Association Between Regional Adipose Tissue Distribution and Both Type 2 Diabetes and Impaired Glucose Tolerance in Elderly Men and Women

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OBJECTIVE — We examined whether regional adipose tissue distribution, specifically that of skeletal muscle fat and visceral abdominal fat aggregation, is characteristic of elderly individuals with hyperinsulinemia, type 2 diabetes, and impaired glucose tolerance (IGT).

RESEARCH DESIGN AND METHODS — A total of 2,964 elderly men and women (mean age 73.6 years) were recruited for cross-sectional comparisons of diabetes or glucose tolerance, generalized obesity with dual-energy X-ray absorptiometry, and regional body fat distribution with computed tomography.

RESULTS — Approximately one-third of men with type 2 diabetes and less than half of women with type 2 diabetes were obese (BMI $\geq$30 kg/m^2). Despite similar amounts of subcutaneous thigh fat, intermuscular fat was higher in subjects with type 2 diabetes and IGT than in subjects with normal glucose tolerance (NGT) (11.2 $\pm$ 9.4, 10.3 $\pm$ 5.8, and 9.2 $\pm$ 5.9 cm^2 for men; 12.1 $\pm$ 6.1, 10.9 $\pm$ 6.5, and 9.4 $\pm$ 5.3 cm^2 for women; both $P < 0.0001$). Visceral abdominal fat was also higher in men and women with type 2 diabetes and IGT than in subjects with NGT (172 $\pm$ 79, 163 $\pm$ 72, and 145 $\pm$ 66 cm^2 for men; 162 $\pm$ 66, 141 $\pm$ 60, and 116 $\pm$ 54 cm^2 for women; both $P < 0.0001$ across groups). Higher rates of intermuscular fat and visceral abdominal fat were associated with higher fasting insulin in normal-weight (BMI <25 kg/m^2) men ($r = 0.24$ for intermuscular fat, $r = 0.37$ for visceral abdominal fat, both $P < 0.0001$) and women ($r = 0.20$ for intermuscular fat, $r = 0.40$ for visceral abdominal fat, both $P < 0.0001$). These associations were not found in obese subjects.

CONCLUSIONS — Elderly men and women with normal body weight may be at risk for metabolic abnormalities, including type 2 diabetes, if they possess an inordinate amount of muscle fat or visceral abdominal fat.

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In middle-aged adults, obesity is associated with impaired glucose tolerance (IGT) and insulin resistance, two hallmark characteristics of type 2 diabetes (1). However, it is unclear whether obesity is as potent a determinant of insulin resistance or type 2 diabetes in elderly men and women. Although the prevalence of type 2 diabetes is highest among men and women >65 years of age (2,3), the prevalence of obesity in this age-group is only 14% compared with 24% for men and women in their fifties (4). It appears then that, in elderly individuals, there might be some dissociation between obesity and the risk for insulin resistance and type 2 diabetes. However, to effectively address this hypothesis, a careful appraisal of body composition should be made, taking into account not simply weight as reflective of obesity but also considerations of regional adipose tissue (AT) distribution.

Obesity is not the only hallmark of insulin resistance. Indeed, some younger normal-weight individuals may be at increased risk for the metabolic syndrome of insulin resistance and cardiovascular disease (5,6). Ruderman et al. (7) first described a metabolic obese phenotype in normal-weight young adults and suggested that accrual of central or abdominal obesity, despite a normal body weight, was a powerful influence on insulin resistance in these individuals (8). Parallel findings in elderly men and women have not been reported.

There are several regional body composition changes associated with aging that might increase the risk for type 2 diabetes or insulin resistance and that bear resemblance to the normal-weight "metabolically obese" syndrome described above. Indeed, elderly individuals tend to accumulate excess abdominal or visceral fat (9–12). Another aspect may be the age-related loss of muscle mass, i.e., sarcopenia (13), or possibly an increase in the AT within muscle. The absolute

amount of thigh muscle is not related to insulin resistance in middle-aged obese men and women (14). However, skeletal muscle in obesity is characterized by a reduced attenuation on computed tomography (CT) (15), which is a marker of muscle lipid content (16), and is associated with skeletal muscle insulin resistance independent of total or abdominal adiposity (14). Moreover, although it has previously been thought that AT deposition in the lower extremities is not related to metabolic dysregulation (17), more recent evidence suggests that accumulation of lipids within the fascia surrounding skeletal muscle is related to insulin resistance and may contribute to the risk of type 2 diabetes (18). Therefore, using baseline data from the large-scale longitudinal Health, Aging and Body Composition (Health ABC) study, we hypothesized that elderly men and women with type 2 diabetes or IGT can be characterized by excess muscle fat or abdominal fat accumulation. Furthermore, we posited that even in normal-weight elderly men and women, the accumulation of muscle fat or visceral abdominal fat is related to fasting hyperinsulinemia as a marker of insulin resistance. Examining the influence of regional fat distribution on hyperinsulinemia in normal-weight as well as in overweight elderly men and women may help define important risk factors for the development of the metabolic syndrome and type 2 diabetes in old age.

