Discriminating Glucose Tolerance Status by Regions of Interest of Dual-Energy X-Ray Absorptiometry

Clinical implications of body fat distribution

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OBJECTIVE — To determine whether measuring body fat distribution by dual-energy X-ray absorptiometry (DEXA) can be used to discriminate glucose tolerance status.

RESEARCH DESIGN AND METHODS — Using a 75-g oral glucose tolerance test, a total of 1,015 Chinese subjects (559 men and 456 women) were categorized as having normal glucose tolerance (NGT), impaired glucose tolerance (IGT), or diabetes. Blood pressure and lipid profiles of these subjects were measured. Waist-to-hip ratio (WHR) and DEXA were used to evaluate the varying patterns of body fat distribution among the groups.

RESULTS — Body fat distribution, as reflected by WHR and the centrality index, showed significant partial correlation coefficients with glycosylated hemoglobin, blood pressure, and lipid profiles in all subjects. After adjusting for age and BMI, there were significant differences among the three glycemic groups for all the cardiovascular risk factors except for total cholesterol level. The diabetic group had a significantly higher WHR and centrality index, but lower femoral fat percentage than the NGT and IGT groups. The diabetic group also showed higher abdominal fat percentage than the NGT group. Moreover, the IGT group had a higher centrality index than the NGT group. However, no significant differences were found in the percentage of lean tissue mass among the three groups. Using multiple stepwise logistic regression models, the centrality index remained a significant factor for discriminating different glucose tolerance status independent of the percentage total body fat.

CONCLUSIONS — Central obesity has shown significant correlation with cardiovascular risk factors among the three different glycemic groups. Centrality index measured by DEXA appears to be the better predictor of glucose intolerance, compared with WHR, abdominal fat, and general obesity (reflected by percentage total body fat or BMI) in a large cohort of the Chinese population.

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Since 1956, when Vague first proposed the concept of body fat distribution (1), android pattern of fat distribution has became an important atherosclerotic risk factor (2,3) and has also been shown to be a risk factor for the development of type 2 diabetes in both obese and nonobese populations (4–8). However, whether glucose tolerance status can be differentiated using the patterns of body fat distribution, independent of general obesity, remains questionable and needs extensive evaluation.

Researchers have suggested that the degree of impaired glucose tolerance is a reflection of insulin insensitivity and/or compensatory hyperinsulinemia (9). Hyperinsulinemia and insulin resistance appear to be strong determinants in the pathogenesis of atherosclerotic diseases (10,11). Meanwhile, central obesity (5), hypertension, and dyslipidemia are also atherosclerotic risk factors (12). Given these considerations, it is reasonable to hypothesize an interrelationship among central obesity, different glucose tolerance status, hypertension, and dyslipidemia (9,13). The degree of influence that exists between each factor is uncertain (14,15), however, and merits further investigation.

Currently, regions of interest (ROIs) in dual-energy X-ray absorptiometry (DEXA) have been suggested as the standard in defining regional body fat distribution (16,17). However, few studies have used the potential of ROIs to evaluate body fat distribution in relation to cardiovascular risk factors (4,18–20). To the best of our knowledge, no studies using the ROIs of DEXA have been conducted to assess the relationship among varying patterns of body fat distribution, different glucose tolerance status, and related cardiovascular risk factors in a Chinese cohort. In the present study, we applied the ROIs of DEXA to assess body fat distribution. At the same time, the clinical importance of body fat distribution in differentiating glucose tolerance status and related cardiovascular risk factors were evaluated. Finally, whether the abdominal fat or the abdominal-to-femoral ratio is the preferred method of evaluating the body fat distribution in a Chinese cohort will also be discussed.

RESEARCH DESIGN AND METHODS

— A total of 1,265 subjects who underwent a 2-day general physical check-up during 1994–1995 were recruited. Those subjects whose physical examination

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Abbreviations: ANCOVA, analysis of covariance; CV, coefficient of variation; DEXA, dual-energy X-ray absorptiometry; IGT, impaired glucose tolerance; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test; ROI, region of interest; WHO, World Health Organization; WHR, waist-to-hip ratio.

