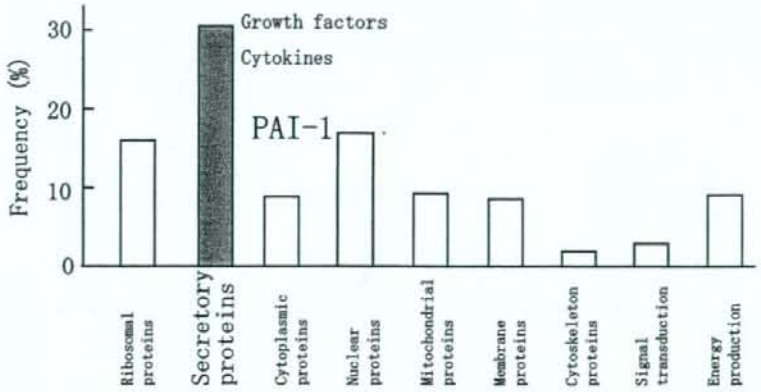


Figure 4. Profile of genes expressed in human visceral fat. Genes expressed in human visceral fat were categorized according to function or subcellular localization. Approximately 30% of genes were those encoding secretory proteins.

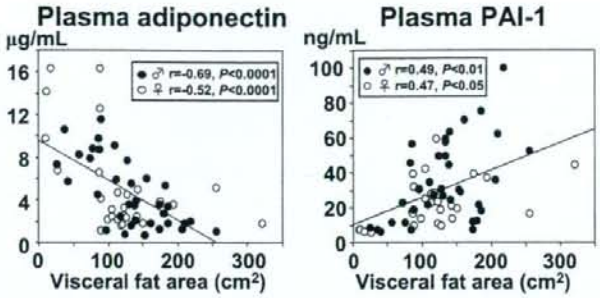


Figure 5. Correlation between CT-determined visceral fat area and plasma levels of adiponectin and plasminogen activator inhibitor type 1 (PAI-1). Plasma adiponectin levels correlated negatively, and plasma PAI-1 levels correlated positively with the visceral fat area determined by CT scan.

two interesting features: 1) Its plasma concentrations decrease with increase of BMI and upon accumulation of abdominal fat (25,26), in contrast to PAI-1 (Figure 5); 2) The protein binds to collagens I, III, and V, which are present in the subendothelial intima (27). In fact, adiponectin adheres to endothelium-injured arterial walls. This is the reason why we named this protein 'adiponectin'.

Subsequent studies identified several functions for the adipocyte-derived protein. Adiponectin suppresses: 1) TNFα-induced expression of adhesion molecules in vascular endothelial cells by inhibiting the nuclear translocation of nuclear factor-kappa B (NF-κB) (28,29); 2) growth factor-induced proliferation of smooth muscle cells by inhibiting classical mitogen-activated protein (MAP) kinase pathway (30); and 3) foam cell transformation and secretion of TNFα by macrophages (31,32) (Figure 6). On the other hand, adiponectin induces the expression of tissue inhibitor of metalloproteinase (TIMP)-1, which suppresses matrix metalloproteinase and inhibits matrix degradation to increases plaque stability (33). Overexpression of adiponectin in apoE knockout (KO) mice downregulated the expression of vascular cell adhesion molecule (VCAM)-1, class A scavenger receptor, and TNFα mRNA in the aorta, and retarded the progression of fatty streak lesion (34). Adiponectin KO mice developed severe neointimal thickening following traumatic injury by a catheter wire (35). Recent studies also demonstrated that adiponectin protects the heart from ischemia-reperfusion injury (36). At least part of these effects is mediated through adenosine monophosphate (AMP)-activated protein kinase (AMPK)- or cyclooxygenase (COX)-2-dependent pathway. These observations confirmed that adiponectin suppresses the development of atherosclerotic CVD. Recently, the high-sensitivity C-reactive protein (hs-CRP), an inflammatory marker, was identified as a novel risk factor for both

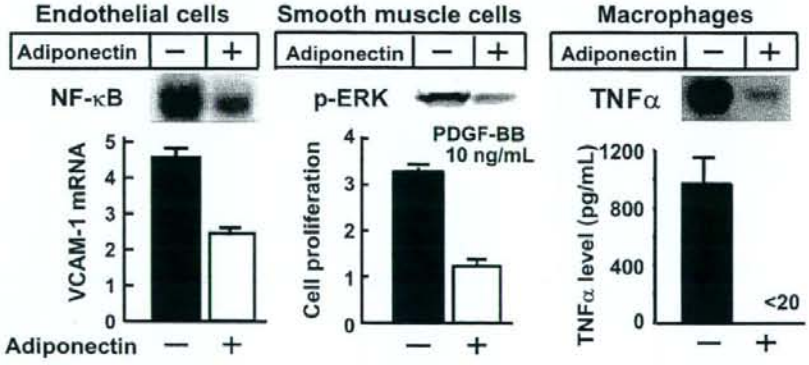


Figure 6. Effects of adiponectin on vascular endothelial cells, vascular smooth muscle cells, and macrophages. Administration of adiponectin suppressed TNFα-induced expression of VCAM-1 in endothelial cells through the inhibition of NF-κB activation, platelet derived growth factor (PDGF) induced proliferation of vascular smooth muscle cells partly by inhibition of ERK activation, and lipopolysaccharide-induced expression and secretion of TNFα.

CVD and type 2 diabetes, and adipose tissue expression levels of TNFα and CRP were augmented in adiponectin KO mice (37).

Clinically, plasma adiponectin levels are significantly lower in patients with CVD than in BMI-matched controls (28). The association with CAD in individuals with plasma adiponectin level less than 4 μg/mL is twice that in the general population (38). The predictive effect of hypoadiponectinemia on CVD was first documented in patients with end-stage renal disease (39). A study of 18,000 US men concluded that serum adiponectin level is a negative risk factor for myocardial infarction (40). Hypoadiponectinemia is also related to an increased risk of 5-year mortality after ischemic stroke, independent of other risk factors (41). Plasma adiponectin levels correlated positively with insulin sensitivity determined by glucose clamp test in humans and nonhuman primates (42,43). The adiponectin KO mice develop severe insulin resistance compared with wild-type (WT) mice (44). Pima Indians with high plasma adiponectin at baseline had low risk of new development of diabetes mellitus (45). Adiponectin has dual functions as it protects against insulin resistance and atherosclerosis. Basically, hypoadiponectinemia is caused by accumulation of visceral fat. However, phenotypic analyses of hypoadiponectinemia caused by the mutation(s) in the adiponectin gene (primary hypoadiponectinemia) will provide valuable information to understand the function(s) of this molecule. Subjects carrying a mutation of isoleucine 164 to threonine in the adiponectin gene show disturbed secretion of this mutant protein and had severe hypoadiponectinemia (46). Such subjects with genetic hypoadiponectinemia are also often hypertensive, hyperlipidemic, diabetic, and develop CVD (47).

Adiponectin activates AMP kinase and Akt, and subsequently phosphorylates endothelial nitric oxide (NO) synthase in vascular endothelial cells (48,49). The endothelium-dependent vasodilation is disturbed in hypoadiponectinemia (50). Adiponectin KO mice develop salt-sensitive hypertension with reduced mRNA levels of endothelial NO synthase and prostaglandin I2 synthase in the aorta (51) and low plasma levels of their metabolites. A more striking feature of adiponectin in hypertension is that reduction of adiponectin causes severe cardiac hypertrophy, resulting from the reduction of AMPK signaling and increase of extracellular signal-regulated kinase (ERK) in the myocardium (52).

