Relationship of body fat with insulin resistance and cardiometabolic risk factors among normal glucose-tolerant subjects

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ABSTRACT

Background: The amount of body fat, rather than the amount of excess weight, determines the health risks of obesity, type 2 diabetes mellitus, and cardiovascular disease. **Aims:** To look at the association of body fat percentage with cardiometabolic risk factors in subjects with normal glucose tolerance (NGT). **Settings and Design:** Cross-section study from the Chennai Urban Rural Epidemiology Study. **Materials and Methods:** Body fat was measured by Beurer body fat analyzer. Metabolic syndrome (MS) was diagnosed based on modified ATPIII guidelines. **Statistical Analysis:** Student's *t* test or one-way ANOVA (with Tukey's HSD) was used to compare groups for continuous variables. **Results:** Body mass index, waist circumference, systolic and diastolic blood pressure, HOMA IR, serum cholesterol, and LDL cholesterol increased significantly with increasing tertiles of body fat ($P<0.001$). There was a linear increase in the percentage of body fat with increase in number of components of MS (no metabolic abnormality: 25±11, one metabolic abnormality: 28±10, two metabolic abnormalities: 33±8, and three and more metabolic abnormalities: 35±7) ($P<0.001$). Regression models showed significant association of body fat with MS after adjusting for age, gender, insulin resistance, and glycated hemoglobin (Odds ratio: 1.04, 95% confidence interval: 1.04 – 1.08, $P<0.001$). In linear regression analysis, body fat showed a significant association with insulin resistance after adjusting for age, gender, and glycated hemoglobin ($\beta=0.030$, $P<0.001$). **Conclusions:** A significant association exists between body fat, MS, and cardiometabolic risk factors even among subjects with NGT.

KEY WORDS: Asian Indians, body fat, cardiometabolic risk factors, insulin resistance

Introduction

Obesity is a rapidly growing nutritional disorder characterized by excessive accumulation of adipose tissue.[1] Increased body weight is associated with insulin resistance and type 2 diabetes mellitus. Body fat content and distribution can be measured by hydrodensitometry, bioelectrical impedance, and dual-energy x-ray absorptiometry (DEXA). Gold standard techniques to determine BF%, such as hydrostatic weighing, deuterium dilution, and DEXA, are costly, time consuming, and not practical for field studies for examining body composition. Therefore, alternate methods of body composition assessment that are easier and safer to administer have been developed. One such technique is bioelectrical impedance analysis, which is a commonly used method for determining body composition, since it is noninvasive, simple, reliable, and inexpensive, using portable equipment.[2] An earlier study from our group showed that in urban south Indians, measurement of body fat by the leg-to-leg impedance method had fairly good agreement with DEXA.[3]

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Insulin resistance, a consequence of abdominal obesity, is believed to be the key pathogenic factor in metabolic syndrome (MS).[4] Asian Indians are unique in that although their BMI is lower than Europeans, abdominal obesity and body fat percentage are higher.[5] To our knowledge, there are no data on the association of body fat percentage with cardiometabolic risk factors in Asian Indians. Hence, the present study was undertaken with the objective of determining the association of

body fat percentage with cardiometabolic risk factors in Asian Indians with normal glucose tolerance (NGT).

Materials and Methods

Study subjects were recruited from the Chennai Urban Rural Epidemiology Study (CURES), an ongoing epidemiological study conducted on a representative population (aged ≥ 20 years) of Chennai (formerly Madras), the fourth largest city in India. The methodology of the study has been published elsewhere.[6] Briefly, in Phase 1 of the urban component of CURES, 26 001 individuals were recruited based on a systematic random sampling technique, which is described in our website *http://www.drmohansdiabetes.com/bio/CURES.pdf*. Fasting capillary blood glucose was determined using a One Touch Basic glucose meter (Life scan, Johnson and Johnson, Milpitas, California, USA) in all subjects. Subjects were classified as "known diabetic subjects" if they stated that they had diabetes and were on the treatment.

Phase 2 of CURES deals with studies of the prevalence of microvascular and macrovascular complications of diabetes among those identified with diabetes in Phase 1, wherein all the known diabetic subjects (n=1529) were invited to the center for detailed studies on vascular complications, and 1 382 responded (response rate, 90.3%). In Phase 3 of CURES, every tenth subject recruited in Phase 1 (n=2 600) was invited to our center for detailed anthropometric measurements and biochemical tests. Of these, 2 350 participated in the study (response rate: 90.4%). Those who were confirmed to have fasting plasma glucose (FPG) <5.5 mmol/l (100 mg/dl) or 2 hour post 75 g glucose value <7.8 mmol/l (140 mg/dl) based on WHO consulting group criteria[7] were labeled as "normal glucose tolerance." For the present study, a subset of subjects with NGT (n=1 185) were randomly selected from Phase 3 to participate in this study. Institutional ethical committee approval was obtained for the study and written informed consent was obtained from all study subjects.

