Influence of Upper and Lower Body Adipose Tissue on Insulin Sensitivity in South Asian Men

Preetha Balakrishnan, MD,* Scott M. Grundy, MD, PhD,†‡ Arsalla Islam, MD,§ Fredrick Dunn, MD, †‡ and Gloria Lena Vega, PhD†‡

Background: South Asians have a high prevalence of insulin resistance, which predisposes to type 2 diabetes.

Rationale: In the current study, we examined whether insulin sensitivity in South Asian men and men of European descent (Europids) relates to truncal and lower body fat, number of adipocytes, and cell size distribution.

Results: Fifteen South Asian men and 15 Europid young men with comparable body mass indexes completed assessments of insulin sensitivity, body composition analysis by dual-energy x-ray absorptiometry, and measurement of adipocyte cellularity in the subcutaneous abdominal (truncal) and gluteal (lower body) adipose tissue. The South Asians and the Europids had similar total body fat and fat contents in truncal and lower body regions. Compared to the Europids, the South Asians had a greater insulin resistance shown by fasting insulin, area-under-the-curve for postprandial insulin, oral glucose insulin sensitivity, homeostatic model assessment of insulin resistance, β-cell index, and triglyceride-to-high-density lipoprotein ratio. The South Asians had similar number of adipocytes to the Europids, but the South Asians had significantly higher ratios of small-to-larger adipocytes. The South Asians further had a higher fraction of very large adipocytes. In both South Asians and Europids, truncal fat was positively associated with insulin resistance. In the South Asians but not in the Europids, lower body fat was associated with severity of insulin resistance.

Conclusions: The results suggest first, a higher ratio of small-to-larger adipocytes in the South Asians consistent with a lesser lipid storage capacity of adipose tissue; and second, the positive association of lower body fat with insulin resistance in the South Asians implies that fat in their lower body worsens insulin resistance. This association was not observed in the Europids.

Key Words: adipocytes, size distribution, number of cells

(J Investig Med 2012;60: 999–1004)

Persons from the Asian subcontinent (South Asians) carry a relatively high prevalence of type 2 diabetes compared to Europids.1 This difference in susceptibility to diabetes in South Asians seems related to high insulin resistance.2,3 The reasons for greater insulin resistance in South Asians are not known, but several possibilities have been proposed, that is, insulin resistance of adipose tissue,4 adipocyte hypertrophy,5,6 excess body fat and/or predominant upper body fat,2,3,7,8 skeletal muscle abnormalities,9 hepatic steatosis,10 and reduced whole body fatty acid oxidation.11 Taken together, these studies reveal that no single cause of greater insulin resistance in South Asians has been pinpointed.

In the current study, we examined whether differences in adipose tissue cellularity contributed to differences in insulin resistance between South Asians and Europids. Recently, Europid subjects with insulin resistance have been reported to manifest a defect in adipose tissue maturation, that is, in conversion of small triglyceride-poor adipocytes into large triglyceride-rich adipocytes.12,13 This abnormality may reflect defective adipose-tissue storage of triglyceride, causing accumulation of fat in muscle and liver. This ectopic fat in turn could lead to insulin resistance and predispose to type 2 diabetes. In the current study, we examined whether a similar adipose-tissue pattern exists in South Asians. We further explored whether other differences in adipose-tissue characteristics link to differences in insulin resistance between South Asians and Europids.

MATERIALS AND METHODS

Fifteen South Asian and 20 Europid men were screened for the study; 15 men of each met the criteria for enrollment. The subjects were recruited through public advertisement in the Dallas Fort Worth area. The participants were either first- or second-generation South Asians who immigrated from the Indian subcontinent including India, Pakistan, Nepal, Bangladesh, or Sri Lanka. The men of European descent were born in the United States. Ethnicity was self-declared. Most volunteers reported sedentary or mild to moderate physical activity. No differences could be discerned in body habitus related to the country of origin.