Physical inactivity and a high fat/low dietary fiber diet are known to be associated with some types of cancers. Several studies have emphasized the significant association between hypoadiponectinemia and increased risk for breast (53,54), endometrial (55), prostatic (56), and colorectal cancer (57). Recently, it has been reported that adiponectin-deficient mice increased hepatic oxidative stress and frequently developed hepatic tumors when they were fed with a choline-deficient l-amino acid-defined diet, which induced steatosis in the liver (58). Future studies are necessary to clarify the causality and underlying mechanisms of hypoadiponectinemia and its potential role in obesity-related cancers.

Reduction of visceral fat improves dysregulation of adipocytokines. Furthermore, regimens that increase plasma adiponectin may be useful for prevention of CVD. At least three types of regimens with different mechanisms to raise plasma adiponectin level have been reported: 1) A selective cannabinoid-1 receptor blocker, rimonabant, has been shown to reduce waist circumference and improved metabolic risk factors including plasma adiponectin levels in high-risk obese subjects (59); 2) Unclassical sequence of the peroxisome-proliferator-responsive element (PPRE) was identified in adiponectin promoter (60). Peroxisome-proliferator-activated receptor-γ (PPARγ) and its ligand, thiazolidinedione, markedly enhanced adiponectin promoter activity and increased the plasma level of adiponectin (61); and 3) Recent studies demonstrated that reactive oxygen species generated in obese adipose tissue designated as fat reactive oxygen species (fat ROS) can cause dysregulation of adipocytokines (62,63). The amount of ROS in urine correlates well with the amount of visceral fat. Administration of angiotensin receptor blocker (ARB), which is known to reduce oxidative stress in organs, did not change plasma adiponectin levels in lean, but resulted in recovery of dysregulation of plasma adiponectin in obesity in association with reduction of fat ROS in rodents (64). Hypoadiponectinemia could be a novel risk factor in the era, in which people are exposed by overnutrition (65). Life-style changes and regimens designed to improve hypoadiponectinemia are potential strategies to prevent CVD. Further clinical evidences for the beneficial effects of correction of hypoadiponectinemia are anticipated in the future.

## Establishment of the definition of metabolic syndrome

The modern life-style characterized by overnutrition and reduced physical activities is rapidly expanding across the world. The World Health Organization (WHO) declared prioritization of prevention of CVD in the new global health care strategies in the 2002 World Health Report (66). While continuing the supply of food and nutrients together with

anti-infection control in developing countries where the average life span is short, the WHO has become aware that health care strategies targeting CVD can further prolong the life span of people. This conceptualization is based on the increase in the incidence of CVD in advanced countries as well as in Asian countries, especially China, due to overnutrition resulting from contentment diet and low physical activity.

The concept of multiple risk factor syndrome arising from visceral obesity has been incorporated within the concept of MetS proposed by the National Cholesterol Education Program (NCEP), and the concept of insulin resistance syndrome is the backbone of the concept of MetS defined by WHO. In such circumstances, it has become necessary also in Japan to establish diagnostic criteria for MetS that are scientifically based and convenient for clinical use. In 2004, a joint working committee for the diagnostic criteria of MetS was established with participation of representative members from eight scientific committees. The Working Committee has thus defined MetS as visceral fat accumulation expressed as gain in waist circumference plus at least two of three conditions: hypertension, dyslipidemia and hyperglycemia. The NCEP and WHO committees harmonized their work and a worldwide definition of MetS was published by IDF in 2005. The definition in Japan is basically similar to the worldwide definition. However, there are two characteristic points in the diagnostic criteria for MetS in Japan (Table I).

The primary goal of defining MetS is to diagnose subjects with visceral fat accumulation among those with two or more risk factors, improve the risk factors, and prevent CVD by reduction of visceral fat. Sometimes such patients need drug therapy. Any such effort should also include efforts to reduce visceral fat for safe therapy. Therefore, the presence of a large waist circumference, indicative of visceral fat accumulation, is a prerequisite for diagnosis. Needless to say, subjects with multiple coronary risk factors without visceral fat accumulation must be managed appropriately, but those individuals may require multiple therapeutic regimens.

The worldwide definition of MetS recommends that a cutoff point of waist circumference should be set for each ethnic population. Generally, cutoff points for the circumference for men and women are set separately. On the other hand, the Japanese criteria adopted visceral fat area of $\geqslant 100\ cm^2$ for both men and women. The policy undertaken by the Japanese definition is not to set more strict cutoff points for each item for women who have lower risk for CVD than men. For similar reasons, the Japanese criteria adopted a cutoff level for high-density lipoprotein cholesterol (HDL-C) of $<40$ mg/dL for both men and women as hypo-HDL-cholesterolemia according to the guideline of the Japan Atherosclerosis Society, while $<40$ mg/dL for men and $<50$ mg/dL for women was used by the IDF as criteria of MetS. The latter cutoff points are also based on the mean values, which is higher for women than for men. The Framingham study indicated a steep rise in the incidence of CVD in patients with HDL-C $<40$ mg/dL, including women. Furthermore, The Lipid Research Clinics Prevalence Mortality Follow-up Study suggested a cutoff value of 40 mg/dL. In the Framingham study, the risk score for CVD was higher by two points in the subgroup with an HDL-C $<40$ mg/dL, irrespective of sex. Although the number of risk factors in subjects with a given visceral fat area is almost similar in both sexes, further investigation should be conducted in the future to set the cutoff point for the amount of visceral fat in men and women with

Table I. Worldwide criteria and Japanese criteria for the diagnosis of the metabolic syndrome.

| | | World-wide Criteria | Japanese Criteria |
|---|---|---|---|
| Waist Circumference | | Men $>94$ cm<br>Women $>80$ cm<br>(Europids)<br>Ethnicity-Specific | Men $>85$ cm<br>Women $>90$ cm<br>Visceral Fat Area $\geqslant 100\ cm^2$<br>(Both men & women) |
| | | Plus 2 or more | |
| Blood Pressure | | $\geqslant$130/85 mmHg | $\geqslant$130/85 mmHg |
| Serum Triglyceride | | $\geqslant$150 mg/dL | $\geqslant$150 mg/dL<br>and/or |
| HDL-C | Men<br>Women | $<40$ mg/dL<br>$<50$ mg/dL | $<40$ mg/dL<br>(Both men & women) |
| Fasting Plasma Glucose | | $\geqslant$100 mg/dL | $\geqslant$110 mg/dL |

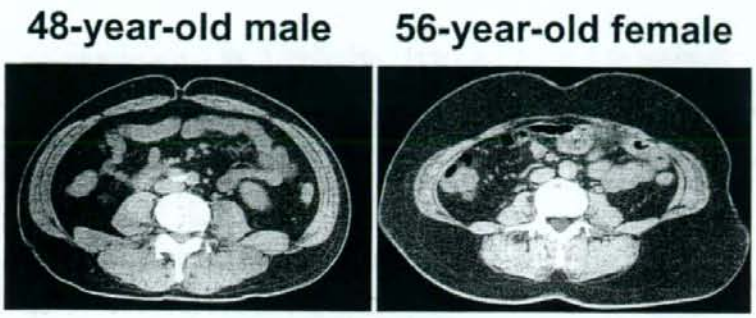


Figure 7. Representative CT scanning images of middle-aged man and woman. In general, women have relatively larger amounts of subcutaneous fat in the abdomen compared to men.

respect to CVD risk. For clinical convenience, increased waist circumference is adopted as an indication of accumulation of visceral fat. Women often have more abdominal subcutaneous fat even though having a similar amount of visceral fat compared to men (Figure 7). The cutoff points of waist circumference of 85 cm for men and 90 cm for women, which correspond to a visceral fat area of 100 $cm^2$ for men and women, respectively, were adopted in the Japanese criteria. However, it is often difficult to estimate visceral fat accumulation by waist circumference in premenopausal women. Nonradiographic methods such as the bioimpedance method may be useful to estimate visceral fat accumulation (26).

