# Dual Energy X-Ray Absorptiometry Assessment of Fat Mass Distribution and Its Association With the Insulin Resistance Syndrome

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**OBJECTIVE** — To determine which dual energy X-ray absorptiometry (DXA)–derived indices of fat mass distribution are the most informative to predict the various parameters of the metabolic syndrome.

**RESEARCH DESIGN AND METHODS** — A total of 87 healthy men, 63 lean (% fat ≤26) and 24 obese (% fat >26), underwent DXA scanning to evaluate body composition with respect to the whole body and the trunk, leg, and abdominal regions from L1 to L4 and from L3 to L4. These regions were correlated with insulin sensitivity determined by the euglycemic-hyperinsulinemic clamp, insulin area under the curve after oral glucose tolerance test (AUC I); triglyceride; total, HDL, and LDL cholesterol; free fatty acids; and blood pressure. The analyses were performed in all subjects, as well as in lean and obese groups separately.

**RESULTS** — Among the various indices of body fat, DXA-determined adiposity in the abdominal cut at L1–4 level was the most predictive of the metabolic variables, showing significant relationships with glucose infusion rate ([GIR], mg · kg$^{-1}$ lean body mass · min$^{-1}$), triglyceride, and cholesterol, independent of total-body mass ($r = -0.267$, $P < 0.05$; $r = 0.316$, $P < 0.005$; and $r = 0.319$, $P < 0.005$, respectively). Upon subanalysis, these correlations remained significant in lean men, whereas in obese men, only BMI and the amount of leg fat (negative relationship) showed significant correlations with triglyceride and cholesterol ($r = 0.438$, $P < 0.05$; $r = 0.458$, $P < 0.05$; $r = -0.439$, $P < 0.05$; and $r = -0.414$, $P < 0.05$, respectively). The results of a multiple regression analysis revealed that 47% of the variance in GIR among all study subjects was predicted by AUC I, fat L1–4, diastolic blood pressure (dBP), HDL, and triglyceride as independent variables. In the lean group, fat L1–4 alone accounted for 33% of the variance of GIR, whereas in obese men, AUC I and dBP explained 68% of the variance in GIR.

**CONCLUSIONS** — The DXA technique applied for the evaluation of fat distribution can provide useful information regarding various aspects of the insulin resistance syndrome in healthy subjects. DXA can be a valid, accurate, relatively inexpensive, and safer alternative compared with other methods to investigate the role of abdominal body fat distribution on cardiovascular risk factors.

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**Abbreviations:** ANOVA, analysis of variance; AUC, area under the curve; CT, computed tomography; dBP, diastolic blood pressure; DXA, dual energy X-ray absorptiometry; FFA, free fatty acid; GIR, glucose infusion rate; IAFM, intra-abdominal fat mass; MRI, magnetic resonance imaging; OGTT, oral glucose tolerance test; sBP, systolic blood pressure; SCFM, subcutaneous fat mass; WHR, waist-to-hip ratio.

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

It is now well recognized that the metabolic syndrome, characterized by insulin resistance, hyperinsulinemia, central fat deposition, hypertension, dyslipidemia, dysfibrinolysis, and endothelial dysfunction, is associated with a two- to threefold increase in the risk of death from myocardial infarction (1–4). Several epidemiologic studies have shown that increased BMI and waist-to-hip ratio (WHR) are strongly associated with the metabolic syndrome (5–7). In particular, several reports have suggested that central abdominal fat distribution, rather than total-body fat, is more closely related to the parameters of the metabolic syndrome (8–11). Some have suggested that adipose tissue from the intra-abdominal region (intra-abdominal fat mass [IAFM]) is more metabolically relevant than subcutaneous fat mass (SCFM) (12), because IAFM exhibits higher catecholamine-induced lipolysis (13–15) and higher triglyceride turnover with an increased ability to release free fatty acid (FFA) directly into the portal vein and impair the hepatic metabolism (16). Other reports have concluded that IAFM is the most potent predictor of the metabolic syndrome (17–21). The value of differentiating IAFM and SCFM and their association with the metabolic syndrome has been recently challenged by several studies. In these studies, using computed tomography (CT) (22) and magnetic resonance imaging (MRI) (23,24) to evaluate the body fat deposition, IAFM was not found to be of greater significance in predicting insulin resistance than SCFM measured in the abdominal area or total abdominal fat (SCFM + IAFM).