RESEARCH DESIGN AND METHODS

— Participants in this study had completed baseline studies of Health ABC cohort, a longitudinal study of 3,075 nondisabled men and women aged 70–79 years residing in Pittsburgh, Pennsylvania, and Memphis, Tennessee. The population was 48.5% male and 58.3% white and had a mean age of 73.6 years. Participants were recruited primarily from a random sample of Medicare-eligible adults over age 65 years from a list provided by the Health Care Financing Administration. Individuals were ineligible if they reported difficulty getting around without assistive devices, reported difficulty performing basic activities of daily living, reported difficulty walking one-quarter mile or climbing 10 steps without resting, reported life-threatening cancers, were not planning to remain in the study area for at least 3 years, or were participating in any research study involving medications or modification of eating or exercise habits. The study was approved by the Universities of Pittsburgh and Tennessee Institutional Review Boards, and written informed consent was obtained from each volunteer.

To determine whether a participant had type 2 diabetes, they completed an in-home interview during which they were asked, "Has a doctor ever told you that you have diabetes or sugar diabetes?" Women were asked not to include diabetes that occurred only during pregnancy. Those who answered "yes" to this question and those with medication inventory data showing use of exogenous insulin or oral hypoglycemic medications were categorized as "diagnosed diabetes." Participants were considered to have type 2 diabetes if they were diagnosed as having type 2 diabetes, if they had a fasting blood glucose during their baseline clinic visit ≥126 mg/dl, or if their 2-h glucose level during an oral glucose tolerance test (OGTT) was ≥200 mg/dl. Among participants without type 2 diabetes, those with a 2-h glucose level >140 mg/dl during the OGTT were classified as having IGT. All other participants were categorized as having normal glucose tolerance (NGT). Of the 3,075 volunteers in the Health ABC study, 2,964 had CT measurements done at baseline and were included in this study.

Age of participants was determined to the nearest year. Standing height and weight were measured on each volunteer, and a BMI was calculated as weight (kg)/ height (m^2). Total body fat was determined using dual-energy X-ray absorptiometry (DEXA) (Hologic QDR 4500, Waltham, MA).

OGTT and fasting insulin

An OGTT was administered only in subjects without diagnosed type 2 diabetes. After an overnight fast, at ~0900, subjects had blood drawn for glucose and insulin determinations. Immediately following, they ingested 75 g glucose in solution (glucola), and an additional blood sample was drawn 2 h later. Plasma glucose was measured using an automated glucose oxidase reaction (YSI 2300 Glucose Analyzer; Yellow Springs Instruments, Yellow Springs, OH). Serum insulin was determined using a commercially available radioimmunoassay kit (Pharmacia, Uppsala, Sweden).

CT of the mid-thigh

An axial CT scan at the mid-thigh level was obtained on each participant during the first examination of the Health ABC protocol. CT images were acquired either in Pittsburgh (9800 Advantage; General Electric, Milwaukee, WI) or Memphis (Somatom Plus [Siemens, Iselin, NJ] or PQ 2000S [Picker, Cleveland, OH]). Skeletal muscle and AT areas of the thigh were calculated from the axial CT images using proprietary IDL development software (RSI Systems, Boulder, CO). This measurement was done on the right leg unless otherwise indicated. Mean muscle attenuation values were determined by averaging the CT number (pixel intensity) values of the regions outlined on the images. CT numbers were defined on a Hounsfield unit (HU) scale where 0 equals the HU of water and −1,000 equals the HU of air. Skeletal muscle and AT areas were distinguished by a bimodal image histogram resulting from the distribution of CT numbers in AT tissues (−190 to −30 HU) and muscle (0 to 100 HU) (19). These peaks are readily separable on CT (18).

The AT interspersed between muscle, termed intermuscular AT, was distinguished from the subcutaneous AT by manually drawing a line along the deep fascial plane surrounding the thigh muscles. Once the AT was segmented from the images, the individual muscles were identified. These borders were outlined manually, ensuring that no bone density pixels were included in the muscle.

CT of the abdomen

To quantify abdominal AT, axial CT scans at the L4–L5 disk space were obtained based on a lateral abdominal scout and a single-axial image at L4–L5 as previously described (14).

