Committee Report 5

Metabolic Syndrome

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Recently, the lifestyles of Japanese are clearly changing¹⁾. Among conditions underling the development of atherosclerotic cardiovascular diseases, particular importance is paid to a cluster of multiple risk factors including hyperglycemia, dyslipidemia, and elevated blood pressure, which are closely related to lifestyle. Lifestyles such as overeating and physical inactivity are threatening to increase the incidence of coronary artery disease (CAD) and stroke.

This condition used to be called “Syndrome X”²⁾, “the deadly quartet”³⁾, “visceral fat syndrome”⁴⁾, or “insulin resistance syndrome”⁵⁾, but those terms were unified to “metabolic syndrome”⁶⁾ in 1999. It is recognized as a condition in which multiple risk factors of cardiovascular diseases clusters on the basis of obesity, particularly accumulation of visceral fat, due to overnutrition and physical inactivity^{7, 8)}.

1. Importance of a Cluster of Multiple Risk Factors in Cardiovascular Diseases in Japan

The Group of ‘The Research for the Association between Host Origin and Atherosclerotic Diseases under the Preventive Measure for Work-related Diseases of the Japanese Ministry of Labor’ performed a case-control study in 122,051 office workers from 31 industries to clarify the risk factors for acute myocardial infarction and angina pectoris in urban industrial workers in Japan^{9, 10)}. The records of annual medical health check-up at workplaces over at least 10 years prior to the onset of attack were reviewed in 94 individuals who developed CAD during a 3-year observation period, and compared to those in age-, gender-matched controls, who were randomly selected from the same workplace of the patient. The surveys revealed that the blood pressure, fasting blood glucose, TC, and TG levels were significantly higher in cases compared with those in controls, even though these abnor-

malities were mild or moderate. It was of particular note that the BMI remained higher 10 years prior to the onset in cases compared with those in controls. The frequency of the subjects having multiple risk factors was consistently higher in cases, and subjects with multiple risk factors had a greatly increased risk for CAD. The analysis of the database of NIPPON DATA80 (National Integrated Project for Prospective Observation of Non-communicable Diseases and Its Trends in the Aged. 1980), which includes more than 10,000 Japanese subjects followed for 14 years, also showed that the relative risk of death due to CAD and stroke increased with the number of combined risk factors (**Fig. 1**)¹⁰⁻¹²⁾. These results clearly indicated the importance of a cluster of multiple risk factors in the development of cardiovascular diseases in Japan. According to a survey of middle-aged and elderly Japanese, the odds ratio to have each risk factor (hypertension, impaired glucose tolerance/diabetes mellitus, hypertriglyceridemia, or low HDL cholesterol) and the frequency to have multiple risk factors was high in both obese and non-obese subjects with visceral fat accumulation compared with non-obese subjects without visceral fat accumulation. The odds ratio was not significant in obese subjects without visceral fat accumulation¹³⁾. The Japan Society for the Study of Obesity proposed a definition of “obesity disease”^{14, 15)} as a clinical designation based on the presence of obesity-associated complications or their likely occurrence among obesity and a situation, which needs to reduce body weight for medical reasons. Obesity disease includes visceral fat obesity having multiple risk factors of cardiovascular disease (**Reference 1**). The fat distribution at umbilical level was evaluated in Japanese patients with CAD by abdominal CT scan, the average visceral fat area was significantly larger compared with that in age-, gender-, and BMI-matched controls, whereas the average subcutaneous fat area was not significantly different¹⁶⁾. The patients having

Fig. 1. Relationship between the number of concurrent risk factors and death due to coronary artery disease and stroke (NIPPON DATA80: 1980-1994)¹¹⁾

Risk factors: Obesity, hypertension, hyperglycemia, hypercholesterolemia
(Nakamura Y, et al: *Circ J*, 2006; 70:960-964)

visceral fat accumulation were frequently associated with a cluster of coronary risk factors. The 10-year follow-up study of the middle-aged or elderly Japanese-American men revealed that the accumulation of visceral fat, hypertension, and hyperglycemia were important risk factors¹⁷⁾.

2. Diagnostic Criteria for Metabolic Syndrome

Definition of the metabolic syndrome in Japan, which is characterized by the accumulation of visceral fat, accompanied by the concurrence of multiple risk factors including elevated blood pressure, dyslipidemia, and hyperglycemia, has been established in 2005 (**Table 1**). In the diagnostic criteria, the waist circumference is used as an index of visceral fat accumulation for practical convenience, and metabolic syndrome is defined as those having visceral fat accumulation expressed by increased waist circumference and 2 or more risk factors⁷⁾. A concept of the Japanese definition is principally coincident with a global definition published by the International Diabetes Federation⁸⁾.