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

Table 1—*Characteristics of different OGTT groups in 1,015 subjects*

	NGT	IGT	Diabetes
n	722	177	116
Sex (M/F)	407/315	90/87	62/54*
Estrogen replacement therapy (%)	1.8	1.7	0.9*
Age (years)	47.5 ± 12.3 (17–80)	52.6 ± 12.0 (27–81)	55.9 ± 10.8 (30–80)†
BMI (kg/m^2)	23.62 ± 3.52 (14.43–35.52)	25.27 ± 3.40 (16.47–36.04)	25.95 ± 3.55 (16.67–34.45)‡
Total body fat (%)	25.70 ± 9.12	30.77 ± 8.08	29.80 ± 9.23‡

Data are *n*, means ± SD, or means ± SD (range). *$P > 0.05$, χ^2 test; †$P < 0.001$, one-way analysis of variance; ‡$P < 0.001$, ANCOVA adjusted for age.

results indicated health problems, such as impaired renal function, hypoalbuminemia, hyper- or hypothyroidism, abnormal liver function, pregnancy, malignancies, severe scoliosis, polio, or cardiovascular accident-related contractions, were excluded. Finally, 1,015 Chinese subjects, 559 men aged 17–81 years (BMI 14.43–36.04 kg/m^2) and 456 women aged 21–80 years (BMI 15.13–35.52 kg/m^2) were enrolled for this analysis.

Each subject had their body weight (to the nearest 0.1 kg) and height (to the nearest 0.1 cm) recorded while wearing only light indoor clothes and no shoes. BMI was calculated as weight divided by height squared (kilograms per square meter). The morning after an overnight fast, waist circumference was measured midway between the lateral lower rib margin and the superior anterior iliac crest while the subjects were standing; hip circumference was measured similarly at the level of the bilateral great trochanters (3,21). Waist-to-hip ratio (WHR) was calculated from these two measurements (3,21). Whole body composition was measured by DEXA (DPX-L and software version 1.3z; Lunar, Madison, WI) for each subject. Percent total body fat was defined as the ratio of total body fat mass to total tissue mass (19). Four ROIs were defined according to the criteria of Ley et al. (19). The proportion of fat (or lean) content in ROIs was determined by the amount of fat (or lean) tissue mass in ROIs (expressed as a percent of total body fat [or lean] content). Abdominal fat (or lean) mass was defined as the sum of the fat (or lean) tissue mass in the upper two ROIs (subscapular and waist). Femoral fat (or lean) content was defined as the sum of the fat (or lean) tissue mass in the lower two ROIs (hip and thigh). Central obesity (expressed as a centrality index) was defined as the ratio of abdominal fat to femoral fat (20). A total of 128 subjects was studied for calculating the coefficients of variations (CVs) of DEXA. Each subject was scanned once, then repositioned 5 min later and rescanned. Intra-observer reproducibility of fat tissue mass and lean tissue mass measurements were calculated from the average root mean square of individual standard deviations and expressed as CV. The CV for replicate measurements was 1.0% for total lean tissue mass and 2.9% for total fat tissue mass. The precision of regional lean tissue mass was 2.0% for the legs and 1.0% for the trunk. The precision of regional fat tissue mass was 4.2% for the legs and 3.5% for the trunk.

After the subjects had been resting in a sitting position for at least 5 min, their blood pressure was measured (DINAMAP vital sign monitor, model 1846SX; Critikon, Irvine, CA) with an appropriate-sized cuff on the right upper arm (22). Blood pressure was measured three times, and the average of three measurements was used throughout the study. Venous blood was sampled after overnight fasting. Total cholesterol and triglyceride levels were measured enzymatically using automated methods. HDL cholesterol was determined after precipitation of apolipoprotein B–containing lipoproteins with sodium phosphotungstate and $MgCl_2$ (23). The atherogenic index was calculated as the ration of total to HDL cholesterol (24). A 75-g oral glucose tolerance test (OGTT) was then performed. Fasting and 2-h plasma glucose concentrations were measured by the glucose oxidase method (25). Glycosylated hemoglobin (HbA_{1c}, normal range 4.1–6.0%) was measured by automatic high-performance liquid chromatography (Bio-Rad, Richmond, CA) (26). Normal glucose tolerance (NGT), impaired glucose tolerance (IGT), and diabetes indices were categorized according to World Health Organization (WHO) criteria (25). None of the subjects had insulin-dependent diabetes or received insulin therapy before or during the study period. The Research Committee of the National Cheng Kung University Hospital approved this study, and written informed consent was obtained from each subject.

Data were analyzed using the Statistical Analysis System (SAS) software. Results are expressed as means ± SD. Triglyceride concentrations were transformed to a logarithmic scale to normalize their distribution. Partial correlation coefficients (adjusted for age and BMI) were calculated between variables in each glycemic group. A χ^2 test was used to evaluate sex and the use of estrogen hormone replacement therapy among the groups. Percent total body fat, total adiposity, and BMI were evaluated by age-adjusted analysis of covariance (ANCOVA) among the groups. Furthermore, age- and BMI-adjusted ANCOVA was applied to analyze the body fat distribution and the metabolic parameters among the groups. The multiple stepwise logistic regression model was used to evaluate sex, age, and anthropometric parameters in predicting glucose tolerance status. Two-sided *P* values of <0.05 were considered to be statistically significant.