Subjects were excluded from participation if they had chronic and/or unstable diseases or had a history of chemical dependencies or were treated with hypolipidemic agents. Self-declared endurance athletes also were excluded from participation in the study.

All volunteers gave written informed consent to participate in the study that was approved by the Institutional Review Board for Investigation in Humans at the University of Texas Southwestern Medical Center at Dallas, Texas. The study was conducted at the Clinical Translational Research Center at the same institution.

This cross-sectional study involved 2 Clinical Translational Research Center visits. During the first visit, the subjects signed the informed consent to participate and underwent a medical history taking, physical examination, anthropometric measurements, and fasting chemistries to determine eligibility. Those who qualified returned for a second visit that included assessment of insulin sensitivity with a glucose tolerance test, body composition analysis by dual-energy x-ray absorptiometry (DXA), and a biopsy of the abdominal and gluteofemoral subcutaneous adipose tissue to measure adipocyte cell volume and size distribution.
Subcutaneous adipose tissue was obtained from the periumbilical and gluteofemoral areas using a 14G × 11-cm Temno Evolution biopsy needle (Care Fusion, McGaw Park, IL) under local anesthesia. Adipocyte cell volume was measured in a coulter counter (Beckman Multisizer 3, Brea, CA) after fixation of an approximately 30-mg sample of adipose tissue in 2% osmium tetroxide dissolved in 0.2-mol/L collidine buffer, pH 7.4 at 37°C for 72 hours.19–21

Briefly, osmium tetroxide fixed cells were counted and sized according to the Coulter principle. An electrode useful to measure particles with diameters ranging from 22 to 240 micrometers was used. Latex beads of diameters 20, 43, 65, and 90 μm (Beckman Coulter, Brea, CA) were used routinely as quality controls for particle diameter before doing a set of sample particle size and number measurements.

**Statistics**

Data are summarized as mean ± SD or SEM. Group means between the South Asians and the Europids were compared by one-way analysis of variance followed by Fisher post hoc analyses; for a data of numbers of parameters with asymmetric distribution were log-transformed before doing comparisons. Spearman correlation coefficients were used to assess the association of continuous variables. The study was powered to detect approximately 20% difference in mean adipocyte diameter between the 2 ethnic groups at a power of 0.87 and an α of 0.05. Statistical analysis was performed using Statview version 5.0.1 (SAS Institute, Cary, NC).

## RESULTS

Anthropometric and body composition characteristics are shown in Table 1. The South Asians and the Europids were of similar age. Mean body mass indexes were the same. There were no significant differences between the 2 groups for weights or heights, or waist or hip girths. Plasma triglycerides were higher and high-density lipoprotein cholesterol levels were lower in the South Asians. Frequencies of prediabetes, prehypertension, elevated triglycerides, and family history of type 2 diabetes were higher in the South Asians.

Parameters related to insulin sensitivity are listed in Table 2. Fasting glucose and glycohemoglobin, fasting insulin, AUC for glucose disposal.

### TABLE 1. Anthropometric Characteristics and Body Composition

| Anthropometry                      | South Asian | Europids |
|------------------------------------|-------------|----------|
| Age, yrs                           | 26.2 ± 2.5  | 27.2 ± 7.5 |
| Waist girth, cm                    | 92.6 ± 13.5 | 89.7 ± 8.9 |
| Hip girth, cm                      | 99.9 ± 14.6 | 101 ± 9.5 |
| Waist-to-hip ratio                 | 0.93 ± 0.06 | 0.89 ± 0.06 |
| Weight, kg                         | 82.7 ± 17.9 | 84.6 ± 10.5 |
| Height, cm                         | 175.9 ± 7.2 | 178.2 ± 6.6 |
| Body mass index, kg/m²             | 26.7 ± 5.3  | 26.6 ± 2.5 |

*Significantly different between the 2 ethnic groups; P < 0.02; medians are provided for triglycerides.