The worldwide criteria for the definition of MetS include hypertriglyceridemia and low HDL cholesterol level as two separate components. Because visceral fat accumulation and resultant insulin resistance are the underlying mechanisms, hypertriglyceridemia and low HDL cholesterol level can commonly occur as associated lipid abnormalities. Thus, hypertriglyceridemia and low HDL cholesterol level are regarded as one criterion in the Japanese definition of MetS, based on the guidelines of the Japan Atherosclerosis Society. The cutoff point of fasting plasma glucose is 110 mg/dL according to the guidelines of the Japan Diabetes Society.

The prevalence of MetS varies among countries and ethnic populations. Some populations show similar prevalence in both men and women. In some populations, the prevalence of MetS is even higher in women than in men. Although the precise molecular mechanism of MetS should be investigated further, MetS is a clinical condition associated with central obesity (visceral obesity) two or more of cardiovascular risk factors, as well as dysregulation of various adipocytokines, proinflammatory, and a tendency for thrombosis, a feature commonly seen in middle-aged men. Such a condition should increase the global cardiometabolic risk and consequently CVD. The purpose of diagnosis of MetS is to reduce waist circumference in order to reduce the number and severity of cardiometabolic risk factors, and consequently to minimize the risk of CVD. In such a process, the selection of an appropriate population is needed.

The National Health and Nutrition Survey 2004 conducted by the Japanese Ministry of Health, Labor, and Welfare reported the prevalence of MetS in the Japanese population including randomly selected 3,421 families. The incidence of MetS increased from less than 10% in individuals aged 30–39 years to 20%–30% in men aged 50–69 years (Figure 8). The incidence of MetS in women was

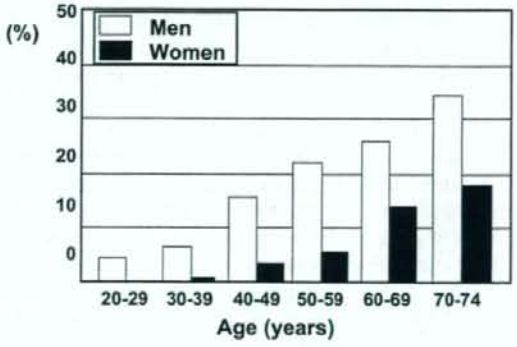


Figure 8. Percentages of Japanese men and women with a provisional diagnosis of metabolic syndrome. A total of 3421 families by stratified sampling were included in the National Health and Nutrition Survey 2004 by the Ministry of Health, Labor, and Welfare. The prevalence of metabolic syndrome was investigated in individuals ≥20 years of age strongly suspected of having the metabolic syndrome, based on findings of occasional blood sampling. The following criteria were adopted for the diagnosis of metabolic syndrome: Waist circumference of 85 cm for men and 90 cm for women, plus two of the following three: 1) HDL-C level <40 mg/dL; 2) blood pressure ≥130/85 mmHg; and 3) hemoglobin A1c ≥5.5%. From the Report of National Health and Nutrition Survey 2004 by the Ministry of Health, Labor, and Welfare, Japan.

lower than in men, but increased after the menopause. The research group on a serum lipid level survey in 2000 also reported that the incidence of MetS in 3,264 people receiving annual health examinations was relatively high in middle-aged men and women after 50 years of age but was less in women than men (67). Such individuals are the target of effective preventive programs against CVD.

### Challenges in combating metabolic syndrome

A survey was conducted through research supported by a grant from the Ministry of Labor (presently, Ministry of Health, Labor, and Welfare) of 122,051 Japanese workers from 31 industries, through regular medical health checks, over 10 years before the onset of CVD. The results of this survey revealed that subjects who suffered CVD had several abnormalities in plasma lipids and glucose, blood pressure level, and increased body weight, even though the degree of abnormalities was mild (68). The survey showed that individuals with at least three of four risk factors (hyperlipidemia, hyperglycemia, hypertension, and obesity) were at 30-fold higher risk of CVD compared with age- and sex-matched controls (no risk factors), and confirmed that the presence of multiple risk factor syndrome also accounted for a large part of morbidity underlying CVD in Japanese workers. Based on the results of the survey, the Ministry of Health, Labor, and Welfare and the Japan Medical Association instituted a scheme in 2001 to support workers with multiple risk factor syndrome for receiving medical checkups for CVD and guidance on life-style changes.

Since the establishment of the definition and criteria of MetS in 2005, several social efforts have been mobilized in Japan. The mass media have recognized the importance of MetS for the public health of Japan and announced its importance to the nation through newspapers, magazines, radio, and television. These activities encouraged many people, from children to elderly people, to know what MetS is and how they should combat it. Currently, many people engage in physical activities aimed to reduce visceral fat and multiple risk factors. The second point is public health activities. Measurement of waist circumference is introduced to regular medical health checks. After the health check, public health nurses provide the individual with scientific information about the risk associated with accumulation of visceral fat, clustering of multiple risk factors, injury of arteries, and development of life-threatening CVD. Furthermore, they also explain the results of the medical checkup and the relationship between the subject's life-style and the abnormalities

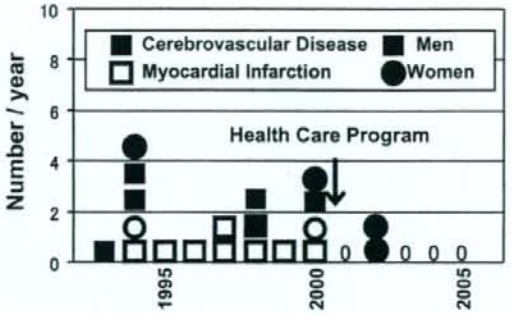


Figure 9. Management of metabolic syndrome leads to reduction of cardiovascular-related deaths. A health promotion program directed against the metabolic syndrome was conducted in Amagasaki Municipal Government offices, Hyogo Prefecture, in 3946 workers from Hyogo. After the introduction of this program in 2000, the incidence of cardiovascular deaths in this office was clearly reduced. From data of Kenko Amagasakishi 21: Health Survey and Health Promotion Program for staff of the Amagasaki Municipal Government office in 2004.

recorded in the health checkup, to promote life-style changes. Management of eating behavior and a bond of affection among family members are essential. The subjects practice such courses in groups or individually. Subjects requiring further examination for CVD or treatment of diabetes, hypertension, and/or dyslipidemia are introduced to family physicians or specialists. Such activities called 'Hokenshido' in Japan eventually resulted in reduction of CVD-related deaths in office workers (Figure 9). The Japanese government plans to extend the MetS-based medical health check to individuals aged 40–75 years from 2008. We expect that these efforts against MetS will result in effective combating of MetS and a reduction of life-style-related diseases and CVD. The network system of regional public health centers, family physicians, and hospitals will be required to combat MetS.

The prevalence of CVD based on a cluster of multiple risk factors is increasing in many countries, where overeating and physical inactivity are a common life-style. However, we should never forget that there are still many countries in which people suffer from starvation and have short life spans because of a high childhood mortality rate linked to malnutrition and infectious diseases.

### References

1. The IDF consensus worldwide definition of the metabolic syndrome, Available from http://www.idf.org/webdata/docs/Metabolic_syndrome_definition.pdf.
2. Tokunaga K, Matsuzawa Y, Ishikawa K, Tarui S. A novel technique for the determination of body fat by computed tomography. Int J Obes. 1983;7:437–45.