RESULTS — According to WHO OGTT (25), a total of 1,015 subjects were categorized into three groups: the NGT group (71.1%), which consisted of 407 men and 315 women; the IGT group (17.5%), which consisted of 90 men and 87 women; and the diabetic group (11.4%), which consisted of 62 men and 54 women. In Table 1, no statistical differences are shown in the proportion of female subjects and the use of estrogen hormone replacement therapy among the groups, whereas the groups revealed statistically significant differences ($P < 0.001$) in terms of age, BMI, and percent total body fat. However, there was no difference between the IGT and diabetic groups for the latter two variables.

Adjusting for age and BMI, the WHR and centrality index showed better partial correlation coefficients with cardiovascular risk factors than waist circumference and abdominal fat percent per se (data not

Table 2—*Partial correlation coefficients adjusted for age and BMI between metabolic parameters and different OGTT groups*

	n	HbA_{1c} (%)	Systolic blood pressure (mmHg)	Diastolic blood pressure (mmHg)	Cholesterol (mmol/l)	Triglyceride (mmol/l)	HDL cholesterol (mmol/l)	Total/HDL cholesterol
NGT	722							
WHR		0.105*	0.128†	0.235†	0.066	0.358†	−0.355†	0.365†
Centrality index		0.145†	0.135†	0.266†	0.087	0.399†	−0.364†	0.379†
IGT	177							
WHR		0.221*	0.033	0.118	0.133	0.401†	−0.355†	0.434†
Centrality index		0.262†	0.041	0.220*	0.128	0.434†	−0.379†	0.435†
Diabetes	116							
WHR		0.330†	0.075	0.128	0.124	0.359†	−0.410†	0.454†
Centrality index		0.234†	0.013	0.091	0.049	0.367†	−0.487†	0.428†
Total subjects	1,015							
WHR		0.210†	0.095*	0.210†	0.095*	0.382†	−0.371†	0.403†
Centrality index		0.222†	0.107†	0.248†	0.101*	0.416†	−0.393†	0.414†

Centrality index: abdominal-to-femoral fat ratio. *$P < 0.01$, †$P < 0.001$.

shown). In Table 2, when analyzing each glycemic group separately, body fat distribution was shown to have significant correlation with HbA_{1c}, triglyceride level, HDL cholesterol level, and atherogenic index. However, due to the effect of relative small sample sizes, no significant correlation was found with total cholesterol level in the three different glycemic groups. Interestingly, body fat distribution showed a significant correlation with blood pressure in the NGT group. Furthermore, there were significant correlations between the body fat distribution and all the cardiovascular risk factors when analyzing across the groups.

Comparison of various metabolic parameters among the NGT, IGT, and diabetic groups are analyzed by ANCOVA (adjusted for the age and BMI) and shown in Table 3. The diabetic group showed the highest HbA_{1c} level among the three groups. In addition, the systolic and diastolic blood pressures of subjects in the NGT group were significantly less than those of subjects in the IGT and diabetic groups. In contrast, no measurable difference was found in total cholesterol levels among the three groups, but significant differences were observed in triglyceride levels. HDL cholesterol and the atherogenic index were shown to be significantly different among the three groups, but no significant difference was found between the NGT and IGT groups.

Differences in various anthropometric measures among the NGT, IGT, and diabetic groups were also analyzed by the method of ANCOVA and are shown in Table 3. For example, the diabetic group had a significantly higher WHR, abdominal fat percent, and centrality index, but lower femoral fat percent than the NGT group after adjusting for age and BMI. On the other hand, the IGT group had a significantly lower WHR and centrality index, but higher femoral fat percent than the diabetic group. Except for the centrality index, no significant differences were found in the NGT and IGT groups. Finally, no significant differences were found in the waist or hip circumferences or the abdominal or femoral lean tissue mass percent for any of the three groups.

To determine the independent factors in predicting glucose tolerance status, sex, age, BMI, percent total body fat, WHR, and centrality index were analyzed using multiple stepwise logistic regression models. As shown in Table 4, centrality index was found to be the significantly independent factor in predicting glucose tolerance status in all three models (NGT vs. IGT, IGT vs. diabetes, NGT vs. diabetes). However, percent total body fat was found to be significant only in the NGT vs. IGT model.