Evaluation of body fat depots, which are closely associated with the insulin-resistance syndrome, is important for the management and prevention of its associate complications. Thus, there is increased interest in the evaluation of various methods for assessing body fat distribution. Dual energy X-ray absorptiometry (DXA) is a validated technique able to accurately determine cross-sectionally the mass of discreet fat deposits. While it cannot distin-

guish between IAFM and SCFM, it is less expensive, available in many research centers, and exposes subjects to smaller doses of radiation than CT and MRI do. Therefore, DXA represents a reliable and convenient research tool to explore which DXA-derived indices of fat mass distribution are the most informative with respect to predicting the various parameters of the metabolic syndrome. To this end, DXA was performed on 63 lean and 24 obese healthy male subjects to determine body composition with respect to the whole body, specific body regions, such as the trunk and the leg, and circumscribed areas reflecting central fat mass distribution. The various DXA indices were then correlated with blood pressure, lipid, and carbohydrate characteristics. The data were further analyzed to ascertain the best independent variables predictive of insulin sensitivity as determined by the euglycemic-hyperinsulinemic clamp technique.

## RESEARCH DESIGN AND METHODS

### Subjects

Over a period of 6 years, a large number of subjects underwent high-dose euglycemic-hyperinsulinemic clamps and total-body DXA scanning as part of different study protocols performed in our laboratory. Of these subjects, 87 are included in the present retrospective analysis because they are all normotensive (systolic blood pressure [sBP] and dBP $<$140 and $<$90 mmHg, respectively) and chemically euthyroid, and they exhibit normal glucose tolerance to a 75-g oral glucose tolerance test (OGTT). None was ingesting any pharmacological agent at the time of the study. Studies were approved by the Indiana University Institutional Review Board.

### Protocol and procedures

After informed consent was obtained, subjects were admitted to the Indiana University General Clinical Research Center in Indianapolis for 2 days before each study and fed a weight-maintenance diet (50% carbohydrate, 20% protein, and 30% fat) in three divided feedings containing one-fifth, two-fifths, and two-fifths of the allotted daily calories given at 0800, 1200, and 1700 h, respectively. Subjects abstained from intake of caffeine and other xanthines, alcohol, and tobacco for 12 h before and during all studies. All subjects were studied after a 10-h overnight fast. Blood samples for analytic assays were collected in fasting conditions before the study was begun.

The glucose metabolism data were obtained from a variety of protocols previously completed in our laboratory over a 6-year period. Therefore, euglycemic-hyperinsulinemic clamps were performed at different insulin doses of 120, 300, and 600 mU $\cdot$ m$^{-2}$ $\cdot$ min$^{-1}$ as previously described (25), depending on the specific protocol. Blood for arterial glucose concentrations was obtained either from a femoral arterial catheter or from a catheter inserted in retrograde fashion in a dorsal hand vein where the hand was kept warm by a heating pad, as previously described (25,26). The serum glucose concentration was kept at the baseline level by administering a 20% dextrose solution at a variable rate according to serum glucose measurements obtained at 5-min intervals. $K_2HPO_4$ ($\sim$0.001–0.0038 meq $\cdot$ kg$^{-1}$ $\cdot$ min$^{-1}$) was infused during the euglycemic-hyperinsulinemic clamps to prevent hypokalemia and hypophosphatemia. Serum potassium levels were maintained $>$3.5 meq/l during all study conditions. The glucose infusion rates ([GIRs], mg $\cdot$ kg$^{-1}$ lean body mass $\cdot$ min$^{-1}$) were determined during each study as the average GIR required to maintain euglycemia during the last 40 min of each study when GIRs were in a nearly steady state ($<$5% change in GIR over 40 min). All clamp studies were carried out for at least 180 min and terminated at 240 min. As expected, high but different insulin levels were achieved using different clamp doses. Insulin levels during the clamps were 460 ± 160 and 280 ± 50; 1,250 ± 256 and 1,021 ± 231; and 2,948 ± 200 and 3,341 ± 254 μU/ml, in lean and obese groups, clamped at 120, 300, and 600 mU $\cdot$ m$^{-2}$ $\cdot$ min$^{-1}$, respectively. Because clamps were performed at varying insulin concentrations, we were concerned that GIR values might differ because equivalent insulin action was not achieved between groups rather than reflecting true biological differences in insulin action. Therefore, we examined whether the subject groups studied differed with respect to GIR. In fact, subject groups studied at 120, 300, and 600 mU $\cdot$ m$^{-2}$ $\cdot$ min$^{-1}$ did not exhibit different GIRs whether they were lean or obese. When clamped at 120, 300, and 600 mU $\cdot$ m$^{-2}$ $\cdot$ min$^{-1}$, respectively, GIR values in lean and obese groups were 13.7 ± 0.6 and 11.5 ± 0.6; 12.7 ± 1.0 and 13.9 ± 2.5; and 14.9 ± 0.4 and 13.7 ± 0.8 mg $\cdot$ kg$^{-1}$ lean body mass $\cdot$ min$^{-1}$, respectively ($P$ = NS by analysis of variance [ANOVA]). Therefore, for the purpose of our analysis, we pooled the GIR data obtained at the various insulin doses.