It has been demonstrated that a condition clustering multiple risk factors like metabolic syndrome (using WHO or NCEP-ATPIII definition) will bring a greater risk of cardiovascular diseases than a single risk factor by epidemiological studies in Japan, including the Tanno and Sobetu Study¹⁸⁾ and the Hisayama Study¹²⁾, as well as numerous foreign epidemiological

Table 1. Japanese diagnostic criteria for metabolic syndrome

Intraperitoneal fat accumulation	
Waist circumference	≥85 cm for males ≥90 cm for females
(The values for both males and females correspond to visceral fat areas of ≥100 cm ² .)	
Two or more of the items mentioned below in addition to the above	
Hypertriglyceridemia and/or Low HDL-cholesterol	≥150 mg/dL <40 mg/dL for both males and females
Systolic pressure and/or Diastolic pressure	≥130 mmHg ≥85 mmHg
Fasting hyperglycemia	≥110 mg/dL

- Measurement of visceral fat by methods such as CT scanning is recommended.
- The waist circumference is measured at the umbilical level in the standing position during light breathing. If the umbilicus is displaced due to marked fat accumulation, measurement is performed at the level of the midpoint between the lower costal margin and iliac crest.
- If a diagnosis of metabolic syndrome has been made, a glucose tolerance test is recommended, but it is not essential for the diagnosis.
- If the examinee is undergoing drug treatments for hypertriglyceridemia, low-HDL-cholesterol, hypertension, and/or diabetes mellitus, each item is considered to be positive.

(Evaluation Committee on Diagnostic Criteria for Metabolic Syndrome: *Internal Medicine*, 2005; 94:794-809)

studies including NHANES II¹⁹⁾ and SAHS²⁰⁾ (2,815 subjects, mean follow-up period 12.7 years) in the United States, the Botnia study²¹⁾ in Finland and Sweden, and the Kuopio Ischemic Heart Study²²⁾ in Finland (**Fig. 2**). Concerning secondary prevention of CAD, it has also been reported that the presence of the metabolic syndrome increased the subsequent cardiac events through the study of long-term outcomes in 748 patients underwent percutaneous coronary intervention²³⁾.

The accumulation of visceral fat is essential for the diagnosis of the metabolic syndrome and is considered to locate upstream of the cascade clustering multiple risk factors and subsequent cardiovascular diseases. Many people with the metabolic syndrome have insulin resistance and confer the increased risk of glucose intolerance and type 2 diabetes, which also increase the risk of cardiovascular diseases. From the recent progress in adipocyte biology, it has been believed that dysregulated production of biologically active products derived from adipose tissues (adipocytokines)

Fig. 2. Relationship between the number of concurrent risk factors and incidences of coronary artery disease and cerebral infarction¹²⁾

Factors that constitute metabolic syndrome: Obesity, impaired glucose tolerance, abnormal lipid metabolism, hypertension, hyperinsulinemia

Adjusted for age, 1,097 males and females in Hisayamacho, aged 60 years or above, 5-year follow-up (1988-1993)

(Reproduced from Ken Okubo, et al: Rinsho to Kenkyu 2004; 81:1736-1740 with partial modification)

including proinflammatory cytokines, plasminogen activator inhibitor-1 and adiponectin is one of the molecular basis of the metabolic syndrome to exacerbate the pathologic conditions such as abnormal glucose metabolism, dyslipidemia, elevated blood pressure, proinflammatory and prothrombotic states and atherosclerosis.

The significance of the metabolic syndrome is that the accumulation of visceral fat is related not only to the development of each risk factor, but also the clustering of risk factors, which substantially increases the risk of cardiovascular diseases, even though the severity of each risk factor is not very serious. Therefore, the chief concept of the metabolic syndrome is the effective reduction of multiple risk factors and subsequent cardiovascular diseases by the reduction of visceral fat. Conventionally, patients having multiple risk factors were sometimes treated for each of the concurrent factors using multiple pharmaceutical regimens. Through the establishment of the concept of metabolic syndrome, the significance of encouraging a reduction of visceral fat by lifestyle modification (particularly, recommendation to increase physical activity) as the first step for the management of individuals with visceral fat accumulation has become strengthened.

