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Characteristic Features of Metabolic Syndrome in Obese Japanese Students

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Abstract：To study how central obesity affects glucose tolerance, the waist circumference was measured in 45 of the subjects, including 1 with type 2 diabetes and 6 with IGT or IFG（combined prevalence of glucose intolerance, 15.6%）. The waist circumference was excessive in 80% of the male subjects and in 20% of the female subjects. Of the 27 centrally obese subjects, 16 had cardiovascular risk factors（dyslipidemia, high blood pressure, and/or glucose intolerance）; 7 had two or more, and thus were considered to have metabolic syndrome（15.6% of 45）. In the centrally obese subjects, insulin sensitivity was significantly reduced, while impaired glucose tolerance was only seen in the centrally obese subjects. In central obesity, insulin resistance thus may be the initial step toward β–cell dysfunction and hyperglycemia. Obese young adults with central obesity need an early initiation of ongoing monitoring to detect type 2 diabetes and cardiovascular risk factor.

Key words：**Central obesity, Glucose intolerance, Disposition index, Metabolic syndrome, Young adults**

Introduction

Obesity continues to increase in prevalence among children and adolescents, and it is accompanied by a marked increase in the frequency of type 2 diabetes among young persons in many regions of the world.[1)–3)] Impaired glucose tolerance represents an intermediate stage in the natural history of type 2 diabetes[4)] and carries a high risk that type 2 diabetes will subsequently develope.[5)] Nonetheless, appropriate changes in the lifestyle of these children and adolescents can delay or prevent the progression from impaired glucose tolerance to full–blown diabetes.[6)7)] Great emphasis, therefore, has been placed recently on the early detection of glucose intolerance in youth. On the other hand, the increasing occurrence of obesity among young persons suggests a need to evaluate cardiovascular disease（CVD）risk factors in this age group. The current diagnostic criteria for CVD–associated metabolic syndrome[8)] were formulated for the mature adult population, while the prevalence of risk factors in question is not well defined in adolescents and young adults. In this study we estimated the relevant risk factors for CVD among obese young adults by identifying visceral or "central "obesity (defined according to waist circumference) and then additionally considering likely risk factors for future development of type 2 diabetes.

Subjects and Methods

We studied 45 obese volunteers who were Fukuoka University students 18.4±0.05 years old (range, 18 to 21). These students were diagnosed to have obesity during a routine physical examination performed at the time of their entry to the uni-

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versity between 2000 and 2003. A total 45 students were weighed during these examinations to the nearest 0.1 kg with a digital scale. Height was measured with a wall-mounted stadiometer. Body mass index (BMI) was calculated as weight in kg/height in m^2. Obesity was diagnosed when the BMI exceeded 26.4 (+20% of the BMI standard). Body fat was estimated as a percentage of body weight based on a bioelectric impedance analysis (TBF 102 ; Tanita, Tokyo). According to diagnostic criteria for the metabolic syndrome established by the Japanese Joint Expert Committee,[8] anthropometric data were obtained 2000 and 2003 in 45 subjects, of whom 30 were male. Visceral obesity was assessed by waist circumference measured at the level of the umbilicus and also at the level of the anterior superior iliac crest. These two waist circumferences were obtained at the end of normal expiration with the subjects standing, and the lesser one was used. In addition, hip circumference was measured in the horizonetal plane with the tape passing posteriorly around the buttocks to obtain the maximum measurement. Before any subject's participation, the nature, purpose, and risks of the study were explained, and informed consent was obtained. A detailed medical and family history was obtained from all subjects, who were asked to fast overnight prior to taking a 75 g oral glucose tolerance test (OGTT), which as a rule was carried out within 4 weeks following the routine physical examination. Participants with a diagnosis of diabetes and those on treatment for diabetes were excluded from the study. No subjects were taking any medications known to affect the glucose metabolism. All of 45 subjects underwent the OGTT at the Medical Health Center of Fukuoka University. Venous blood samples for glucose and insulin measurements were drawn into evacuated tubes containing EDTA at baseline and at 30, 60, and 120 min after glucose ingestion for glucose determinations, and at 30 and 60 min for insulin measurements. Plasma samples for other biochemical analyses were also drawn at baseline. The subjects were classified as having normal glucose tolerance (NGT), impaired fasting glucose (IFG), impaired glucose tolerance (IGT), or diabetes according to the criteria proposed by the American Diabetes Association (ADA) Expert Committee.[9] NGT was defined as a fasting plasma glucose <100 mg/dl and 2-h plasma glucose <140 mg/dl. IGT was defined as a fasting plasma glucose <100 mg/dl and 2-h plasma glucose between 140 and 200 mg/dl. Type 2 diabetes was defined as a fasting glucose >126 mg/dl and a 2-h plasma glucose >200 mg/dl. In addition to impaired fasting glucose (>100 mg/dl) as a diagnostic criterion for the metabolic syndrome, IGT (2-h plasma glucose above 140 mg/dl) was accepted.