The sBP and dBP were measured using the standard blood pressure cuff (a large cuff was substituted if the arm circumference exceeded 33 cm) and auscultation of the Korotkoff sounds (appearance of sound = systolic; disappearance of sound = diastolic) every 10 min during the 30 min before the study.

Total body DXA scanning was performed at the Indiana University General Clinical Research Center on a Lunar DPX-L scanner (Lunar Radiation, Madison, WI). Such scans require $\sim$30 min and have a 2–3% precision for soft tissue assessments (27). The soft tissue assessments were the % fat, total grams of fat, and lean tissue mass. With this technique, subjects undergo a small total radiation exposure of 0.015–0.06 mrem dependent on the anteroposterior thickness of the subject. The DXA data obtained were further evaluated using the new Lunar 1.3V program, which allows the operator to determine specific body regions. The conventional DXA-derived body composition regions include the trunk and legs. The trunk region includes the chest and abdomen, excluding the pelvis. The leg region includes the entire hip, thigh, and leg. Using the Lunar 1.3V software program, two precise abdominal regions were defined: *1*) the top of L1 to the bottom of L4 (L1–4), and 2) the top of L3 to the bottom of L4 (L3–4). The conventional DXA body composition regions, the new DXA-derived body region cuts, and indirect anthropometric body fat distribution indices, such as BMI, waist, hip, and WHR, were then correlated with the carbohydrate and lipid parameters (Fig. 1).

### Analytical methods

Plasma glucose levels were measured by the glucose oxidase method with a YSI 2300 (Yellow Springs Instruments, Yellow Springs, OH). Insulin levels were determined by solid-phase 125I radioimmunoassay (Coat-A-Count; DPC, Los Angeles, CA). FFAs were measured according to the Novak's method (28). Total cholesterol and triglyceride were determined on a Kodak Ektachem 702 Analyzer with an enzymatic method (Eastman Kodak, Rochester, NY). HDL cholesterol levels were determined with the Magnetic HDL kit (Reference Diagnostics, Arlington, MA), and LDL cho-

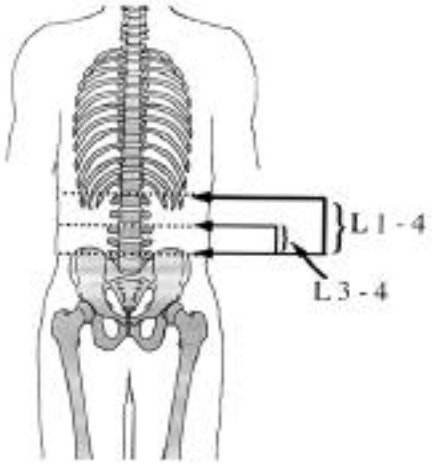


**Figure 1**—*Illustration of the areas of evaluation using the Lunar 1.3V program. Two abdominal regions were defined by body region cuts: 1) the top of L-1 to the bottom of L-4 (L1–4,and 2) the top of L-3 to the bottom of L-4 (L3–4).*

lesterol levels were calculated according to the Friedewald formula (29).

### Statistical methods

All of the analyses were performed in all subjects and in two subgroups of lean (percent of total-body fat = 26, $n$ = 63), and obese (percent of total-body fat >26, $n$ = 24). This criterion was chosen according to a cluster analysis that identified the percent body fat of 26 as the best cutoff to differentiate subjects in relation to their metabolic characteristics. When appropriate, data were tested for statistical significance using simple correlation, partial correlation, unpaired $t$ test, and ANOVA with Fisher's protected least differences. A stepwise multiple regression analysis was performed in all subjects and in the two subgroups to indicate which metabolic and fat distribution variables had an independent relation with GIR. The following variables were used: insulin area under the curve (AUC) (calculated by the trapezoidal rule), triglyceride, total cholesterol, HDL cholesterol, LDL cholesterol, sBP, dBP, mean arterial blood pressure, BMI, waist, hip, WHR, DXA total-body fat, trunk, leg, L1–4, and L3–4. $P < 0.05$ was accepted for significance. Data are given as means ± SD. Statistics were performed on a Power Macintosh computer with StatView 4.5 and SuperANOVA (Abacus Concepts, Berkeley, CA).