3. Fujioka S, Matsuzawa Y, Tokunaga K, Tarui S. Contribution of intraabdominal fat accumulation to the impairment of glucose and lipid metabolism in human obesity. Metabolism. 1987;36:54–9.
4. Kanai H, Matsuzawa Y, Kotani K, Keno Y, Kobatake T, Nagai Y, et al. Close correlation of intra-abdominal fat accumulation to hypertension in obese women. Hypertension. 1990;16:484–90.
5. Matsuzawa Y, Fujioka S, Tokunaga K, Tarui S. Classification of obesity with respect to morbidity. Proc Soc Exp Biol Med. 1992;200:197–201.
6. Reaven GM. Banting lecture 1988. Role of insulin resistance in human disease. Diabetes. 1988;37:1595–607.
7. Kaplan NM. The deadly quartet. Upper-body obesity, glucose intolerance, hypertriglyceridemia, and hypertension. Arch Intern Med. 1989;149:1514–20.
8. DeFronzo RA, Ferrannini E. Insulin resistance. A multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. Diabetes Care. 1991;14:173–94.
9. Vague J. La differentiation sexuelle facteur determinant des formes de l'obesite. Presse Med. 1947;30:339–40.
10. Kissebah AH, Vydelingum N, Murray R, Evans DJ, Hartz AJ, Kalkhoff RK, et al. Relation of body fat distribution to metabolic complications of obesity. J Clin Endocrinol Metab. 1982;54:254–60.
11. Larsson B, Svardsudd K, Welin L, Wilhelmsen L, Bjorntorp P, Tibblin G. Abdominal adipose tissue distribution, obesity, and risk of cardiovascular disease and death: 13 year follow up of participants in the study of men born in 1913. Br Med J Clin Res Ed. 1984;288:1401–04.
12. Nakamura T, Tokunaga K, Shimomura I, Nishida M, Yoshida S, Kotani K, et al. Contribution of visceral fat accumulation to the development of coronary artery disease in non-obese men. Atherosclerosis. 1994;107:239–46.
13. Koutsari C, Jensen MD. Thematic review series: patient-oriented research. Free fatty acid metabolism in human obesity. J Lipid Res. 2006;47:1643–50.
14. Kuriyama H, Yamashita S, Shimomura I, Funahashi T, Ishigami M, Aragane K, et al. Enhanced expression of hepatic acyl-coenzyme A synthetase and microsomal triglyceride transfer protein messenger RNAs in the obese and hypertriglyceridemic rat with visceral fat accumulation. Hepatology. 1998;27:557–62.
15. White AL, Graham DL, LeGros J, Pease RJ, Scott J. Oleate-mediated stimulation of apolipoprotein B secretion from rat hepatoma cells. A function of the ability of apolipoprotein B to direct lipoprotein assembly and escape presecretory degradation. J Biol Chem. 1992;267:15657–64.
16. Kishida K, Kuriyama H, Funahashi T, Shimomura I, Kihara S, Ouchi N, et al. Aquaporin adipose, a putative glycerol channel in adipocytes. J Biol Chem. 2000;275:20896–902.
17. Maeda N, Funahashi T, Hibuse T, Nagasawa A, Kishida K, Kuriyama H, et al. Adaptation to fasting by glycerol transport through aquaporin 7 in adipose tissue. Proc Natl Acad Sci U S A. 2004;101:17801–06.
18. Shimomura I, Hammer RE, Richardson JA, Ikemoto S, Bashmakov Y, Goldstein JL, et al. Insulin resistance and diabetes mellitus in transgenic mice expressing nuclear SREBP-1c in adipose tissue: model for congenital generalized lipodystrophy. Genes Dev. 1998;12:3182–94.
19. Maeda K, Okubo K, Shimomura I, Mizuno K, Matsuzawa Y, Matsubara K. Analysis of an expression profile of genes in the human adipose tissue. Gene. 1997;190:227–35.
20. Shimomura I, Funahashi T, Takahashi M, Maeda K, Kotani K, Nakamura T, et al. Enhanced expression of PAI-1 in visceral fat: possible contributor to vascular disease in obesity. Nat Med. 1996;2:800–03.
21. Funahashi T, Nakamura T, Shimomura I, Maeda K, Kuriyama H, Takahashi M, et al. Role of adipocytokines on the pathogenesis of atherosclerosis in visceral obesity. Intern Med. 1999;38:202–06.
22. Hotamisligil GS, Shargill NS, Spiegelman BM. Adipose expression of tumor necrosis factor-alpha: direct role in obesity-linked insulin resistance. Science. 1993;259:87–91.
23. Zhang Y, Proenca R, Maffei M, Barone M, Leopold L, Friedman JM. Positional cloning of the mouse obese gene and its human homologue. Nature. 1994;372:425–32.
24. Maeda K, Okubo K, Shimomura I, Funahashi T, Matsuzawa Y, Matsubara K. cDNA cloning and expression of a novel adipose specific collagen-like factor, apMa (Adipose Most Abundant gene transcript 1). Biochem Biophys Res Commun. 1996;221:286–9.
25. Arita Y, Kihara S, Ouchi N, Takahashi M, Maeda K, Miyagawa J, et al. Paradoxical decrease of an adipose-specific protein, adiponectin, in obesity. Biochem Biophys Res Commun. 1999;257:79–83.
26. Ryo M, Nakamura T, Kihara S, Kumada M, Shibazaki S, Takahashi M, et al. Adiponectin as a biomarker of the metabolic syndrome. Circ J. 2004;68:975–81.
27. Okamoto Y, Arita Y, Nishida M, Muraguchi M, Ouchi N, Takahashi M, et al. An adipocyte-derived plasma protein, adiponectin, adheres to injured vascular walls. Horm Metab Res. 2000;32:47–50.
28. Ouchi N, Kihara S, Arita Y, Maeda K, Kuriyama H, Okamoto Y, et al. Novel modulator for endothelial adhesion molecules: adipocyte-derived plasma protein, adiponectin. Circulation. 1999;100:2473–6.
29. Ouchi N, Kihara S, Arita Y, Okamoto Y, Maeda K, Kuriyama H, et al. Adiponectin, adipocyte-derived plasma protein, inhibits endothelial NF-kB signaling through cAMP-dependent pathway. Circulation. 2000;102:1296–301.
30. Arita Y, Kihara S, Ouchi N, Maeda K, Kuriyama H, Okamoto Y, et al. Adipocyte-derived plasma protein, adiponectin, acts as a platelets growth factor-BB-binding protein and regulates growth factor-induced common post-receptor signal in vascular smooth muscle cell. Circulation. 2002;105:2893–8.
31. Ouchi N, Kihara S, Arita Y, Nishida M, Matsuyama A, Okamoto Y, et al. Adipocyte-derived plasma protein, adiponectin, suppresses lipid accumulation and class A scavenger receptor expression in human monocyte-derived macrophages. Circulation. 2001;103:1057–63.
32. Yokota T, Oritani K, Takahashi I, Ishikawa J, Matsuyama A, Ouchi N, et al. Adiponectin, a novel member of soluble defense collagens, negatively regulates the growth of myelomonocytic progenitors and the functions of macrophages. Blood. 2000;96:1723–32.
33. Kumada M, Kihara S, Ouchi N, Kobayashi H, Okamoto Y, Ohashi K, et al. Adiponectin specifically increased tissue inhibitor of metalloproteinase-1 through interleukin-10 expression in human macrophages. Circulation. 2004;109:2046–9.
34. Okamoto Y, Kihara S, Ouchi N, Nishida M, Arita Y, Kumada M, et al. Adiponectin reduces atherosclerosis in apolipoprotein E-deficient mice. Circulation. 2002;106:2767–70.
35. Matsuda M, Shimomura I, Sata M, Arita Y, Nishida M, Maeda N, et al. Role of adiponectin in preventing vascular