3. Relationship with High Elevated LDL-Cholesterol

A global consensus has been reached that high elevated LDL-cholesterol is a major risk factor of atherosclerotic cardiovascular diseases, and its management has been established. Metabolic syndrome has been proposed as a high-risk condition for cardiovascular diseases independent of high elevated LDL-cholesterol⁷⁾. Therefore, the diagnostic criteria of the metabolic syndrome include no criterion concerning the LDL-C level. Subjects with the metabolic syndrome, however, are sometimes accompanied by elevated level of plasma LDL-C. Combination of the metabolic syndrome and high elevated LDL-cholesterol will increase the risk of cardiovascular disease further. Thus, strong recommendation to reduce visceral fat and global control of risk factors including high elevated LDL-cholesterol are necessary in such cases.

References

- 1) Ministry of Health, Labour and Welfare: Kokuminkenkou-eiyouchousahoukoku, 2006 (in Japanese)
- 2) Reaven GM: Banting lecture 1988. Role of insulin resistance in human disease. *Diabetes*, 1988; 37:1595-1607
- 3) Kaplan NM: The deadly quartet. Upper-body obesity, glucose intolerance, hypertriglyceridemia, and hypertension. *Arch Intern Med*, 1989; 149:1514-1520
- 4) Fujioka S, Matsuzawa Y, Tokunaga K, and Tarui S: Contribution of intra-abdominal fat accumulation to the impairment of glucose and lipid metabolism in human obesity. *Metabolism*, 1987; 36:54-59
- 5) DeFronzo RA and Ferrannini E: Insulin resistance. A multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. *Diabetes Care*, 1991; 14:173-194
- 6) World Health Organization Definition, diagnosis, and classification of diabetes and its complications: report of a WHO consultation. Part I: World Health Organization, 1999
- 7) Nihon Naikagakkai Zassi, 2005; 94:188-203 (in Japanese)
- 8) Alberti KG, Zimmet P, Shaw J, IDF Epidemiology Task Force Consensus Group: The metabolic syndrome—a new worldwide definition. *Lancet*, 2005; 366:1059-1062
- 9) Roudoushousagyoukanrensikkansougoutaisakukenkkyu, 1994 (in Japanese)
- 10) Nakamura T, Tsubono Y, Kameda-Takemura K, Funahashi T, Yamashita S, Hisamichi S, Kita T, Yamamura T, and Matsuzawa Y; Group of the Research for the Association between Host Origin and Atherosclerotic Diseases under the Preventive Measure for Work-related Diseases of the Japanese Labor Ministry; Origin and Atherosclerotic Diseases under the Preventive Measure for Work-related Diseases of the Japanese Labor Ministry: Magnitude of sustained multiple risk factors for ischemic heart disease in Japanese employees: a casecontrol study. *Circ J*, 2001;

- 65:11-17
- 11) Nakamura Y, Yamamoto T, Okamura T, Kadowaki T, Hayakawa T, Kita Y, Saitoh S, Okayama A, and Ueshima H; The NIPPON DATA80 Research Group: Combined Cardiovascular Risk Factors and Outcome-NIPPON DATA80, 1980-1994. *Circ J*, 2006; 70:960-964
 - 12) Okubo K and Kiyohara Y: *Rinshoutokenkyu*, 2004; 81:1736-1740 (in Japanese)
 - 13) Roudoushoukenkoukagakusougoukenkyuzigyohoukoku, 2001 (in Japanese)
 - 14) *Journal of Japan Society for the Study of Obesity*, 2000; 6:18-28 (in Japanese)
 - 15) 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*, 2002; 66:987-992
 - 16) Nakamura T, Tokunaga K, Shimomura I, Nishida M, Yoshida S, Kotani K, Islam AH, Keno Y, Kobatake T, and Nagai Y: Contribution of visceral fat accumulation to the development of coronary artery disease in non-obese men. *Atherosclerosis*, 1994; 107:239-248
 - 17) Fujimoto WY, Bergstrom RW, Boyko EJ, Chen KW, Leonetti DL, Newell-Morris L, Shofer JB, and Wahl PW: Visceral adiposity and incident coronary heart disease in Japanese-American men. The 10-year follow-up results of the Seattle Japanese-American Community Diabetes Study. *Diabetes Care*, 1999; 22:1808-1812
 - 18) Takeuchi H, Saitoh S, Takagi S, Ohnishi H, Ohhata J, Isobe T, and Shimamoto K: Metabolic syndrome and cardiac disease in Japanese men: applicability of the concept of metabolic syndrome defined by the National Cholesterol Education Program-Adult Treatment Panel III to Japanese men—the Tanno and Sobetsu Study. *Hypertens Res*, 2005; 28:203-208
 - 19) Malik S, Wong ND, Franklin SS, Kamath TV, L'Italien GJ, Pio JR, and Williams GR: Impact of the metabolic syndrome on mortality from coronary heart disease, cardiovascular disease, and all causes in United States adults. *Circulation*, 2004; 110:1245-1250
 - 20) Hunt KJ, Resendez RG, Williams K, Haffner SM, and Stern MP; San Antonio Heart Study: National Cholesterol Education Program versus World Health Organization metabolic syndrome in relation to all-cause and cardiovascular mortality in the San Antonio Heart Study. *Circulation*, 2004; 110:1251-1257
 - 21) Isomaa B, Almgren P, Tuomi T, Forsen B, Lahti K, Nissen M, Taskinen MR, and Groop L: Cardiovascular morbidity and mortality associated with the metabolic syndrome. *Diabetes Care*, 2001; 24:683-689
 - 22) Lakka HM, Laaksonen DE, Lakka TA, Niskanen LK, Kumpusalo E, Tuomilehto J, and Salonen JT: The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. *JAMA*, 2002; 288:2709-2716
 - 23) Kasai T, Miyauchi K, Kurata T, Ohta H, Okazaki S, Miyazaki T, Kajimoto K, Kubota N, and Daida H: Prognostic value of the metabolic syndrome for long-term outcomes in patients undergoing percutaneous coronary intervention. *Circ J*, 2006; 70:1531-1537