**Table 1**—*Anthropometric characteristics of the subjects*

| | All subjects | Lean | Obese |
|---|---|---|---|
| Age (years) | 34.4 ± 8.3 | 34.9 ± 8.5 | 32.8 ± 7.8 |
| Weight (kg) | 77.6 ± 11.3 | 73.6 ± 9.2 | 88.1 ± 9.5* |
| BMI | 24.9 ± 3.6 | 23.4 ± 2.6 | 28.9 ± 2.8* |
| Waist (cm) | 87.4 ± 9.1 | 84.4 ± 6.9 | 98.1 ± 7.8* |
| WHR† | 0.92 ± 0.08 | 0.91 ± 0.09 | 0.95 ± 0.05 |
| Fat | | | |
| Total body | | | |
| g | 17,160 ± 7,279 | 13,772 ± 4,584 | 26,056 ± 5,238* |
| % | 22.6 ± 6.9 | 19.3 ± 4.9 | 30.9 ± 3.9* |
| Trunk | | | |
| g | 7,749 ± 3,702 | 6,238 ± 2,389 | 11,715 ± 3,632* |
| % | 21.7 ± 7.2 | 18.6 ± 5.5 | 29.8 ± 3.9* |
| Leg | | | |
| g | 6,395 ± 2,523 | 5,264 ± 1,708 | 9,364 ± 1,798* |
| % | 23.9 ± 6.8 | 20.9 ± 4.8 | 31.9 ± 3.9* |
| L1–4 | | | |
| g | 2,150 ± 1,175 | 1,649 ± 788 | 3,466 ± 999* |
| % | 27.9 ± 10.4 | 23.5 ± 8.2 | 39.6 ± 5.3* |
| L3–4 | | | |
| g | 1,046 ± 629 | 803 ± 422 | 1,683 ± 641* |
| % | 29.6 ± 11 | 24.9 ± 8.9 | 41.9 ± 4.8* |

Data are means ± SD. *$P < 0.0001$ between lean and obese subjects. †$n$ = 51 and $n$ = 14 in lean and obese subjects, respectively.

**Table 2**—*Metabolic characteristics of the subjects*

| | All subjects | Lean | Obese |
|---|---|---|---|
| Fasting glucose (mg/dl) | 90.4 ± 10.5 | 89.3 ± 10.5 | 93.6 ± 9.7 |
| Glucose AUC 0–180 | 24,185 ± 3,425 | 23,575 ± 3,021 | 25,762 ± 3,945* |
| Fasting insulin (μU/ml) | 7.4 ± 5.6 | 6.6 ± 5.5 | 9.5 ± 5.5† |
| Insulin AUC 0–180 | 8,597 ± 5,276 | 7,263 ± 4,137 | 11,932 ± 6,349‡ |
| GIR (mg · kg$^{-1}$ lean body mass · min$^{-1}$) | 13.8 ± 2.8 | 14.3 ± 2.7 | 12.6 ± 2.8† |
| Triglyceride (mg/dl) | 146 ± 86 | 141 ± 92 | 157 ± 68 |
| Total cholesterol (mg/dl) | 178 ± 42 | 176 ± 42 | 181 ± 44 |
| HDL cholesterol (mg/dl)§ | 36 ± 10 | 37 ± 10 | 33 ± 8 |
| LDL cholesterol (mg/dl)§ | 105 ± 37 | 101 ± 35 | 113 ± 40 |
| FFA (mg/dl)‖ | 477 ± 184 | 446 ± 188 | 523 ± 175 |
| sBP (mmHg) | 119 ± 13 | 118 ± 13 | 122 ± 12 |
| dBP (mmHg) | 72 ± 8 | 72 ± 8 | 74 ± 8 |
| Mean arterial pressure (mmHg) | 88 ± 8 | 87 ± 8 | 90 ± 8 |

Data are means ± SD. *$P < 0.01$, †$P < 0.03$, and ‡$P < 0.0001$, between lean and obese subjects. §$n$ = 47 and $n$ = 21 in lean and obese subjects, respectively. ‖$n$ = 18 and $n$ = 12 in lean and obese subjects, respectively.

**RESULTS** — Anthropometric characteristics of lean and obese men are shown in Table 1. As expected, obese subjects had significantly greater morphological indices of fat deposition, both indirect and direct, compared with the lean group. However, compared with indirect measures, DXA indices exhibited greater differences between the two study groups. In particular, compared with the lean subjects, the proportion of fat at L1–4 and L3–4 cuts was ~40% higher in obese men ($P < 0.0001$), while differences in BMI and waist girth between lean and obese were only ~19 and ~14%, respectively ($P < 0.0001$).