stenosis—the missing link of adipo-vascular axis. J Biol Chem. 2002;277:37487–91.
36. Shibata R, Sato K, Pimentel DR, Takemura Y, Kihara S, Ohashi K, et al. Adiponectin protects against myocardial ischemia-reperfusion injury through AMPK- and COX-2-dependent mechanisms. Nat Med. 2005;11:1096–103.
37. Ouchi N, Kihara S, Funahashi T, Nakamura T, Nishida M, Kumada M, et al. Reciprocal association of C-reactive protein with adiponectin in blood stream and adipose tissue. Circulation. 2003;107:671–4.
38. Kumada M, Kihara S, Sumitsuji S, Kawamoto T, Matsumoto S, Ouchi N, et al. Association of hypo-adiponectinemia with coronary artery disease in men. Arterioscl Thromb Vasc Biol. 2003;23:85–9.
39. Zoccali C, Mallamaci F, Tripepi G, Cutrupi S, Parlongo S, Malatino L, et al. Adiponectin, the most abundant adipocyte-derived protein, is functionally related to metabolic risk factors and predicts cardiovascular outcomes in end stage renal disease. J Am Soc Nephrol. 2002;13:134–41.
40. Pischon T, Girman CJ, Hotamisligil GS, Rifai N, Hu FB, Rimm EB. Plasma adiponectin levels and risk of myocardial infarction in men. JAMA. 2004;291:1730–7.
41. Efstathiou SP, Tsioulos DI, Tsiakou AG, Gratsias YE, Pefanis AV, Mountokalakis TD. Plasma adiponectin levels and five-year survival after first-ever ischemic stroke. Stroke. 2005;36:1915–19.
42. Weyer C, Funahashi T, Tanaka S, Hotta K, Matsuzawa Y, Pratley RE, et al. Hypoadiponectinemia in obesity and type 2 diabetes: Evidence for a role of insulin resistance and/or hyperinsulinemia. J Clin Endocrinol Metab. 2001;86:1930–5.
43. Hotta K, Funahashi T, Bodkin NL, Ortmeyer HK, Arita Y, Hansen BC, et al. Circulating concentrations of the adipocyte protein, adiponectin, are decreased in parallel with reduced insulin sensitivity during the progression to type-2 diabetes in rhesus monkeys. Diabetes. 2001;50:1126–33.
44. Maeda N, Shimomura I, Kishida K, Nishizawa H, Matsuda M, Nagaretani H, et al. Diet-induced insulin resistance in mice lacking adiponectin/ACRP30. Nat Med. 2002;8:731–7.
45. Lindsay RS, Funahashi T, Hanson RL, Matsuzawa Y, Tanaka S, Tataranni PA, et al. Adiponectin protects against development of type 2 diabetes in the Pima Indian population. Lancet. 2002;360:57–8.
46. Kondo H, Shimomura I, Matsukawa Y, Kumada M, Takahashi M, Matsuda M, et al. Association of adiponectin/ACRP30/AdipoQ mutation with type 2 diabetes mellitus. A candidate gene for the insulin resistance syndrome. Diabetes. 2002;51:2325–58.
47. Ohashi K, Ouchi N, Kihara S, Funahashi T, Nakamura T, Sumitsuji S, et al. Adiponectin I164T mutation is associated with the metabolic syndrome and coronary artery disease. J Am Coll Cardiol. 2004;43:1195–200.
48. Ouchi N, Kobayashi H, Kihara S, Kumada M, Sato K, Inoue T, et al. Adiponectin stimulates angiogenesis by promoting cross-talk between AMP-activated protein kinase and Akt signaling in endothelial cells. J Biol Chem. 2004;279:1304–09.
49. Chen H, Montagnani M, Funahashi T, Shimomura I, Quon MJ. Adiponectin stimulates production of nitric oxide in vascular endothelial cells. J Biol Chem. 2003;278:45021–6.
50. Ouchi N, Ohishi M, Kihara S, Funahashi T, Nakamura T, Nagaretani H, et al. Association of hypoadiponectinemia with impaired vasoreactivity. Hypertension. 2003;42:231–4.
51. Ohashi K, Kihara S, Ouchi N, Kumada M, Fujita K, Hiuge A, et al. Adiponectin replenishment ameliorates obesity-related hypertension. Hypertension. 2006;47:1108–16.
52. Shibata R, Ouchi N, Ito M, Kihara S, Shiojima I, Pimentel DR, et al. Adiponectin-mediated modulation of hypertrophic signals in the heart. Nat Med. 2004;10:1384–9.
53. Miyoshi Y, Funahashi T, Kihara S, Taguchi T, Tamaki Y, Matsuzawa Y, et al. Association of serum adiponectin levels with breast cancer risk. Clin Cancer Res. 2003;9:5699–704.
54. Mantzoros C, Petridou E, Dessypris N, Chavelas C, Dalamaga M, Alexe DM, et al. Adiponectin and breast cancer risk. J Clin Endocrinol Metab. 2004;89:1102–07.
55. Petridou E, Mantzoros C, Dessypris N, Koukoulomatis P, Addy C, Voulgaris Z, et al. Plasma adiponectin concentrations in relation to endometrial cancer. A case-control study in Greece. J Clin Endocrinol Metab. 2003;88:993–7.
56. Goktas S, Yilmaz MI, Caglar K, Sonmez A, Kilic S, Bedir S. Prostate cancer and adiponectin. Urology. 2005;65:1168–72.
57. Wei EK, Giovannucci E, Fuchs CS, Willett WC, Mantzoros CS. Low plasma adiponectin levels and risk of colorectal cancer in men. a prospective study. J Natl Cancer Inst. 2005;97:1688–94.
58. Kamada Y, Matsumoto H, Tamura S, Fukushima J, Kiso S, Fukui K, et al., Hypoadiponectinemia accelerates hepatic tumor formation in a nonalcoholic steatohepatitis mouse model. J Hepatol. 2007 Apr 9 [Epub ahead of print].
59. Despres JP, Golay A, Sjostrom L; Rimonabant in Obesity-Lipids Study Group. Effects of rimonabant on metabolic risk factors in overweight patients with dyslipidemia. N Engl J Med. 2005;353:2121–34.
60. Maeda N, Takahashi M, Funahashi T, Kihara S, Nishizawa H, Kishida K, et al. PPARγ ligands increase expression and plasma concentration of adiponectin, an adipose-derived protein. Diabetes. 2001;50:2094–9.
61. Iwaki M, Matsuda M, Maeda N, Funahashi T, Matsuzawa Y, Makishima M, et al. Induction of adiponectin, a fat-derived antidiabetic and antiatherogenic factor, by nuclear receptors. Diabetes. 2003;52:1655–63.
62. Furukawa S, Fujita T, Shimabukuro M, Iwaki M, Yamada Y, Nakajima Y, et al. Increased oxidative stress in obesity and its impact on metabolic syndrome. J Clin Invest. 2004;114:1752–61.
63. Iwashima Y, Katsuya T, Ishikawa K, Kida I, Ohishi M, Horio T, et al. Association of hypoadiponectinemia with smoking habit in men. Hypertension. 2005;45:1094–100.
64. Kurata A, Nishizawa H, Kihara S, Maeda N, Sonoda M, Okada T, et al. Blockade of Angiotensin II type-1 receptor reduces oxidative stress in adipose tissue and ameliorates adipocytokine dysregulation. Kidney Int. 2006;70:1717–24.
65. Funahashi T, Matsuzawa Y. Hypoadiponectinemia. A common basis for diseases associated with overnutrition. Curr Atheroscler Rev. 2006;8:433–8.
66. Reducing Risks, Promoting Health Life. The World Health Report. Geneva: World Health Organization, 2002.
67. Arai H, Yamamoto A, Matsuzawa Y, Saito Y, Yamada N, Oikawa S, et al. Prevalence of metabolic syndrome in the general Japanese population in 2000. J Atheroscler Thromb. 2006;13:202–08.
68. Nakamura T, Tsubono Y, Kameda-Takemura K, Funahashi T, Yamashita S, Hisamichi S, et al. Magnitude of sustained multiple risk factors for ischemic heart disease in Japanese employees. A case-control study. Circ J. 2001;65:11–17.