A structured questionnaire was administered to the subjects to collect information on medical history and anthropometric measurements, which included height, weight, waist and hip circumferences, were taken using standard techniques as described in the definition section.[6] Blood samples were collected for estimating FPG and lipids. The samples were immediately transferred to the central laboratory where they were analyzed. Plasma glucose and serum lipids were estimated using a Hitachi 912 Auto analyzer (Mannheim, Germany) using kits supplied by Roche Diagnostics GmbH (Mannheim, Germany).

Serum insulin was estimated using enzyme-linked immunosorbent assay (Dako, Glostrup, Denmark). The intra-assay and the inter-assay coefficients of variation for insulin assay were 5.7% and 8.9%, respectively, and the lower detection limit was 0.5 mIU/ml.

Bioelectric impedance measurements were made using the Beurer body fat analyzer (Beurer BF 60, Ulm - Germany), which incorporates weighing scales and measures both weight and bioimpedance. Subjects were asked to stand barefoot on the metal sole plates of the machine. Age, gender, and height details were entered manually into the system. The bioelectrical impedance analysis method is based on the conduction of electrical current in the body and differences in electrical conductivity between the fat and water components of the body. Thus, electrical resistance and reactance together with body weight and height can reliably estimate body composition. Impedance measurements allow assessment of the fat-free mass and by difference with body weight, assessment of body fat percentage. Body weight and percentage body fat, estimated using the standard built-in prediction equation for the given age group, were displayed on the machine. The reproducibility of the body fat measurement was assessed by repeating the measurements on 50 patients on the same day[3] and the kappa statistics was 0.86 indicating good reproducibility.

Height was measured with a tape to the nearest 0.1 cm. Subjects were requested to stand upright without shoes with their back against the wall, heels together, and eyes directed forward. Weight was measured with a spring balance that was kept on a firm horizontal surface. Subjects wore light clothing, stood upright without shoes, and weight was recorded to the nearest 0.5 kg. Body mass index (BMI) was calculated as body weight in kilogram divided by the height in meter (kg/m^2). Waist circumference was measured using a nonstretchable fiber measuring tape. The subjects were asked to stand erect in a relaxed position with both feet together on a flat surface. Waist girth was measured as the smallest horizontal girth between the costal margins and the iliac crests. Two measurements were made and the mean of the two was taken as the waist circumference. Blood pressure was recorded in the sitting position in the right arm to the nearest 2 mmHg using the mercury sphygmomanometer (Diamond Deluxe BP apparatus, Pune, India). Two readings were taken 5 minutes apart and the mean of the two was taken as blood pressure.

Hypertension was diagnosed based on medical history, drug treatment for hypertension, and/or if the subjects had systolic blood pressure (SBP) ≥130 mmHg or greater and/or diastolic blood pressure (DBP) ≥85 mmHg.[8] MS was diagnosed using the IDF criteria.[9] If an individual had abdominal obesity plus two or more risk factors of the following criteria, he/she was diagnosed to have MS; waist circumference ≥90 cm in men and ≥80 cm in women; FPG ≥100 mg/dl; blood pressure ≥130/85 mm/Hg; Triglycerides ≥150 mg/dl; and serum HDL cholesterol <40 mg/dl in men and <50 mg/dl in women. Insulin resistance was calculated using the homeostasis assessment model (HOMA-IR) using the formula: Fasting insulin (lIU/ml) fasting glucose (mmol/l)/22.5.

Student's t test or one-way ANOVA (with Tukey's HSD) as appropriate was used to compare groups for continuous variables and Chi-square test was used to compare proportions. Study subjects were categorized into tertiles of percentage of body fat; unequal numbers were found in the tertiles, due to decimals. Pearson's correlation analysis was carried out to determine

the correlation of body fat with cardiometabolic risk factors. Logistic regression analysis was carried out using MS as the dependent variable and other risk factors as independent variables. All analyses were done using Windows-based SPSS statistical package (Version 10.0, Chicago) and *P* values <0.05 were taken as significant.

Results

The clinical and biochemical characteristics of the study subjects stratified according to tertiles of percentage of body fat are shown in Table 1. Age, BMI, waist circumference, SBP and DBP, HOMA IR, FPG, glycated hemoglobin, serum cholesterol, LDL cholesterol, and HDL cholesterol increased significantly with increasing tertiles of body fat (*P* for trend <0.001 for all) and log serum triglycerides (*P*<0.001).