Table 2 shows the metabolic features of the subjects. Compared with the obese group, lean men exhibited ~12% higher GIRs (14.3 vs. 12.6, $P < 0.03$), significantly lower fasting insulin levels, and lower insulin and glucose AUCs in response to an OGTT. Triglyceride, total cholesterol, as well as sBP and dBP were

**Table 3—*Relationships of indirect and direct body fat distribution measures with carbohydrate, lipid, and blood pressure patterns***

| | GIR | Insulin AUC | Triglyceride | Total cholesterol | HDL | LDL | FFA | sBP | dBP | MAP |
|---|---|---|---|---|---|---|---|---|---|---|
| Indirect fat distribution index | | | | | | | | | | |
| BMI | −0.394* | 0.476* | 0.226 † | 0.302‡ | −0.095 | 0.264† | 0.324 | 0.224† | 0.252† | 0.270‡ |
| Waist | −0.461* | 0.426§ | 0.309 ‡ | 0.294† | −0.056 | 0.198 | 0.271 | 0.338‖ | 0.347‖ | 0.384‖ |
| Hip | −0.300† | 0.295† | 0.235 | 0.081 | −0.095 | 0.129 | 0.256 | 0.338‡ | 0.200 | 0.290† |
| WHR | −0.269† | 0.212 | 0.103 | 0.296† | 0.029 | 0.177 | 0.179 | 0.064 | 0.205 | 0.162 |
| DXA fat distribution index | | | | | | | | | | |
| % Fat, total body | −0.413* | 0.496* | 0.190 | 0.228† | –0.074 | 0.268† | 0.280 | 0.245† | 0.392§ | 0.368§ |
| Fat | | | | | | | | | | |
| Total body | −0.431* | 0.519* | 0.178 | 0.201 | –0.051 | 0.210 | 0.316 | 0.263† | 0.379§ | 0.369§ |
| Trunk | −0.433* | 0.521* | 0.209 | 0.202 | –0.035 | 0.183 | 0.283 | 0.237† | 0.386§ | 0.360‖ |
| Leg | −0.373§ | 0.480* | −0.057 | 0.109 | −0.030 | 0.159 | 0.302 | 0.239† | 0.341‖ | 0.333‖ |
| L1–4 | −0.484* | 0.513* | 0.263† | 0.286‡ | −0.059 | 0.259† | 0.303 | 0.257† | 0.391§ | 0.374§ |
| L3–4 | −0.420* | 0.455* | 0.237† | 0.240† | −0.081 | 0.235 | 0.333 | 0.270† | 0.349‖ | 0.354‖ |

MAP, mean arterial pressure. *$P < 0.0001$, †$P < 0.05$, ‡$P < 0.01$, §$P < 0.0005$, ‖$P < 0.005$.

slightly, but not significantly, higher in obese men.

The simple linear correlations computed for all subjects between indirect measures of fat deposition, DXA indices of fat distribution, and the metabolic variables are given in Table 3. Among indirect measures, BMI was predictive of carbohydrate and lipid parameters, exhibiting significant correlations with all, except for HDL and FFA. Interestingly, however, waist girth displayed a stronger association with GIR, triglyceride, and blood pressure than BMI.

Among DXA-derived fat distribution indices, those reflecting a discreet area of central adiposity, such as fat mass at the L1–4 and L3–4 levels, presented a greater number of significant relationships with the various metabolic variables than other measures. In particular, fat mass at L1–4 correlated significantly with GIR (Fig. 2) and other parameters, but not with HDL and FFA. Interestingly, both fat mass at L1–4 and BMI exhibited significant relationships with similar metabolic parameters.

Because there were strong relationships between total-body fat and other DXA indices as well as with anthropometric measures, all of the univariate analyses were repeated after adjustment for this interaction to evaluate the independent contribution of each index of adiposity. After this correction, among indirect body fat distribution measures, BMI, waist, and WHR showed significant correlation only with plasma cholesterol ($r = 0.260$, $P < 0.05$; $r = 0.321$, $P < 0.01$; $r = 0.267$, $P < 0.05$, respectively) (Table 4). Similarly, most of the DXA-derived indices of regional body fat failed to exhibit significant relationships with the metabolic parameters (Table 4). Exceptions were observed for fat depots of the leg and at L1–4 level, where the former presented significant negative relationships with triglyceride and cholesterol ($r = −0.413$, $P < 0.0001$, and $r = −0.309$, $P < 0.005$, respectively), and the latter correlated with GIR, triglyceride, and cholesterol ($r = −0.267$, $P < 0.05$; $r = 0.316$, $P < 0.005$; $r = 0.319$, $P < 0.005$, respectively). Thus, these findings suggest that the DXA index representing abdominal fat at the level of L1–4 has the best independent predictive value for cardiovascular factors such as insulin sensitivity, triglyceride, and cholesterol. Moreover, the data indicate that a relatively high amount of leg fat seems to be beneficial for the levels of triglyceride and cholesterol. When the same analyses were computed separately in lean and obese groups, we were unable to observe significant differences between lean men compared with the whole group (lean plus obese). In the lean group, fat at L1–4 level was still the most representative of the metabolic variables, showing significant correlations with GIR, triglyceride, total cholesterol, and LDL ($r = −0.346$, $P < 0.005$; $r = 0.314$, $P < 0.01$; $r = 0.379$, $P < 0.005$ and $r = 0.335$, $P < 0.05$, respectively). Among anthropometric measures, waist and WHR exhibited significant correlations with cholesterol ($r = 0.336$, $P < 0.05$, and $r = 0.359$, $P < 0.05$, respectively). In contrast, in the obese group, only BMI and the amount of leg fat showed significant correlation with triglyceride and