HDL indicates high-density lipoprotein.

### TABLE 2. Metabolic Parameters

| Parameter                          | South Asians | Europids |
|------------------------------------|--------------|----------|
| Fasting glucose, mg/dL             | 92 ± 8*      | 85 ± 6   |
| Glycohemoglobin, %                 | 5.6 ± 2.5†   | 5.2 ± 0.3 |
| Fasting insulin, pmol/dL‡          | 95.5*        | 65.9     |
| Insulin AUC × 10^5                 | 7.21 ± 3.16  | 4.52 ± 1.8 |
| HOMA-IR, %‡                        | 23.3†        | 16.8     |
| Insulin sensitivity index, mL/pmol per square meter‡ | 303‡ | 347 |
| Beta cell index‡                   | 63.9*        | 38.3     |
| Triglyceride/HDL cholesterol ratio | 2.8 ± 1.4*   | 1.7 ± 0.8 |
| Nonesterified fatty acids, mmol/L | 446 ± 200    | 431 ± 149 |
| 3-Hydroxybutyrate, mmol/L          | 134 ± 96     | 153 ± 100 |

*Significantly different between the 2 ethnic groups; P ≤ 0.04.
†Significantly different between the 2 ethnic groups; P ≤ 0.01.
‡Median levels.
Body fat content and composition in South Asians and Europids. A, Total, truncal, and lower body fat content were similar in both groups. B, Ratio of truncal/lower extremity fat was also similar.

postprandial insulin, homeostatic model assessment of insulin resistance (HOMA-IR), β-cell index, ratio of triglyceride-to-HDL cholesterol, insulin sensitivity determined by OGIS were significantly higher in the South Asians. Fasting nonesterified fatty acids and 3-hydroxybutyrate levels were not different between the 2 groups.

Total body fat content was similar between the 2 groups (Fig. 1). There were no differences in fat content in the truncal or lower body regions, nor were there differences in the truncal-to-lower body fat ratio (Fig. 1, A and B, respectively).

The total number of adipocytes and the number of small adipocytes in the truncal region were significantly greater in the South Asians compared to the Europids (Table 3). In the truncal region, the South Asians had fewer medium-sized adipocytes, whereas they had more very large adipocytes than the Europids. In the lower body, the South Asians had more small adipocytes and very large adipocytes compared to the Europids.

Ratios of small-to-larger adipocytes were higher in both truncal and lower body adipose tissue for the South Asians (Fig. 2). The ratios of large + very large adipocytes to medium-sized adipocytes were greater in the South Asians than the Europids for truncal fat but not for lower body fat.

The distributions of adipocyte volumes according to cell-size category are shown in Figure 3. The major finding was a greater mean volume among very large adipocytes in both truncal and lower body fat for the South Asians. However, for both the South Asians and the Europids, more than half the fat volume was contained in large cells.

**DISCUSSION**

In this study, we observed that the South Asians had greater insulin resistance and more metabolic risk factors than the Europids. The South Asians also had a higher β-cell index. There were no differences in body fat distribution; but within adipose tissue, the South Asians had higher ratios of small-to-larger adipocytes and overall larger adipocytes. Further, body fat parameters were more strongly associated with insulin resistance measures in the South Asians compared to the Europids, and in