Body fat percentages in subjects with and without varying metabolic abnormalities are presented in Table 2. Percentage of body fat was significantly higher in subjects with elevated fasting glucose (*P*=0.009), hypertension (*P*<0.001), hypertriglyceridemia (*P*=0.003), low HDL cholesterol (*P*<0.001), and MS (*P*<0.001) compared with their counterparts without the respective metabolic abnormalities.

There was a linear increase in the percentage of body fat with increase in number of components of MS (no metabolic abnormality: 25±11, one metabolic abnormality: 28±10, two metabolic abnormalities: 33±8, and three and more metabolic abnormalities: 35±7) (*P* for trend<0.001) [Figure 1].

Table 1: Clinical characteristics of study subjects in tertiles of percentage of body fat

Parameters	Body fat (%)		
	1st tertile (19±6) (*n*=390)	2nd tertile (31±3**) (*n*=400)	3rd tertile [a] (41±3**#) (*n*=395)
Age (years)	32±9	36±10**	43±12**#
Body mass index (kg/m²)	21±3.0	23±4.0**	25±5.0**#
Waist circumference (cm)	77±10	83±11**	84±11**#
Systolic blood pressure (mm Hg)	112±14	115±16*	119±19**#
Diastolic blood pressure (mm Hg)	70±10	72±12*	74±11**#
Fasting plasma glucose (mg/dl)	82±8	84±8*	85±8**
HbA1c (%)	5.4±0.4	5.5±0.4*	5.6±0.5**
HOMA IR	1.3±0.8	1.7±1.2**	1.9±1.4**#
Total serum cholesterol (mg/dl)	162±37	172±32**	183±36**#
Log triglycerides (mg/dl)	2.0±0.2	2.07±0.22	2.14±0.27*
LDL cholesterol (mg/dl)	100±32	108±29**	115±30**#
HDL cholesterol (mg/dl)	44±10	42±9**	41± 10**

*P<0.01, **P<0.001 compared with 1st tertile of body fat percentage. #P<0.05 compared with 2nd tertile of body fat percentage. Values are presented as mean±standard deviation [a]Student's *t*-test; *P<0.05. HOMA IR - Homeostasis Model of Assessment - Insulin Resistance; LDL – Low-density lipoprotein; HDL - High-density lipoprotein

Logistic regression analysis done using MS as dependant variable showed that body fat had a significant association with MS (Odds ratio [OR]: 1.07, 95% confidence interval (CI): 1.05 – 1.09, *P*<0.001]. This association remained statistically significant even after adjustment for age and gender, insulin resistance, and glycated hemoglobin (OR: 1.04, 95% CI: 1.04 – 1.08, *P*<0.001) [Table 3]. Multiple linear regression analysis was done to determine the association of body fat with insulin resistance. Body fat showed a significant association with insulin resistance (β=0.029, *P*<0.001), even after adjusting for age, gender, and glycated hemoglobin (β=0.030, *P*<0.001).

Discussion

The main findings of the study are that in south Indians, a significant association exists between body fat and MS and cardiovascular risk factors even among subjects with NGT.

Several cross-sectional epidemiological studies suggest

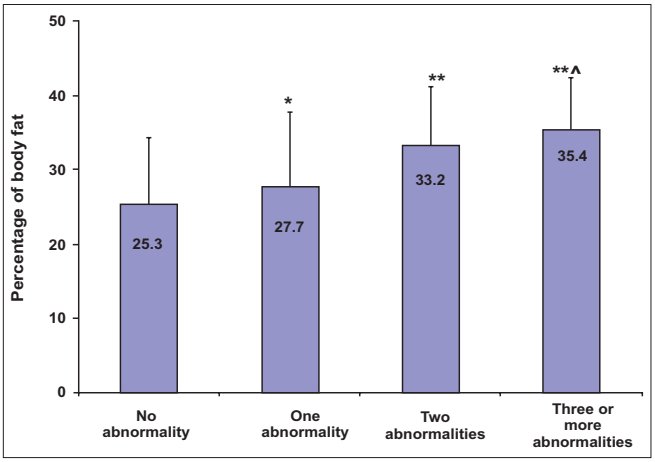

Figure 1: Mean body fat percentage in relation to number of metabolic abnormalities. *P<0.01, **P<0.001 compared with no abnormality. ^P for trend<0.001

Table 2: Mean percentage of body fat in subjects with and without various metabolic abnormalities