Assays

Plasma glucose was assayed by a glucose dehydrogenese method using an automatic analyzer (Hitachi 7600, Tokyo). The plasma insulin was determined by a microparticle enzyme immunoassay (Insulin Dainapack, Dainabott, Tokyo). This assay is specific for insulin and it does not recognize proinsulin. Intra- and interassay coefficients of variance were 3.2 and 2.3, respectively; The sensitivity of the method was 1.0 μU/ml. Plasma total cholesterol and triglyceride were determined by an automatic analyzer (Hitachi) using a TCH kit (UV method ; KL-Kokusai) and a Pure-auto S TNG kit (Daiichi-Kagaku), respectively.

Calculations

To assess the β-cell function, we used the insulinogenic index which was calculated as the ratio of the increment in the plasma insulin concentration to that in the plasma glucose concentration during the first 30 min after the ingestion of the glucose load. This ratio has been shown to be a good measure of early insulin secretion in adolescents as well as a predictor of diabetes in adults.[10][11] The homeostasis model assessment (HOMA) of insulin resistance (HOMA-IR)[12] was calculated from the fasting glucose and the insulin concentration as described by Matthews et al.[12] using the equation, resistance = glucose (mg/dl) x insulin (μU/ml)/405, which is equivalent to the equation originally reported. In order to evaluate the insulin secretory function, the disposition index, as proposed by Kahn et al.[13] was also calculated as the insulinogenic index divided by HOMA-IR.[14]

Statistical analysis

Analyses were conducted using the Statview statistical package for Windows, version 5.0. When data were compared between male and female subjects concerning the criteria for the metabolic syndrome, or were compared between central and non-central obesity, Student's T-test was used. Differences were considered statistically significant at a value of p below 0.05. Data are presented as the mean±SEM.

Results

As the initial criterion for metabolic syndrome, waist circumference was measured in 45 obese students including 30 men ; the metabolic syndrome profiles are summarized in Table 1. The waist circumference was significantly larger in males than in females. Of these 45 obese young adults, 27 were predicted to have central obesity based on waist circumference (male, 24 ; female, 3) as shown in Table 2. Among the 45, hypertriglyceridemia was presented in 9 (20%), while 4 (8.9%) had low HDL-cholesterol. Systolic hypertension was seen in 12 (26.7%); diastolic hypertension was not detected. Glucose intolerance including 1 with diabetes was seen in 7 (15.6%), and 3 of the 7 subjects had impaired fasting glucose above 100 mg/dl Frequency of glucose intolerance in the subjects with or without central obesity is shown in Table 3. Of the 27 subjects with central obesity, 7 had glucose intolerance including 1 with diabetes and 3, impaired fasting glucose. Among the obese subjects without central obesity (n=18), none showed any impaired glucose tolerance (Table 3). Therefore, the centrally obese individuals with or without metabolic syndrome were thus considered to be at an increased risk for developing an impaired glucose tolerance. Of the 27 obese young adults whose measurements indicated central obesity, 16 (59.3%) had at least one of three CVD risk factors (dyslipidemia, high blood pressure, and/or glucose intolerance) ; 7 had two or more risk factors, thus having metabolic syndrome as shown in Table 4. Insulin sensitivity, the disposition index, fasting plasma glucose and insulin, and 2-h plasma glucose in subjects with or without central obesity are shown in Table 5. No significant difference was evident in fasting plasma glucose or insulin concentration between the subjects with central and non-central obesity. However, in subjects with metabolic syndrome, 2-h plasma glucose and HOMA-IR were significantly higher than in subjects without central obesity ($p<0.05$). The disposition index tended to be lower, but not significant in the subjects with metabolic syndrome than in the subjects without central obesity, but the difference did not reach statistical significance ($p=0.07$).

Table 1. Metabolic syndrome profile in obese young adults undergoing measurement of anthropometric indices

	Male	Female	Total
n	30	15	45
Age (year)	18.3± 0.3	18.3± 0.2	18.3± 0.2
Body weight (kg)	90.2± 2.2*	72.3± 1.5	84.0± 3.5
BMI (kg/m^2)	31.0± 0.7	29.3± 0.4	30.5± 0.8
Waist circumference (cm)	93.1± 1.7*	81.7± 1.5	89.1± 2.5
WHR	0.9± 0.0	0.8± 0.0	0.9± 0.0
Systolic BP (mmHg)	126.3± 1.7	109.6± 2.5	120.6± 3.2
Diastolic BP (mmHg)	70.7± 1.6	65.4± 1.9	68.9± 2.2
Total cholesterol (mg/dl)	177.0± 9.4	182.1± 8.6	178.7±11.9
Triglyceride (mg/dl)	108.0±11.7	115.3±14.6	110.4±15.9
HDL-cholesterol (mg/dl)	47.2± 1.4	60.9± 9.3	51.8± 5.9
Fasting glucose (mg/dl)	89.8± 4.0	85.5± 1.3	88.4± 4.7
Fasting insulin (μu/ml)	11.5± 1.1	11.5± 1.3	11.5± 1.4
2-h glucose (mg/dl)	121.0± 8.2	110.6± 5.3	117.5±10.0

WHR ; waist-hip-ratio ; *$p<0.01$ vs. female.