---

**TABLE 3. Adipose Tissue Cellularity**

| South Asians     | Euromids  |
|------------------|-----------|
| **Truncal Cellularity × 10^9** | **Lower Extremity Cellularity × 10^9** |
| Mean ± SE        | Mean ± SE |
| Total no. adipocytes | 12.98 ± 1.32 | 11.11 ± 0.71† | 9.82 ± 1.02 | 8.32 ± 0.59 |
| Small            | 5.14 ± 0.63‡ | 3.58 ± 0.25‡ | 3.52 ± 0.36* | 2.51 ± 0.18 |
| Medium (M)       | 3.8 ± 0.27† | 4.6 ± 0.31† | 3.06 ± 0.21 | 3.2 ± 0.26 |
| Large (L)        | 3.39 ± 0.46 | 2.71 ± 0.31 | 2.85 ± 0.45 | 2.46 ± 0.26 |
| Very large (VL)  | 0.65 ± 0.17* | 0.21 ± 0.05 | 0.39 ± 0.09* | 0.15 ± 0.03 |
| L + VL           | 4.05 ± 0.61 | 2.93 ± 0.34 | 3.24 ± 0.53 | 2.61 ± 0.28 |
| M + L + VL       | 7.84 ± 0.08 | 7.53 ± 0.51† | 6.3 ± 0.7 | 5.81 ± 0.42 |

*Significantly different between ethnicities; P ≤ 0.03.
†Significantly different between truncal and lower extremity fat depots within each ethnic group; P ≤ 0.03.
South Asians, lower body fat was correlated positively with insulin resistance measures, whereas in the Europids, there was no correlation.

In this study, the South Asians had higher levels of fasting insulin, greater AUC for postprandial insulin, and higher HOMA-IR than the Europids. This finding confirms that for a given amount of total body fat, the South Asians are more likely to be insulin resistant. Insulin sensitivity by OG1S was lower in the South Asians, and \( \beta \)-cell index was increased. The latter suggests that \( \beta \) cells were under metabolic stress; a high \( \beta \)-cell index implies a high secretion of insulin in response to glucose without a reduction in \( \beta \)-cell function. Whether elevated insulin secretion in the South Asians compensates for an underlying peripheral insulin resistance or itself causes insulin resistance is uncertain.

We carried out the current study to further explore whether defects in adipose tissue were associated with insulin resistance in the South Asians. Several abnormalities in adipose tissue are reported to be accompanied by elevated insulin resistance. Each possibility can be considered briefly in the light of current results.

First, subjects with lipodystrophy, that is, a gross deficiency of adipose tissue, manifest insulin resistance. In the current study, we observed no reduction in the total number of adipocytes in the South Asians. Hence, the insulin resistance in the South Asians cannot be explained by a deficiency of adipose tissue.

Second, it has been reported that Europids with insulin resistance commonly have a maturation defect in adipogenesis. The finding suggesting a maturation defect was a high ratio of small (immature) adipocytes to larger adipocytes. In our study, the South Asians did in fact have a higher ratio of small- to-large adipocytes compared to the Europids; this finding accords with the putative maturation defect in adipogenesis. Such a defect could lead to decreased fat storage capacity of adipose tissue, favoring ectopic fat distribution and insulin resistance.

Third, Chandalia et al. and Anand et al. reported that South Asians have abnormally large adipocytes compared to Europids. The presence of very large adipocytes can signify overloading of adipose tissue with triglycerides, which could produce ectopic fat distribution. We likewise found that the South Asians display enrichment in very large adipocytes. They further exhibit a lower ratio of medium sized to large + very large adipocytes. These findings support overloading of adipocytes with triglycerides, which should limit fat storage capacity of adipose tissue. This overload may have shifted fat to muscle and liver, causing insulin resistance.

Fourth, others report that South Asians are prone to upper body obesity. Upper body obesity in Europids has been correlated with insulin resistance. Recent studies have suggested that in Europids, upper body fat is positively associated with insulin resistance, whereas lower body fat is not. The concept that adipose tissue in the lower body does not worsen insulin resistance derives support from several studies. For example we reported that lower body fat in large populations of Europids and African Americans correlates poorly with HOMA-IR, whereas truncal fat correlates more strongly. Recently, Tchoukalova et al. reported a mechanism whereby upper body obesity can impair insulin sensitivity. They found that weight gain induces adipocyte hypertrophy in the upper body, which suggests a limitation in fat storage capacity in truncal adipose tissue. In contrast, with weight gain, lower body adipose tissue undergoes hyperplasia, suggestive of an expansion of fat storage capacity. With onset of obesity, adipocyte hyperplasia in the lower body may protect against insulin resistance, whereas adipocyte hypertrophy in the upper body accords with limited capacity to store fat, leading to “spillover” of fat into ectopic depots and insulin resistance.