Table 3—*Comparison of anthropometric variables and metabolic parameters among different OGTT groups in 1,015 subjects*

	NGT	IGT	Diabetes
n	722	177	116
Waist circumference (cm)	78.03 ± 16.9	82.91 ± 17.04	83.73 ± 20.00
Hip circumference (cm)	89.78 ± 17.0	91.60 ± 16.75	89.83 ± 20.20
WHR	0.868 ± 0.078*	0.904 ± 0.073	0.932 ± 0.074‖#
Abdominal fat (%)	26.21 ± 6.03†	28.02 ± 5.24	29.18 ± 6.07§
Femoral fat (%)	25.35 ± 3.78‡	24.38 ± 2.79	23.23 ± 3.26¶#
Centrality index	1.057 ± 0.281*	1.171 ± 0.280§	1.278 ± 0.29‖#
Abdominal lean (%)	21.53 ± 3.04	21.89 ± 1.95	22.58 ± 2.72
Femoral lean (%)	21.65 ± 2.78	21.57 ± 1.53	21.37 ± 2.43
Fasting glucose (mmol/l)	4.95 ± 0.66*	5.45 ± 0.58‖	9.59 ± 3.85‖**
OGTT 2-h glucose (mmol/l)	5.66 ± 1.27*	8.93 ± 0.97‖	15.63 ± 7.01‖**
HbA_{1c} (%)	4.85 ± 0.61*	5.06 ± 0.66§	7.26 ± 2.25‖**
Systolic blood pressure (mmHg)	119.6 ± 20.9*	131.5 ± 26.4‖	132.9 ± 22.9¶
Diastolic blood pressure (mmHg)	72.9 ± 11.7‡	78.0 ± 12.3¶	78.5 ± 10.9§
Total cholesterol (mmol/l)	4.92 ± 0.94	5.13 ± 1.03	5.27 ± 0.98
Triglyceride (mmol/l)	1.21 ± 0.76*	1.56 ± 1.19¶	1.87 ± 1.37‖#
HDL cholesterol (mmol/l)	1.16 ± 0.32†	1.13 ± 0.32	1.07 ± 0.35§
Total/HDL cholesterol	4.52 ± 1.49*	4.84 ± 1.61	5.46 ± 2.02‖††

Data are means ± SD and were compared with ANCOVA, adjusted for age and BMI. Centrality index: abdominal-to-femoral fat ratio. *$P < 0.001$, †$P < 0.05$, ‡$P < 0.01$ compared among all three groups; §$P < 0.05$, ‖$P < 0.001$, ¶$P < 0.01$ compared with NGT; #$P < 0.05$, **$P < 0.001$, ††$P < 0.01$ compared with IGT.

Table 4—*Multiple stepwise logistic regression models with various factors in predicting glucose tolerance status in 1,015 subjects*

	Glucose tolerance status		
	NGT vs. IGT	NGT vs. diabetes	IGT vs. diabetes
Sex (male = 0, female = 1)	—	2.73 (1.56–4.78)*	—
Age (years)	1.02 (1.01–1.04)†	1.03 (1.01–1.06)†	—
BMI (kg/m^2)	—	—	—
Percent total body fat	74.49 (10.10–549.27)*	—	—
WHR	—	247.30 (2.25–27,217.08)‡	—
Centrality index	4.31 (2.20–8.44)*	10.31 (2.81–37.94)*	3.91 (2.51–6.10)†

Data are odds ratios (95% CI). Centrality index: abdominal-to-femoral fat ratio. *$P < 0.001$, †$P < 0.01$, ‡$P < 0.05$.

Further analysis across the groups found that centrality index was the significant factor for different glucose tolerance status, independent of percent total body fat (data not shown).

CONCLUSIONS — Whether the abdominal fat or the abdominal-to-femoral ratio is the preferred method of evaluating the body fat distribution and its interrelationship with glucose metabolism or cardiovascular risk factors is still controversial. Although Lean et al. (27) suggested that a larger waist circumference could identify increased cardiovascular risk in people of the Netherlands, it may not be a good indicator in other races, such as the Chinese population (28). In fact, both abdominal fat and the abdominal-to-femoral fat ratio are suggested for use by the WHO in evaluating body fat distribution (29). Furthermore, in our study, nearly all of the cardiovascular risk factors were shown to have better correlation with the abdominal-to-femoral fat ratio (WHR, centrality index) than with abdominal fat per se (waist circumference, abdominal fat) (data not shown). Therefore, the abdominal-to-femoral fat ratio was used as the optimal indicator of central obesity in this Chinese cohort, not the abdominal fat per se used in Caucasians. This racial difference could be due to several reasons: First, only 5% of the population had BMIs >30 kg/m^2 in a recent epidemiological survey of a Chinese cohort (30). Thus, the relative smaller body size may amplify the insensitivity of a single measurement of abdominal fat per se (28). Second, the report that Chinese subjects, who have a relatively smaller waist circumference, had similar WHR but higher prevalence of glucose intolerance compared with the Europids seemed to suggest the importance of a genetic factor (31). Finally, a sedentary lifestyle and Westernized food may also influence the racial differences of body fat distribution and related measurements. Generally speaking, there is an apparent lack of consistency in selection of anthropometric indicators for classification of abdominal fatness across racial differences (32).