# Reduction of Visceral Fat Is Associated With Decrease in the Number of Metabolic Risk Factors in Japanese Men

YUKIYOSHI OKAUCHI, MD[1]
HITOSHI NISHIZAWA, MD[1]
TOHRU FUNAHASHI, MD[1]
TOMOKO OGAWA, RN[2]
MIDORI NOGUCHI, RN[2]
MIWA RYO, MD[1]
SHINJI KIHARA, MD[1]
HIROMI IWAHASHI, MD[1]
KAZUYA YAMAGATA, MD[1]
TADASHI NAKAMURA, MD[1]
IICHIRO SHIMOMURA, MD[1]
YUJI MATSUZAWA, MD[3]

Visceral fat accumulation is associated with the development of metabolic disorders such as glucose intolerance, dyslipidemia, hypertension, and atherosclerotic cardiovascular diseases (1–8). However, the relationship between reduction of visceral fat and decrease in the number of metabolic risk factors has not been defined in the general population. Recently, we developed a new technique, the abdominal bioelectrical impedance analysis (BIA), to evaluate visceral fat area (VFA) (9). The aim of this study was to investigate whether reduction of visceral fat, estimated by the BIA, is associated with a decrease in the number of metabolic risk factors.

## RESEARCH DESIGN AND METHODS

The study group comprised 2,336 Japanese men (aged mean ± SD 48.0 ± 10.5 years, BMI 24.2 ± 2.9 kg/m$^2$), who were employees of Amagasaki City Office, an urban area, and had undergone annual health check-ups in both 2004 and 2005. After the health check-up, the medical staff provided risk factor–oriented, rather than obesity-oriented, health promotion programs to select individuals with visceral fat accumulation and multiple risk factors, with the aim of encouraging a scientific understanding of the spectrum of metabolic syndrome from visceral fat accumulation to atherosclerotic cardiovascular diseases. In this study, we used VFA estimated by the BIA, which was shown to correlate significantly with VFA determined by computed tomography (9). The measurement of VFA by BIA complied with the Guidelines of the Ethical Committees of Osaka University. Informed consent was obtained from all subjects.

Overall obesity was defined as BMI of ≥25 kg/m$^2$ (10). We investigated the presence of three metabolic risk factors: elevated blood pressure (systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥85 mmHg), dyslipidemia, and dysglycemia/impaired glucose tolerance. Dyslipidemia represented hypertriglyceridemia (fasting or postprandial triglyceride of ≥1.69 or 2.27 mmol/l [11,12], respectively, and/or low HDL cholesterol [HDL cholesterol <1.04 mmol/l]). Dysglycemia/impaired glucose tolerance represented hyperglycemia (fasting or postprandial serum glucose concentration of ≥6.1 or ≥7.77 mmol/l [13], respectively). Subjects who received specific treatment(s) for each of the metabolic risk factors were considered positive for that factor.

### Statistical analysis

Fischer's protected least significant difference test and Kruskal-Wallis were used to analyze the relationship between the number of metabolic risk factors and body fat distribution and between change in the number of metabolic risk factors and change in VFA, respectively. Significance level was set at $P < 0.05$.

## RESULTS

BMI and VFA varied considerably among individuals. We divided subjects into two groups according to BMI and into two groups according to VFA (Fig. 1*A*). Visceral fat accumulation was defined as VFA of ≥100 cm$^2$ (10,14). Among 1,497 nonobese subjects (BMI <25 kg/m$^2$), 401 (26.8%) had visceral fat accumulation. The mean number of metabolic risk factors in subjects with VFA ≥100 cm$^2$ was significantly higher than in those with VFA <100 cm$^2$, irrespective of BMI. Importantly, the mean number of metabolic risks was significantly higher in subjects with VFA ≥100 cm$^2$ plus BMI <25 kg/m$^2$ than in those with VFA <100 cm$^2$ plus BMI ≥25 kg/m$^2$ ($P < 0.0001$) (Fig. 1*A*). These results suggest that assessment of visceral fat accumulation is important in identifying subjects with multiple risk factors.

Next, we investigated the correlation between a 1-year change in VFA (ΔVFA) and change in the number of metabolic risk factors (Δ*n*) within the same period in the 2,336 subjects. VFA decreased within 1 year in 53.1% (1,241 of 2,336) of participants, increased in 33.2% (776 of 2,336), and did not change in 13.7% (319 of 2,336).

We divided these subjects into six bins of ΔVFA (every 15 cm$^2$). ΔVFA correlated significantly with Δ*n* ($P < 0.0001$) (Fig. 1*B*). When the subjects who received new treatment after 2004 were excluded from the analysis, reduction of visceral fat was also associated with a significant decrease in the number of metabolic risk factors ($P < 0.0001$) (data not shown).

## CONCLUSIONS

We demonstrated that *1*) irrespective of BMI (< or ≥25 kg/m$^2$), subjects with visceral fat accumulation estimated by BIA had a cluster of metabolic risk factors and *2*) falls in VFA within 1 year were associated with a significant decrease in the number of metabolic risk factors.

From the [1]Department of Metabolic Medicine, Graduate School of Medicine, Osaka University, Suita, Japan; the [2]Amagasaki City Office, Hyogo, Japan; and the [3]Sumitomo Hospital, Osaka, Japan.

Address correspondence and reprint requests to Hitoshi Nishizawa, Department of Metabolic Medicine, Graduate School of Medicine, Osaka University, 2-2 Yamadaoka, Suita, Osaka 565-0871, Japan. E-mail: hitoshin@imed2.med.osaka-u.ac.jp.

Received for publication 2 February 2007 and accepted in revised form 30 May 2007.

Published ahead of print at http://care.diabetesjournals.org on 11 June 2007. DOI: 10.2337/dc07-0218.

**Abbreviations:** BIA, bioelectrical impedance analysis; VFA, visceral fat area.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