In the present study, we did not observe a difference in body fat distribution between the 2 groups; we did however observe apparent differences in correlations between upper and lower body fat and insulin resistance in the South Asians and the Europids. We found that in both the Europids and the South Asians, upper body fat was positively associated with insulin resistance, although more strongly in the South Asians. In contrast, lower body fat was not associated with insulin-resistance measures in the Europids, but it was positively associated in the South Asians. Thus, both the stronger overall association for

![Adipocyte cell volume distribution. The South Asians had lower volume of medium-sized cells in the trunk (TR) and higher volumes of very large cells in trunk and lower extremity (LE) compared to the Europids (\( P < 0.03 \)). The South Asians had similar truncal and lower extremity cell volumes for all sizes. The Europids had a higher volume of the medium-sized cells in the trunk compared to the lower extremity. Europids also had a lower cell volume for the large cells in the trunk compared to their lower extremity (\( P < 0.04 \)).](image)

### TABLE 4. Spearman Correlation Coefficients (\( \rho \)) for Insulin Resistance Parameters Versus Body Fat and Cellularity

|                | Insulin | HOMA  | OGIS  | Insulin AUC |
|----------------|---------|-------|-------|-------------|
|                | \( r \) | \( r \) | \( r \) | \( r \)      |
| Total body fat |         |       |       |             |
| South Asian    | 0.78*   | 0.79* | -0.44 | 0.77*       |
| Europids      | 0.36    | 0.39  | -0.49 | 0.12        |
| Truncal fat    |         |       |       |             |
| South Asian    | 0.76†   | 0.78* | -0.45†| 0.76*       |
| Europids      | 0.46    | 0.49  | -0.58 | 0.18        |
| Lower extremity fat |       |       |       |             |
| South Asian    | 0.74*   | 0.75* | -0.38 | 0.64†       |
| Europids      | 0.16    | 0.20  | -0.34 | 0.05        |
| Truncal cell number (M, L, VL) |         |       |       |             |
| South Asian    | 0.69*   | 0.69* | -0.49†| 0.15        |
| Europids      | 0.56*   | 0.59* | -0.15 | 0.37†       |
| Lower extremity cell number (M, L, VL) |       |       |       |             |
| South Asian    | 0.54*   | 0.55* | -0.48*| 0.46*       |
| Europids      | 0.33    | 0.36  | -0.02 | 0.11        |

*\( P < 0.01 \)
†\( P < 0.05 \)
body fat and especially the positive association for lower body fat
could contribute to the greater insulin resistance in the South
Asians. In contrast to the findings of Tchoukaleva et al.,29 we
found no difference in total number of adipocytes in the lower
extremities of the South Asians versus the Europids; but the dif-
fences in cellularity observed in upper body fat were retained
in lower body fat, that is, higher ratios of small-to-large adi-
pocytes and more very large adipocytes in the South Asians.

Finally, another possible mechanism for the association
between adiposity parameters and hyperinsulinemia might be
considered. It is in the realm of possibility that hyperinsulinemia
is secondary to a primary overproduction of insulin by β cells
or insulin resistance in muscle. If such is the case, elevated levels
of insulin could cause changes in adipose tissue metabolism
and contribute to the changes noted in the study.