Metabolic abnormalities	Mean percentage of body fat	*P* value[a]
Elevated fasting glucose		0.009
Present	34±8	
Absent	30±9	
Hypertension		<0.001
Present	34±9	
Absent	30±10	
Hypertriglyceridemia		0.003
Present	32±8	
Absent	30±10	
Low HDL cholesterol		<0.001
Present	31±9	
Absent	29±10	
Metabolic syndrome		<0.001
Present	35±7	
Absent	29±10	

Values are presented as mean±standard deviation [a]Student's *t*-test; *P<0.05 HDL

Table 3: Logistic regression analysis-dependent variable: Metabolic syndrome

Parameter	Odds ratio (OR)	95% confidence interval (CI)	*P* value
Model 1: Body fat - Unadjusted	1.07	1.05–1.09	<0.001
Model 2: (Model 1 + adjusted for age and gender)	1.06	1.03–1.07	<0.001
Model 3: (Model 2 + adjusted for insulin resistance and glycated hemoglobin)	1.04	1.04–1.08	<0.001

that obesity and abdominal obesity are strongly linked to diabetes. [10,11] Indeed, obesity is considered to be the link between insulin resistance and metabolic abnormalities, which includes diabetes, hypertension, and dyslipidemia, all of which are risk factors for coronary artery disease.[4] Fat storages in adipose tissue have been shown to be linked to insulin resistance and diabetes. Though studies have shown both total fat and visceral fat to be associated with diabetes, visceral fat is considered to be more important as it has been shown to have a strong correlation with glucose intolerance and insulin resistance.[12,13] In this context, this study yielded interesting information with regard to insulin resistance. It was observed that body fat percentage increased in NGT subjects with increased insulin resistance as measured by HOMA IR compared with those without increased insulin resistance, and body fat percentage is independently associated with insulin resistance.

Earlier studies[14,15] on Asian Indians have reported an association of waist circumference with diabetes, suggesting that increased accumulation of fat in the abdominal cavity may be one of the contributors to diabetes in this ethnic group. Waist circumference showed a strong correlation with visceral and central abdominal fat in both diabetic and nondiabetic subjects.[16] In the present study, body fat percentage showed a correlation both with waist circumference and BMI. Glucose intolerance and other metabolic abnormalities may cluster together, resulting in increased risk for coronary artery disease.[4] We have observed that subjects with MS had higher levels of body fat percentage compared with subjects without MS. It was also observed that body fat percentage increased with increase in number of metabolic abnormalities indicating a dose–response relationship between body fat percentage and metabolic abnormalities.

Accumulation of body fat, particularly in the abdominal region, has several health implications, including cardiovascular health risk.[17,18] Previous studies have reported a positive association of both BMI[19] and waist-to-hip ratio[20]with hsCRP concentrations. Total white blood cell count has been found to be significantly associated with BMI, percentage body fat, and insulin concentrations.[21] In our earlier study, we have shown that the association of body fat with diabetes is mediated through inflammation.[22] Evidence for the link between obesity and diabetes comes from the epidemiological and intervention studies, with weight reduction as the main target. The Diabetes Prevention Programme demonstrated that a 7% reduction in body weight by exercise and diet could prevent diabetes in subjects with impaired glucose tolerance by as much as 58%.[23] A study on Japanese women suggested that reducing the intra-abdominal fat to 60 cm^2 was beneficial in reducing cardiovascular risk factors.[24]

It is well established that coronary artery disease can be prevented by interventions like lifestyle modification, use of statins, fibrate, or antihypertensive therapy.[25,26] Hence, it is imperative to identify subjects with cardiovascular risk at the earliest. Screening for body fat percentage as an indicator of increased cardiovascular risk would be extremely useful for large epidemiological studies, especially in a developing country like India. In this context, the body fat percentage appears to be of great significance as it identifies individuals with higher cardiovascular risk since it is noninvasive, simple, reliable, and inexpensive, using portable equipment for determining body composition. Thus, bioimpedance analysis systems are increasingly being used to quantify body composition in both clinical and research settings, as they are cheaper and more readily available compared with the gold standard, i.e., measurement of body composition using DEXA.[3,27] Thus, for practical and scientific reason, bioimpedance are often one of the most suitable options for clinical assessment of fatness.

One of the limitations of the study is that being a cross-sectional design, we are unable to demonstrate a cause and effect relation between body fat percentage and cardiometabolic risk factors. However, the strength of the study is that it is a large population-based sample in Asian Indians who have a high prevalence of premature coronary artery disease and diabetes and is one of the first in this ethnic group.

In conclusion, this study reports that among Asian Indians, a significant association exists between body fat percentage, insulin resistance, and cardiometabolic risk factors.

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