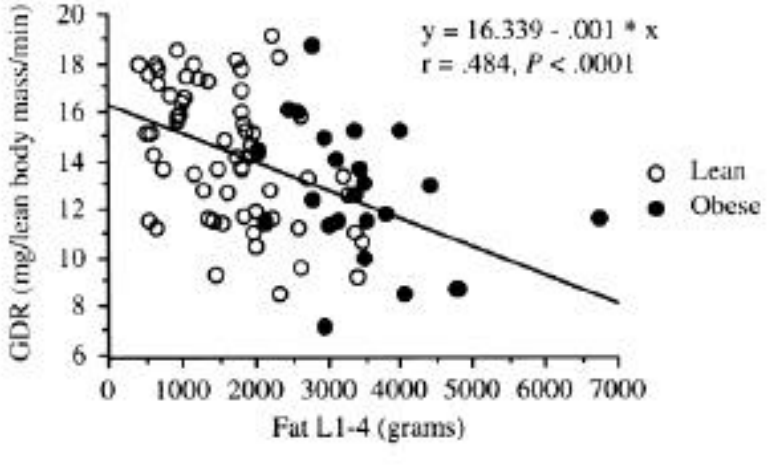


**Figure 2—***Relationships between GIR (mg · kg$^{-1}$ lean body mass · min$^{-1}$) and fat mass at level L1–4 in lean and obese subjects.*

**Table 4—*Relationships of indirect and direct body fat distribution measures with carbohydrate, lipid, and blood pressure patterns after correction for total-body fat mass***

| | GIR (mg · kg$^{-1}$ FFM · min$^{-1}$) | Insulin AUC | Triglyceride | Total cholesterol | HDL | LDL | FFA | sBP | dBP | MAP |
|---|---|---|---|---|---|---|---|---|---|---|
| Indirect fat distribution index | | | | | | | | | | |
| BMI | −0.050 | 0.064 | 0.146 | 0.260* | −0.111 | 0.175 | 0.092 | −0.007 | −0.159 | −0.101 |
| Waist | −0.204 | 0.099 | 0.197 | 0.321† | 0.160 | 0.269 | −0.192 | 0.073 | 0.103 | 0.103 |
| Hip | −0.002 | −0.029 | 0.093 | −0.036 | −0.095 | 0.110 | −0.082 | 0.134 | −0.064 | 0.024 |
| WHR | −0.184 | 0.122 | 0.043 | 0.267* | 0.108 | 0.159 | −0.131 | −0.028 | 0.129 | 0.070 |
| DXA fat distribution index | | | | | | | | | | |
| Fat | | | | | | | | | | |
| Trunk | −0.120 | 0.114 | 0.127 | 0.041 | 0.038 | −0.043 | −0.014 | −0.034 | 0.095 | 0.041 |
| Leg | 0.164 | −0.073 | −0.413‡ | −0.309§ | 0.077 | −0.180 | −0.013 | −0.052 | −0.088 | −0.082 |
| L1–4 | −0.267* | 0.074 | 0.316§ | 0.319§ | −0.034 | 0.213 | −0.014 | 0.021 | 0.108 | 0.078 |
| L3–4 | −0.093 | 0.004 | 0.172 | 0.136 | −0.076 | 0.107 | 0.112 | 0.083 | 0.035 | 0.066 |

FFM, fat-free mass; MAP, mean arterial pressure. *$P < 0.05$, †$P < 0.01$, ‡$P < 0.0001$, §$P < 0.005$.

cholesterol ($r = 0.438$, $P < 0.05$; $r = 0.458$, $P < 0.05$; $r = -0.439$, $P < 0.05$; and $r = -0.414$, $P < 0.05$, respectively). Interestingly, in this group, none of the central fat deposition indices, either direct or indirect, presented significant independent relationships with the metabolic parameters.

The results of a stepwise multiple regression analysis revealed that ~47% of the variance in GIR in all study subjects was predicted by insulin area, fat L1–4, dBP, HDL cholesterol, and triglyceride as independent variables (Table 5). Analyzing the lean group separately, we observed that fat at L1–4 was the first variable accepted in the model, which alone accounted for ~33% of the variance in GIR (Table 5). In contrast, in obese men, insulin AUC was the first variable accepted in the model, being able to explain 46% of the variance in GIR value. HDL, dBP, and fat L1–4 together accounted for an additional 26% of GIR variance. The indirect measures of fat deposition did not contribute to the regression model in either lean or obese groups.