The primary limitation of the current study was its small
size. To confirm the results, a larger investigation is needed.
Moreover, if insulin resistance in the South Asians is due to
nonadipose tissue factors, the postulated mechanisms could be
confounded. Nonetheless, we have identified 2 adipose tissue
factors that might contribute to greater insulin resistance in the
South Asians compared to the Europids. First, the South Asians
compared to the Europids had a disproportionately high frac-
tion of small adipocytes, suggestive of a “maturation defect” for
adipogenesis; this adipocyte pattern has been reported previ-
ously to be associated with insulin resistance in the Europids.12,21
Second, lower body adipose tissue in the South Asians was more
strongly correlated with insulin resistance than in the Europids;
for the Europids, the lesser effect of lower body fat on insulin resis-
tance observed here is consistent with what has been reported
previously.12,28 Seemingly, the South Asians do not have this
“benign effect” of lower body fat.

ACKNOWLEDGMENT

The author thanks for the excellent work of Laura Caldwell,
PAC, Amit Gode and the clinical research staff of the Clinical
Translational Research Center (CTRC). The excellent technical
assistance of Thanalakshmi Seenivasan, Ph.D., Johnathan Kim
B.S., Bryce Hamilton, B.S., Anh Nguyen, B.S. and Ronnie A.
Barakat, B.S is also appreciated. The authors also gratefully
acknowledge the information on the use of the coulter counter for
adipocyte sizing provided by the laboratory of Steven R. Smith,
M.D., Ph.D. at the Translational Research Institute for Metab-
olism and Diabetes, Florida Hospital, Sanford Berham Institute
of Medicine, and the Clinical Research staff of the Transla-
tional Research Center (CTRC). The excellent technical
assistance of Thanalakshmi Seenivasan, Jr. Johnathan Kim
B.S., Bryce Hamilton, B.S., Anh Nguyen, B.S. and Ronnie A.
Barakat, B.S. is also appreciated. The authors also gratefully
acknowledge the information on the use of the coulter counter for
adipocyte sizing provided by the laboratory of Steven R. Smith,
M.D., Ph.D. at the Translational Research Institute for Metab-
olism and Diabetes, Florida Hospital, Sanford Berham Institute
and the laboratory of Samuel W. Cushman, Ph.D. of the Ex-
perimental Diabetology, Metabolism and Nutrition Section of the
NIDDK, National Institutes of Health, Bethesda, MD.

REFERENCES

1. Mohan V. Why are Indians more prone to diabetes? J Assoc Phys India.
2004;52:468–474.

2. McKeigue PM, Shah B, Marmot MG. Relation of central obesity and
diabetes with high prevalence of abdominal obesity in the urban population of North India.
J Assoc Phys India. 2004;52:468–474.

3. Chandalia M, Abate N, Garg A, et al. Adiponectin in non-diabetic Asian Indian men. J Clin Endocrinol Metab. 1999;84:2329–2335.

4. Abate N, Chandalia M, Snell PG, et al. Adipose tissue metabolites and insulin resistance in nondiabetic Asian Indian men. J Clin Endocrinol Metab. 2004;89:2750–2755.

5. Chandalia M, Lin P, Seenivasan T, et al. Insulin resistance and body fat distribution in South Asian men compared to Caucasian men. PLoS One. 2007;2:e812.

6. Anand SS, Tarnopolsky MA, Rashid S, et al. Adipocyte hypertrophy, fatty liver and metabolic risk factors in South Asians: the molecular Study of Health and Risk in Ethnic Groups (moll-SHARE). PLoS One. 2011;6:e22112.

7. Singh RB, Niaz MA, Agarwal P, et al. Epidemiologic study of central obesity, insulin resistance and associated disturbances in the urban population of North India. Acta Cardiol. 1995;50:215–225.

8. Bhandrav S, Misra A, Misra R, et al. High prevalence of abdominal, intra-abdominal and subcutaneous adiposity and clustering of risk factors among urban Asian Indians in North India. PLoS One. 2011;6:e24362.

9. Nair KS, Bigelow ML, Asmann YW, et al. Asian Indians have enhanced skeletal muscle mitochondrial capacity to produce ATP in association with severe insulin resistance. Diabetes 2008;57:1166–1175.