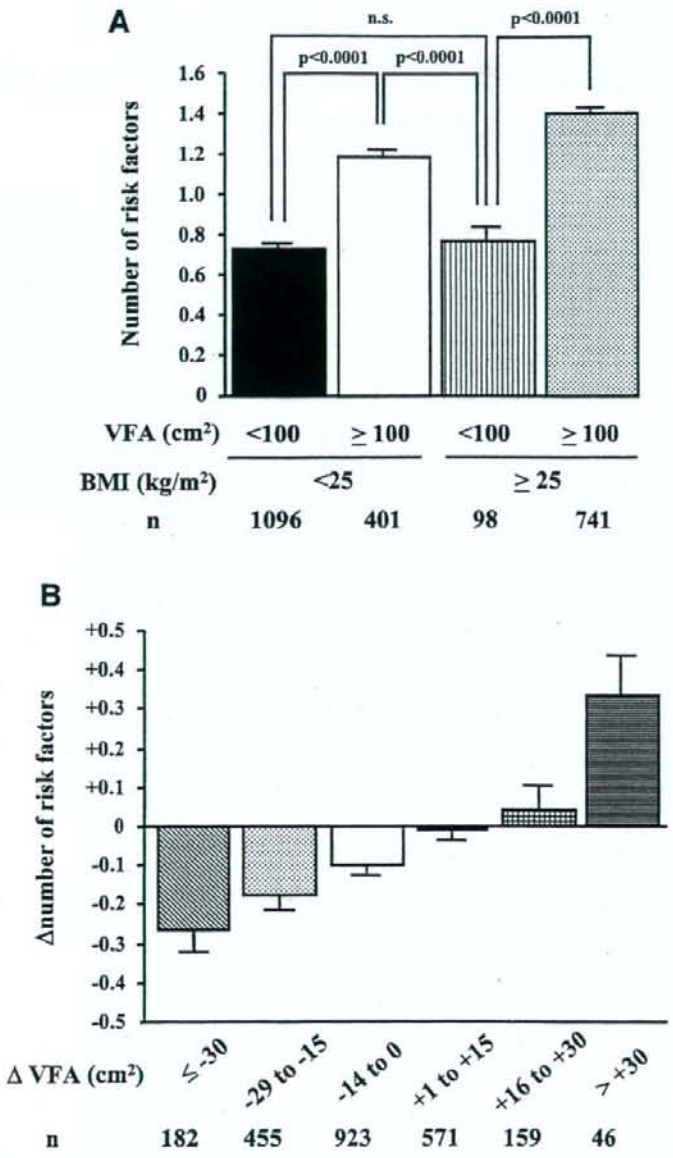


**Figure 1**—A: *Relationship between number of metabolic risk factors and body fat distribution. Subjects were divided according to their BMI (cutoff value 25 kg/m²) and VFA (cutoff value 100 cm²), measured in 2004. Data are means ± SE.* B: *Correlation between changes in VFA and changes in the number of metabolic risk factors. Δnumber of metabolic risk factors represents changes in the number of metabolic risk factors from 2004 to 2005. ΔVFA indicates change in VFA from 2004 to 2005. Subjects were divided into six 15-cm² bins of ΔVFA. Data are means ± SE.*

Importantly, our results also demonstrated that subjects with visceral fat accumulation but without overall obesity (VFA ≥100 cm² plus BMI <25 kg/m²) exhibited significantly more metabolic risk factors than overall obese subjects without visceral fat accumulation (VFA <100 cm² plus BMI ≥25 kg/m²). There is ample evidence for the role of visceral fat accumulation in the development of metabolic disorders (4–8,15). Collectively, the above results indicate that assessment of visceral fat accumulation using VFA estimated by BIA is useful for identifying high-risk groups for atherosclerotic cardiovascular diseases.

Our results also demonstrated in a large population sample that changes in VFA within 1 year correlated significantly with Δ*n*. Several reports demonstrated in obese subjects that reduction of visceral fat correlated with improvement in glucose and lipid metabolism (16–19). However, there is little information on the effect of reduction of visceral fat on the number of metabolic risk factors in a large general population sample. Here, we showed in 2,336 subjects that changes in VFA within 1 year correlated significantly with changes in the number of metabolic risk factors. These results suggest that intervention strategies directed toward reduction of visceral fat could result in the reduction or disappearance of risks for atherosclerotic cardiovascular diseases. Since BIA is quite simple and noninvasive for evaluation of visceral fat amount, it could be used in routine clinical practice and large-scale studies for assessment of visceral fat accumulation.

In conclusion, we demonstrated that reduction of visceral fat was closely associated with a decrease in the number of metabolic risk factors in Japanese men.


References

1. Eckel RH, Grundy SM, Zimmet PZ: Metabolic syndrome. *Lancet* 365:1415–1428, 2005
2. Isomaa B, Almgren P, Tuomi T, Forsen B, Lahti K, Nissen M, Taskinen M, Groop L: Cardiovascular morbidity and mortality associated with the metabolic syndrome. *Diabetes Care* 24:683–689, 2001
3. Alberti KG, Zimmet P, Shaw J; IDF Epidemiology Task Force Consensus Group: The metabolic syndrome: a new worldwide definition. *Lancet* 366:1059–1062, 2005
4. Despres JP, Lemieux I: Abdominal obesity and metabolic syndrome. *Nature* 444: 881–887, 2006
5. Kissebah AH, Vydelingum N, Murray R, Evans DJ, Hartz AJ, Kalkhoff RK, Adams PW: Relation of body fat distribution to metabolic complications of obesity. *J Clin Endocrinol Metab* 54:254–260, 1982
6. Lean MEJ, Han TS, Seidell JC: Impairment of health and quality of life in people with

large waist circumference. *Lancet* 351: 853–856, 1998
7. Nakamura T, Tokunaga K, Shimomura I, Nishida M, Yoshida S, Kotani K, Islam AHMW, Keno Y, Kobatake T, Nagai Y, Fujioka S, Tarui S, Matsuzawa Y: Contribution of visceral fat accumulation to the development of coronary artery disease in non-obese men. *Atherosclerosis* 107:239–246, 1994
8. Lemieux I, Pascot A, Couillard C, Lamarche B, Tchernof A, Almeras N, Berqeron J, Gaudet D, Tremblay G, Prud'homme D, Nadeau A, Despres JP: Hypertriglyceridemic waist: a marker of the atherogenic metabolic triad (hyperinsulinemia; hyperapolipoprotein B; small, dense LDL) in men. *Circulation* 102:179–184, 2000
9. Ryo M, Maeda K, Onda T, Katashima M, Okumiya A, Nishida M, Yamaguchi T, Funahashi T, Matsuzawa Y, Nakamura T, Shimomura I: A new simple method for the measurement of visceral fat accumulation by bioelectrical impedance. *Diabetes Care* 28:451–453, 2005
10. Examination Committee of Criteria for 'Obesity Disease' in Japan; Japan Society for the Study of Obesity: New criteria for 'obesity disease' in Japan. *Circ J* 66:987–992, 2002
11. Eberly LE, Stamler J, Neaton JD, Multiple Risk Factor Intervention Trial Research Group: Relation of triglyceride levels, fasting and nonfasting, to fatal and nonfatal coronary heart disease. *Arch Intern Med* 163:1077–1083, 2003
12. Ahmad J, Hameed B, Das G, Siddiqui M, Ahmad I: Postprandial hypertriglyceridemia and carotid intima-media thickness in north Indian type 2 diabetic subjects. *Diabetes Res Clin Pract* 69:142–150, 2005
13. American Diabetes Association: Clinical practice recommendations 2000: screening for type 2 diabetes. *Diabetes Care* 23 (Suppl. 1):S20–S23, 2000
14. Despres JP, Lamarche B: Effects of diet and physical activity on adiposity and body fat distribution: implications for the prevention of cardiovascular disease. *Nutr Res Rev* 6:137–159, 1993
15. Janssen I, Katzmarzyk PT, Ross R: Waist circumference and not body mass index explains obesity-related health risk. *Am J Clin Nutr* 79:379–384, 2004
16. Fujioka S, Matsuzawa Y, Tokunaga K, Kawamoto T, Kobatake T, Keno Y, Kotani K, Yoshida S, Tarui S: Improvement of glucose and lipid metabolism associated with selective reduction of intra-abdominal visceral fat in premenopausal women with visceral fat obesity. *Int J Obes* 15: 853–859, 1991
17. Ross R, Dagnone D, Jones PJ, Smith H, Paddags A, Hudson R, Janssen I: Reduction in obesity and related comorbid conditions after diet-induced weight loss or exercise-induced weight loss in men: a randomized, controlled trial. *Ann Intern Med* 133:92–103, 2000
18. Miyatake N, Nishikawa H, Morishita A, Kunitomi M, Wada J, Suzuki H, Takahashi K, Makino H, Kira S, Fujii M: Daily walking reduces visceral adipose tissue areas and improves insulin resistance in Japanese obese subjects. *Diabetes Res Clin Pract* 58:101–107, 2002
19. Slentz CA, Aiken LB, Houmard JA, Bales CW, Johnson JL, Tanner CJ, Duscha BD, Kraus WE: Inactivity, exercise, and visceral fat: STRRIDE: a randomized, controlled study of exercise intensity and amount. *J Appl Physiol* 99:1613–1618, 2005

Original Article

# Overview of nutrition reference and dietary recommendations in Japan: application to nutrition policy in Asian countries

Melissa K Melby PhD, Megumi Utsugi PhD MPH RD, Miki Miyoshi RD MPhil RPHNutr, and Shaw Watanabe MD PhD
*National Institute of Health and Nutrition, Tokyo, Japan*

The nutritional needs of Asian populations have changed dramatically in the last century. The role of nutrition, not only in preventing diseases associated with deficiency, but also in preventing lifestyle diseases such as cardiovascular disease and cancer, has become increasingly clear. Japan established the world's first nutrition institute almost 100 years ago, and initially focused on combating malnutrition and food insecurity. The current focus is prevention of lifestyle diseases, and along with revised dietary reference intakes, Japan has launched a program of Shokuiku (eating education) for children and families. As developing countries are simultaneously facing continuing undernutrition and increasing obesity and lifestyle diseases, collaboration in research and programs is urgently needed to prevent disease through nutrition intervention. This symposium and the Asian network are initial steps toward integrating nutriology into Asia-wide nutrition-based public health research and programs such as Japanese *Shokuiku* (eating education).