**CONCLUSIONS** — The central distribution of body fat has been identified as a significant risk factor for the development of cardiovascular disease (1,9,10,30). Understanding the link between topographic features of adipose tissue and the various parameters of the metabolic syndrome in lean and obese healthy subjects is critical for the development of management strategies to prevent macrovascular complications. DXA scanning as a method of quantitating abdominal fat mass has been criticized because it does not differentiate IAFM versus SCFM in contrast to techniques like CT and MRI (31,32). However, the usefulness of this differentiation in predicting insulin resistance has been recently questioned (22–24). Therefore, increased interest in the use of DXA to evaluate specific body fat depots has arisen, in particular because the technique is more readily accessible, inexpensive, and rapid than CT or MRI techniques. The purpose of this study was to determine *1*) whether DXA is useful for predicting various parameters of the metabolic syndrome, and, if so, *2*) what are the DXA-derived indices of fat mass distribution that correlate best with the parameters of the metabolic syndrome.

We found, in a large group of men, that DXA-determined cross-sectional evaluation of body fat at the level of L1–4 provided the best predictive index of insulin resistance and other relevant cardiovascular risk factors, independent of total-body fat mass. It is noteworthy that, although classic indirect indices of fat distribution and the other DXA-derived body composition regions exhibited significant relationships with several parameters of the metabolic syndrome, they failed to show the same correlations after correction for total-body fat mass. While the reason that the abdominal fat of L1–4 was the most representative index of various parameters of the metabolic syndrome is not clear, it is likely that at this abdominal level, the cumulative cross-sectional mass is largely represented by peritoneal, subcutaneous, and retroperitoneal fat, with solid organs and bone being relatively less important.

Consistently, we found that the indirect anthropometric measure of waist girth exhibited the strongest correlations with most of the metabolic parameters studied. However, as already mentioned, the value of this simple anthropometric measure in explaining the metabolic variables was somewhat lower after adjustment for total-fat mass. Thus, although waist girth represents a useful marker of obesity-associated cardiovascular risk factors, total adipose mass at L1–4 exhibited a better independent power in predicting the various metabolic parameters. Our findings are consistent with a study of normal and overweight women by Carey et al. (33), who were able to find a relationship between DXA-derived central abdominal fat (measured at L2–4 level, excluding ~30% of the subcutaneous fat) and whole-body insulin sensitivity.

**Table 5—*Multiple regression analysis for estimations of insulin resistance by euglycemic-hyperinsulinemic clamp in all subjects***

| | Regression coefficients | $R^2$ | $P$ |
|---|---|---|---|
| Independent variables | | | |
| Insulin AUC | −2.064E-4 | 0.328 | <0.0001 |
| Fat L1–4 | −0.001 | 0.412 | <0.0001 |
| dBP | −0.082 | 0.442 | <0.0001 |
| HDL | 0.045 | 0.454 | <0.0001 |
| Triglyceride | 0.007 | 0.475 | <0.0001 |
| Intercept | 21.605 | | |

Data are for all subjects (lean and obese), $n = 64$. $R^2$ for estimations is adjusted $R^2$.

**Table 6—*Multiple regression analysis for estimations of insulin resistance by euglycemic-hyperinsulinemic clamp in lean subjects***

| | Regression coefficients | $R^2$ | *P* |
|---|---|---|---|
| Independent variables | | | |
| Fat L1–4 | −0.002 | 0.333 | <0.0001 |
| HDL | 0.095 | 0.377 | <0.0001 |
| Triglyceride | 0.010 | 0.403 | <0.0001 |
| Insulin AUC | −1.677E-4 | 0.440 | <0.0001 |
| Intercept | 14.161 | | |

$n$ = 43 for lean subjects. $R^2$ for estimations is adjusted $R^2$.

Interestingly, while L1–4 was the better predictor of the metabolic syndrome variables in the lean group (significant correlation with GIR, triglyceride, total cholesterol, and LDL cholesterol), we did not observe similar results in obese subjects. In this group, only BMI and adipose mass of the leg exhibited significant relationships with triglyceride and cholesterol. While it is possible that a lack of significance of some of the correlations between fat distribution indices and metabolic variables could be due to a relatively small sample size, it is noteworthy that the amount of adipose tissue of leg, adjusted for total adiposity, showed negative relationships with triglyceride and cholesterol. A recent study found similar results showing significant inverse correlations between femoral adipose tissue (CT determined) to triglyceride in obese men, but not in lean men (17). Thus, this result seems to confirm that in obese men, a relatively high depot of fat at the femoral level may protect against the adverse effects of increased adiposity.