10. Petersen KE, Dufour S, Feng J, et al. Increased prevalence of insulin resistance and nonalcoholic fatty liver disease in Asian-Indian men. Proc Natl Acad Sci USA. 2006;103:18273–18277.

11. Hall LM, Moran CN, Milne GR, et al. Fat oxidation, fitness and skeletal muscle expression of oxidative/lipid metabolism genes in South Asians: implications for insulin resistance? PLoS One. 2010;5:e14197.

12. McLaughlin T, Sherman A, Tsao P, et al. Enhanced proportion of small adipose cells in insulin-resistant vs insulin-sensitive obese individuals implicates impaired adipogenesis. Diabetologia. 2007;50:1707–1715.

13. Kursawe R, Ezelinger M, Narayan D, et al. Cellularity and adipogenic profile of the abdominal subcutaneous adipose tissue from obese adolescents: association with insulin resistance and hepatic steatosis. Diabetes. 2010;59:2288–2296.

14. Vega GL, Adams-Huet B, Pesheck R, et al. Influence of body fat content and distribution on variation in metabolic risk. J Clin Endocrinol Metab. 2006;91:4459–4466.

15. McGuire EHA, Helderman JH, Tobin JD, et al. Effects of arterial versus venous sampling on analysis of glucose kinetics in man. J Appl Physiol. 1976;41:565–573.

16. Vega GL, Dunn FL, Grundy SM. Effect of coelestevam hydrochloride on glycemia and insulin sensitivity in men with the metabolic syndrome. Am J Clin Nutr. 2011;8:1129–1135.

17. Mari A, Pacini G, Murphy E, et al. A model-based method for assessing insulin sensitivity from the oral glucose tolerance test. Diabetes Care. 2001;24:539–548.

18. Mari A, Pacini G, Brazzale AR, et al. Comparative evaluation of simple insulin sensitivity methods based on the oral glucose tolerance test. Diabetologia. 2005;48:748–751.

19. Hirsch J, Gallian E. Methods for the determination of adipose cell size in man and animals. J Lipid Res. 1968;9:110–119.

20. Cushman SW, Salans LB. Determinations of adipose cell size and number in suspensions of isolated rat and human adipose cells. J Lipid Res. 1978;19:269–273.

21. Pasarica M, Xie H, Hymel D, et al. Lower total adipocyte number in suspensions of isolated rat and human adipose cells. J Lipid Res. 1978;19:269–273.

22. Garg A. Acquired and inherited lipodystrophies. N Engl J Med. 2004;350:1220–1234.

23. Singh RB, Niaz MA, Agarwal P, et al. Epidemiologic study of central obesity, insulin resistance and associated disturbances in the urban population of North India. Acta Cardiol. 1995;50:215–225.
24. Bhardwaj S, Misra A, Misra R, et al. High prevalence of abdominal, intra-abdominal and subcutaneous adiposity and clustering of risk factors among urban Asian Indians in North India. *PLoS One*. 2011;6:e24362.

25. Raji A, Seely EW, Arky RA, et al. Body fat distribution and insulin resistance in healthy Asian Indians and Caucasians. *J Clin Endocrinol Metab*. 2001;86:5366–5371.

26. Jensen MD, Haymond MW, Rizza RA, et al. Influence of body fat distribution on free fatty acid metabolism in obesity. *J Clin Invest*. 1989;83:1168–1173.

27. Abate N, Garg A, Peshock RM, et al. Relationships of generalized and regional adiposity to insulin sensitivity in men. *J Clin Invest*. 1995;96:88–98.

28. Snijder MB, Dekker JM, Visser M, et al. Trunk fat and leg fat have independent and opposite associations with fasting and postload glucose levels: the Hoorn study. *Diabetes Care*. 2004;27:372–377.

29. Tchoukalova YD, Votruba SB, Tchkonia T, et al. Regional differences in cellular mechanisms of adipose tissue gain with overfeeding. *Proc Natl Acad Sci U S A*. 2010;107:18226–18231.