Table 2. Risk factors for the metabolic syndrome in obese young adults

	Male (n=30)	Female (n=15)	Total (n=45)
Waist			27 (60.0)
male>85 cm	24 (53.3)	—	24
female>90 cm	—	3 (6.6)	3
Dyslipidemia	10 (22.2)	3 (6.6)	13 (28.9)
elevated triglyceride	6	3	9
decreased HDL-cholesterol**	4	0	4
Elevated blood pressure			
Systolic	11 (74.4)	1 (2.2)	12 (26.7)
Diastolic	0	0	0
Glucose intolerance*	6 (13.3)	1 (2.2)	7 (15.6)

( ), % ; *2-h blood glucose >140 mg/dl during OGTT ; **with normal triglyceride.

Table 3. Frequency of glucose intolerance in subjects with or without central obesity

	Central obesity	Non-central obesity
n (male/female)	27 (24/3)	18 (6/12)
Glucose intolerance	7 (6/1)*	0

* ; 4 diagnosed as metabolic syndrome and including diabetes mellitus (n=1).

Table 4. Prevalence of the metabolic syndrome in 45 obese young adults

	Male (n=30)	Female (n=15)	Total (n=45)
Central obesity*	24	3	27 (60.0%)
Two or three CVD risk factors	7	0	7 (15.6%)
One risk factor	8	1	9 (20.0%)

*Waist circumference in a male subject, >85 cm ; in a female subject, >90 cm
CVD, cardiovascular disease.

Table 5. Mean values of the metabolic parameters according to central obesity and metabolic syndrome

	Central obesity		Noncentral obesity
	Metabolic syndrome (n=7)	No metabolic syndrome (n=20)	(n=18)
Fasting glucose (mg/dl)	103.3±16.9	85.8±1.1	85.5±1.4
Fasting insulin (μu/ml)	14.1±2.9	11.9±1.1	9.9±1.3
2-h glucose (mg/dl)	151.9±29.0*	111.7±6.1[a]	110.8±5.5
HOMA-IR (μu/ml×mg/dl/405)	3.54±0.71*	2.56±0.26	2.11±0.44
Insulinogenic index $\Delta I_{30}/\Delta G_{30}$ (μu/ml)	1.48±0.47	1.60±0.16	1.71±0.36
Disposition index $(\Delta I_{30}/\Delta G_{30})$/HOMA-IR [1/(mg/dl)^2]	0.56±0.21	0.78±0.13	1.05±0.28

*p<0.05 vs. noncentral obesity ; a, p<0.05 vs. metabolic syndrome.
HOMA-IR, homeostasis model assessment.

Discussion

In the present study, we analyzed a relatively small number of 45 obese young adults in terms of the metabolic syndrome profile. Of these 45 obese young adults, 27 had central obesity as defined by waist circumference ; 24 of the 27 were male. Among the 27 centrally obese young adults, metabolic syndrome was recognized in 7 subjects (15.6%) ; all males. In the future, risk factors should be examined in a larger young obese population as well as in youths closer to normal weight. In our study, only 3 subjects among our 45 obese subjects showed IFG (>100 mg/dl). However, 15.6% of the 45 (7 subjects, including 1 with diabetes) met the criteria for IGT according to the 2-h glucose concentration during the OGTT. We used a cut off value for the IFG as 100 mg/dl. When >110 mg/dl was used as the cut off value, the prevalence of IFG was extremely low ; only 1 had IFG when it was defined as 110 to 125 mg/dl. This suggests that fasting hyperglycemia is indicative of a more advanced stage of clinical diabetes than that ordinarily found by screening for IGT with glucose loading tests. Recently, the American Diabetes Association lowered the clinical range for IFG to 100-125 mg/dl[9] IFG criteria above 110 mg/dl, which thus would appear to be insensitive in identifying insulin resistance individuals among obese Japanese young adults. The rationale for lowering this cut off was to optimize the sensitivity and specificity of fasting glucose measurements for predicting future type 2 diabetes. Our subjects with a fasting glucose above 100 mg/dl had a high HOMA-IR and their early insulin secretory function was also poorer than that in subjects with non-central obesity (Table 5). If insulin/glucose dynamics indeed are altered in IFG, then the subjects discovered to have IFG by diabetes screening might justifiably be considered to be at higher risk for the future development of type 2 diabetes than in those subjects with normal fasting glucose concentrations. A significantly larger proportion of subjects with central obesity had impaired glucose tolerance than peripherally obese subjects (Table 3). We also determined the disposition index to assess β-cell function (Table 5). Since the decrease in insulin sensitivity itself may have contributed to the decrease in this disposition index, a lower insulin sensitivity may also be involved in the progression to type 2 diabetes. Therefore, individuals with central obesity may have a higher relative risk for developing type 2 diabetes. Centrally obese patients with IFG concentrations below 110 mg/dl, even where this value is used as a cut off for detecting metabolic syndrome,[8] should undergo OGTT to increase the sensitivity of screening in order to thus prevent the future development of diabetes.

In conclusion, we herein demonstrated that central obesity contributed greatly to glucose intolerance in obese young adults. These individuals should thus be monitored for type 2 diabetes and CVD risk factors beginning early in life and continuing regularly during their ongoing medical care.

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