**Key Words: Japan, nutrition reference, public health, epidemiology**

## ESTABLISHMENT OF NUTRIOLOGY (NUTRITIONAL SCIENCE) IN JAPAN

Following World War II, the increased life expectancy of Japanese resulted not only from improvements in sanitation, but also from improvements in diet. During the *Meiji* and *Taisho* eras (1868-1926), beriberi and tuberculosis were the major endemic diseases in Japan. In order to prevent these diseases through nutrition, Dr. Tadasu Saiki established the world's first nutrition institute in 1914. The institute was nationalized in 1920 as the Imperial State Institute for Nutrition. It subsequently became the National Institute of Health and Nutrition (NIHN), and has made significant contributions to the nutritional improvement of the nation for more than 85 years.

In the early 20th century, rice, miso soup and pickles constituted the typical diet in Japan. The institute endeavored to promote a well-balanced diet by reducing rice intake and increasing protein and fat intake. Food security concerns in part motivated studies of applied nutrition that included study of foods for use during famine and discovery of new foods. Dr. Saiki played a crucial role as a pioneer in establishing "nutrition" as an academic discipline in its own right, making theoretical as well as applied contributions to improve the diet of the population, including the training of dietitians and nutrition education.

Dr. Saiki, the 'father of nutrition' in Japan, established science-based nutrition, or nutriology, in 1910 and in 1926 wrote a report entitled "Progress of the Science of Nutrition in Japan" for the League of Nations.[1,2] The concept of nutriology covered nutrients in food, alterations by cooking, and bioavailability in the body. It was an integrated theory for improving public health through nutrition, including consideration of socio-economic policies and covering the continuum from the kitchen to the table to the body (Fig. 1). He described the importance to nutrition research in accounting for the interdependence of physiological and economic aspects of nutrition, while also recognizing the socioeconomic inequalities that exist in all populations, which he referred to as the 'social aspect'. After identifying the natural products best able to meet physiological requirements, and selecting those that also meet the requirements of the national economy, the goal was to design a 'food code' or dietary recommendations based on social considerations that would optimize nutrition for the greatest number of people in Japan.

Highlights of Japanese nutritional science research featured in the report included data on basal metabolism, body surface area, metabolic changes during fasting and improvements of physical conditions of malnourished children. Studies of digestibility and physico-chemical properties of rice under various processing conditions, other grains such as millet and buckwheat, and vitamins in Japanese foods and animal feed, and finally a rat study of gastric carcinoma in relation to diet also were included. Dr. Saiki and colleagues determined the energy requirements for Japanese and created food composition tables,

**Corresponding Author:** Melissa K. Melby, PhD, Nutrition Education Program, National Institute of Health and Nutrition, 1-23-1, Toyama, Shinjuku, Tokyo, 162-8636
Tel: +81-3-3203-5418; Fax: +81-3-5155-0573
E-mail: melby-m@nih.go.jp
Manuscript accepted 16 January 2008.


**Figure 1.** Integrated theory for improving public health through nutrition by Dr. Saiki[1]. Figure 1 illustrates the flow of food components, which starts from obtaining food items and cooking. Then, when we eat meals on the table, nutrients can be taken into one's body, which will bring physiological effects and improve one's health.

which permitted analysis of nutritional intake.

Based on research on energy metabolism, they developed nutrition standards, which constituted the basis for the recommended dietary allowances (current "Dietary Reference Intakes") first established in 1970.

Under the order of General Headquarters Supreme Commander for the Allied Power (GHQ/SCAP) during the post-WWII U.S. occupation of Japan, the Institute conducted several food consumption and national nutrition surveys to estimate nutrient intake and provide data for the food distribution program to respond to the post-war food shortage.[3] Utilizing post-war food aid from the USA, dietary improvement campaigns like "Eat foods from three colors" were implemented, and Japan overcame the problems of malnutrition.

In addition, there were two well-known programs by the graduates of Saiki Nutrition School: (1) the "Use frying pan for cooking once a day" and (2) "Kitchen car" cooking classes conducted throughout the country to teach people how to use flour, dairy products, oil, meat, sausage and eggs in cooking.[4] While undernutrition and infectious disease (e.g. tuberculosis) were significant public health problems in Japan before 1960, the nutritional situation greatly improved with rapid economic growth and nutrition education and programs.

## RECENT EPIDEMIC OF OBESITY IN JAPAN AND ASIA AND INCREASE IN LIFESTYLE-RELATED DISEASES

In the 1980s, paralleling the growth in the economy, the Japanese population's waistline also increased. By the 1980s, obesity and overweight, rather than undernutrition, had become significant problems for many segments of the Japanese population,[5,6] leading to an increase in lifestyle-related diseases (e.g. diabetes, hypertension, and cardiovascular diseases).[7] An examination of the historical changes in the recommended dietary allowances (RDAs), which describe adequate dietary intake for 97-98% of the population,[8] provides some insight into this transition.

As seen in Table 1, the 2005 RDAs for energy intake

**Table 1.** RDAs for energy and protein intake by children in Japan (1940-2005)

| | Institute of Health Sciences | | Committee of food inspectors on nutrition standards | | Dietary Reference Intakes | |
|---|---|---|---|---|---|---|
| | 1940* | | 1944* | | 2005 | |
| | M | F | M | F | M | F |
| Energy (kcal) | | | | | | |
| 0~1 | 850 | 850 | 600 | 600 | 650 | 600 |
| 1~3 | 1,200 | 1,200 | 1,250 | 1,250 | 1050 | 950 |
| 4~5 | 1,460 | 1,460 | 1,450 | 1,450 | 1400 | 1250 |
| 6~8 | 1,690 | 1,570 | 1,700 | 1,700 | 1650 | 1450 |
| 9~11 | 1,880 | 1,740 | 1,900 | 1,900 | 2300 | 2150 |
| 12~14 | 2,160 | 2,030 | 2,200 | 2,100 | 2650 | 2300 |
| 15~20 | 2,500 | 2,100 | 2,100 | 1,700 | 2750 | 2200 |
| Protein (g) | | | | | | |
| 0~1 | 35 | 35 | 30 | 30 | 15 | 15 |
| 1~3 | 50 | 50 | 40 | 40 | 20 | 20 |
| 4~5 | 60 | 60 | 45 | 45 | 25 | 25 |
| 6~8 | 70 | 65 | 50 | 50 | 35 | 30 |
| 9~11 | 80 | 70 | 65 | 65 | 50 | 50 |
| 12~14 | 90 | 85 | 75 | 70 | 60 | 55 |
| 15~20 | 100 | 90 | 75 | 70 | 65 | 50 |

* Recommendation of introducing school lunch (Joint message by Ministry of Education, Ministry of Health, Ministry of Agriculture. (December 11, 1946)