Reference 1. New Criteria for the Diagnosis of 'Obesity Disease' in Japanese

- (1) Obesity: this is judged by BMI at initial screening and defined as a BMI ≥ 25 .
- (2) Definition of 'obesity disease': 'obesity disease' is a clinical designation based on the presence of associated complications or their likely occurrence. A person in this situation needs to reduce their weight for medical reasons.
- (3) Criteria for 'obesity disease':
 - (I) high-risk obesity as specified by an excess of visceral fat confirmed by CT scan (visceral fat obesity).
 - (II) obesity with complications that require weight reduction for their improvement or elimination:
 - (i) noninsulin-dependent diabetes mellitus (NIDDM) and impaired glucose tolerance
 - (ii) dyslipidemia
 - (iii) hypertension
 - (iv) hyperuricemia and gout
 - (v) coronary artery disease: myocardial infarction and angina pectoris
 - (vi) sleep apnoea syndrome and Pickwickian syndrome
 - (vii) fatty liver
 - (viii) cerebral infarction: cerebral thrombosis and tran-sient ischemic attacks of brain
 - (ix) orthopedic diseases: osteoarthritis and lumbago
 - (x) amenorrhoea and infertility.

An obese subject with at least 1 of these 10 obesity-related disorders has 'obesity disease' regardless of fat distribution.

Although many other diseases, such as gallstones, carcinoma of the gallbladder, pancreatitis, breast cancer, uterine fibroid, endometrial carcinoma, proteinuria, renal dysfunction, pseudoacanthosis nigricans, dermatites, such as inter-trigo and miliaris, tonsillar hypertrophy and carcinoma of the parotid gland, are also considered to be related to obesity, they were not included because the correlation is weaker and/or weight reduction has little effect.

- (4) Criteria for visceral fat obesity:
 - (I) waist circumference (W) at the umbilical level measured in the exhalation phase of respiration while standing. A BMI ≥ 25 and a W ≥ 85 cm in men or ≥ 90 cm in women is suspected as having visceral fat obesity.
 - (II) abdominal CT scan at the umbilical level in the exhalation phase in those suspected of having visceral obesity for determination of VFA. A VFA ≥ 100 cm² in both men and women is diagnostic of visceral fat obesity.
- (5) Flow chart for diagnostic processing of 'obesity disease' (**Appendix**). A person with a BMI ≥ 25 is diagnosed as obese. An obese person with obesity-associated complications and/or visceral fat obesity is diagnosed as having 'obesity disease'. Even an obese person without complications has the W measured as a screening tool for visceral fat obesity: W ≥ 85 cm in men or W ≥ 90 cm in women is suspicious for visceral fat obesity. Such subjects are examined by CT scan at umbilical level and a VFA ≥ 100 cm² is diagnostic for visceral fat obesity and consequently for 'obesity disease'.

Appendix. Flow chart for the diagnosis of 'obesity disease'. VFA, visceral fat area.