Compared with WHR, the body fat distribution measured by DEXA had better correlations with cardiovascular risk factors, which were consistent with other reports (16,17). Moreover, the centrality index, not the WHR, was an independent predictor for glucose intolerance in regression models. Given these reasons, it is plausible to use ROIs of DEXA to directly assess the patterns of body fat distribution among different glycemic groups. Furthermore, through the logistic regression models, body fat distribution (centrality index) was shown to be a better independent predictor for glucose intolerance than general obesity (percent total body fat or BMI). These findings are consistent with the results from other studies demonstrating that body fat distribution was independent and superior to general obesity in correlating with atherosclerotic risk factors (4,6,20).

Concerning the atherosclerotic risk factors, evidence suggests that glucose intolerance is a reflection of hyperinsulinemia (9). Thus, it is not uncommon for a higher insulin concentration and higher blood pressure to be found concomitantly (10). Our results support the view that abnormalities in glucose tolerance status and/or insulin sensitivity may play some role in the regulation of blood pressure (33). On the other hand, hyperinsulinemia may lead to hypertriglyceridemia and low HDL cholesterol concentrations (23). Thus, in our study, subjects with glucose intolerance tend to have hypertriglyceridemia and low HDL cholesterol concentration, consistent with reports from other studies (14,34). In contrast, no statistically significant correlation was found in total cholesterol level; this finding was compatible with previously published work (34,35). However, further research, and especially with larger sample sizes, are necessary to ascertain the causal relationship between these factors.

Recently, accumulating evidence indicates that IGT identifies subjects at high risk of developing type 2 diabetes and cardiovascular disease (36,37). In our cross-sectional reports, some of the characteristics of the IGT group were similar to those of the NGT group (HDL cholesterol level, atherogenic index, WHR, abdominal and femoral fat percent), but some characteristics were similar to those of the diabetic group (blood pressure, HDL cholesterol level, abdominal fat percent). Thus, our findings seem to confirm previous studies that IGT may form part of the insulin resistance syndrome and appears to be a risk factor for the development of cardiovascular disease (38). However, it should be kept in mind that the unique manifestation of IGT is genuinely heterogeneous and needs to be monitored in future investigations.

There are several possible explanations for our findings. First, it could be that the central pattern of body fat distribution and glucose intolerance status are parallel phenomena secondary to some common factors, such as stress, psychosocial factors, or hormone aberrations (39). In support of this hypothesis, previous researchers have suggested that hyperglycemia is either a part of the plurimetabolic syndrome or only an innocent bystander (15). Another possibility is that a causal relationship exists between central obesity and glucose tolerance status. The vast majority of patients with IGT or type 2 diabetes have insulin resistance or compensatory hyperinsulinemia (10). Meanwhile, insulin therapy may increase trunk fat and the central-to-peripheral fat ratio, but not the lean tissue mass of type 2 diabetes (40); this hypothesis is compatible with our results. Moreover, insulin insensitivity may precede both the development of overt hypertension and the redistribution of body fat (33). Therefore, the mechanism that leads to the central pattern of body fat distribution associated with glucose intolerance may be due to direct stimulation of lipogenesis by hyperinsulinemia (41). Furthermore, insulin-related physiological changes such as an increase in appetite through hypothalamic neuropeptide Y synthesis (42), counterregulatory effects with

leptin (43,44), and other hormonal aberrations (45) or feeding behavior changes (46) may also play some role in promoting weight gain and android fat accumulation.

In summary, our findings support the hypothesis that there is an independent association between body fat distribution, glucose intolerance, and metabolic perturbations, such as blood pressure and lipid profiles. Centrality index measured by ROIs of DEXA appears to be the better predictor of glucose intolerance compared with WHR, abdominal fat per se, and general obesity (reflected by percent total body fat or BMI) in a large cohort of the Chinese population.

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