**Table 7—*Multiple regression analysis of insulin resistance by euglycemic-hyperinsu - linemic clamp in obese subjects***

| | Regression coefficients | $R^2$ | *P* |
|---|---|---|---|
| Independent variables | | | |
| Insulin AUC | −2.611E-4 | 0.462 | <0.0004 |
| dBP | −0.169 | 0.684 | <0.0001 |
| HDL | 0.062 | 0.700 | <0.0001 |
| Fat L1–4 | −1.163E-4 | 0.721 | <0.0001 |
| Intercept | 26.211 | | |

$n$ = 21 for obese subjects. $R^2$ for estimations is adjusted $R^2$.

Because clamps were performed in this study at varying insulin concentrations (as addressed in METHODS), we were concerned that a potential source of bias was introduced into the analysis. While maximal insulin-mediated GIRs were achieved in lean subjects at an insulin infusion rate of 120 mU · $m^{-2}$ · $min^{-1}$, it is possible that among obese subjects, only those studied at the higher insulin dose of 600 mU · $m^{-2}$ · $min^{-1}$ achieved maximal insulin-mediated glucose infusion. Thus, it is conceivable that within this group, subjects with different amounts of adipose tissue at L1–4 level could exhibit different GIRs because they were clamped at different insulin doses rather than reflecting true differences in insulin responsiveness. If this scenario is true (i.e., if obese subjects had lower than true maximal GIRs), we would have expected to observe a highly significant inverse relationship between GIR and fat at L1–4 as well as between GIR and percent total body fat. In other words, this relationship would be artificially strengthened by underestimating the GIR in the fatter subjects. However, we found that GIR was, in fact, not significantly correlated with percent of total body fat, suggesting that if GIR was underestimated in obese subjects studied at the lower insulin infusion rate, this underestimate was too small to introduce any major bias into our analysis.

To better discriminate the independent contribution of DXA-derived body fat distribution measures in predicting insulin sensitivity, we used stepwise multivariate regression. When lean and obese groups were analyzed together, the best index of fat distribution chosen by the model was the fat mass at L1–4, which, with insulin area, accounted for 41% of variance in insulin sensitivity (Table 5). This finding is particularly relevant because it provides evidence that in healthy men, central fat distribution is a more potent independent predictor of insulin sensitivity than lipid parameters or blood pressure. Because none of the indirect body composition indices was accepted in the regression, this finding also supports the assumption that BMI and waist and hip girth are relatively weak parameters for the evaluation of insulin sensitivity (33).

Given that overall obesity is associated with insulin resistance (34), we performed separate multivariate regression analyses in both lean and obese groups (Tables 6 and 7). Conforming to the above statement, in obese subjects, the contribution of fat at L1–4 to explain the variance of insulin sensitivity was very little (~2%). In contrast, in lean men, fat at L1–4 alone accounted for ~33% of the insulin sensitivity, suggesting that central fat distribution could account for the wide variation in insulin sensitivity exhibited by lean subjects (35). These findings are consistent with results from previous studies indicating that once a determined threshold value of obesity is achieved (i.e., BMI = 30 $kg/m^2$), the contribution of central fat mass per se is a relatively weak element of variance of insulin sensitivity (36–38). Thus, in these subjects, other variables, such as insulin AUC and blood pressure, are more useful to predict insulin sensitivity.

Increased triglyceride and low HDL cholesterol circulating concentrations are considered essential features of the metabolic syndrome. However, in our hands, their independent ability to predict insulin sensitivity across all subjects (lean and obese) was marginal compared with insulin area, body fat distribution, and dBP. The reason for this is not completely clear, but much evidence indicates that the relationship between insulin resistance to triglyceride and HDL is mediated, at least in part, by compensatory hyperinsulinemia (39,40). Therefore, it is possible that because the study patients were euglycemic with normal insulin levels, the inclusion of insulin area in the regression might reduce the value of triglyceride and HDL in predicting insulin resistance.

In summary, the results of the present work suggest that central fat distribution measured with the DXA technique is a useful marker of insulin sensitivity in healthy subjects. Specifically, in lean men, fat mass at L1–4 is a strong predictor of insulin sensitivity, independent of other parameters of the metabolic syndrome. Whether differentiating subcutaneous from intra-abdominal fat depots is particularly advantageous in predicting cardiovascular risk factors cannot be determined by the current study. Nevertheless, the data presented indicate that a simple total abdominal measurement of fat mass is highly predictive of such risk factors and may be equally as effective as measuring intra-abdominal fat depots. Therefore, this method can represent a useful, readily available, and valid alternative to other techniques with which to further study the complex relationships between body fat distribution and cardiovascular risk factors.

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