Statistical analysis

Differences in clinical characteristics and body composition in men and women with NGT, IGT, and type 2 diabetes were analyzed using one-way ANOVA. Another hypothesis was that regional adiposity had an influence on insulin resistance in both normal-weight and obese men and women. Therefore, we used linear regression analysis to determine whether any of the regional fat de-

Table 1—*Descriptive characteristics of subjects with NGT, IGT, and type 2 diabetes*

	NGT	IGT	Type 2 diabetes	*P*
Men				
n	815	235	397	—
% White	59.3	16.8	23.9	0.001
Age (years)	73.7 ± 2.9	73.8 ± 2.9	73.9 ± 2.8	0.56
Weight (kg)	80 ± 12.5	81.8 ± 14.3	84.5 ± 14.1	0.0001
BMI (kg/m^2)	26.5 ± 3.7	27.5 ± 4.2*	28.1 ± 4.1†	0.0001
% Body fat	24.8 ± 5.2	26.0 ± 5.5*	26.1 ± 5.2†	0.0001
Women				
n	823	365	329	—
% White	59.5	25.1	15.4	0.001
Age (years)	73.4 ± 2.9	73.7 ± 2.9	73.5 ± 2.8	0.14
Weight (kg)	68.4 ± 14.0	71.3 ± 15.2	76.1 ± 14.9	0.0001
BMI (kg/m^2)	26.7 ± 5.1	28.2 ± 5.8*	30.0 ± 5.6†‡	0.0001
% Body fat	36.6 ± 6.1	38.2 ± 6.1*	37.9 ± 5.6†	0.0001

Data are means ± SD. *P* values reflect differences across the three groups determined by ANOVA. % Body fat determined by whole-body DEXA. A multiple comparison procedure was performed using a Bonferoni correction to determine specific group differences in BMI and % body fat. *P* values <0.016 are considered significant in multiple comparisons; *NGT vs. IGT, †NGT vs. type 2 diabetes, ‡IGT vs. type 2 diabetes.

pots were associated with fasting insulin or glucose tolerance within each sex, stratifying by BMI groups. In these race-adjusted analyses, subjects with type 2 diabetes were excluded on the basis of the lack of fasting insulin or 2-h glucose data for this group (see RESEARCH DESIGN AND METHODS). The stratified analyses demonstrated an interaction between visceral abdominal fat and BMI or total body fat (by DEXA) and between intermuscular fat and BMI or total body fat. Tests for interaction were significant (*P* < 0.01). The results were similar for BMI and total fat strata; thus, we elected to present the BMI strata for ease of interpretation. All analyses were performed using SAS 6.12 for Windows (SAS, Cary, NC).

RESULTS

Subject characteristics

The majority (55%) of subjects were classified as having NGT, whereas 21% were classified as having IGT and 24% as having type 2 diabetes (Table 1). The proportion of type 2 diabetes was higher in African-American men and women. Because of the narrow age range studied, age was similar among the three groups. Type 2 diabetic men and women were heavier and had a higher BMI than men and women with IGT or NGT. However, the differences in BMI across the three groups were only modest (Table 1), and the proportion of total body fat, also shown in

Table 1, was not different between men and women with IGT and type 2 diabetes and only modestly higher in those with NGT. Despite having a higher proportion of body fat, the mean BMI in women was similar to that in men.

Given the apparent lack of dramatic differences in BMI or percent body fat among the three groups, the proportion of normal-weight (BMI <25.0 kg/m^2), overweight (BMI 25.0–29.9 kg/m^2), and obese (BMI >29.9 kg/m^2) subjects with type 2 diabetes, IGT, or NGT was determined. The prevalence of diabetes was higher among obese subjects than among overweight or normal-weight subjects, with 39% of obese men and 34% of obese women having type 2 diabetes. It was notable, however, that 22% of normal-weight men and 12% of normal-weight women had type 2 diabetes, and another 14% of normal-weight men and 22% of normal-weight women had IGT. Thus, approximately one-third of normal-weight men and women had a combined prevalence of type 2 diabetes and IGT. Another perspective was that 24% of men with type 2 diabetes were normal weight and an additional 44% of men with type 2 diabetes were overweight, indicating that approximately two-thirds of men with type 2 diabetes were not obese. A similar pattern emerged for women; 18% of women with type 2 diabetes were normal weight and another 34% of women with type 2 diabetes were overweight. This suggests that obesity, per se, is not requisite for diabetes or glucose intolerance in elderly men and women.

The metabolic profiles of the study groups are presented in Table 2. Men and women with type 2 diabetes had fasting hyperglycemia compared with nondiabetic subjects. Fasting glucose was also higher in men and women with IGT than in subjects with NGT. The HbA$_{1c}$ and 2-h glucose values followed similar patterns.

Skeletal muscle composition

Skeletal muscle composition determined by CT, including the muscle area attenuation characteristics as a marker of muscle

Table 2—*Markers of insulin resistance and glucose tolerance in subjects with NGT, IGT, and type 2 diabetes*

	NGT	IGT	Type 2 diabetes	*P*
Men				
n	815	235	397	—
Fasting glucose (mg/dl)	92.8 ± 8.7	99.1 ± 10.2	146.9 ± 53.7	0.0001
Fasting insulin (pmol/l)	7.55 ± 4.8	9.1 ± 5.6	—	0.0001
2-h glucose (mg/dl)	103.7 ± 21.1	161.8 ± 15.7	—	0.0001
HbA$_{1c}$ (%)	5.9 ± 0.52	6.1 ± 0.6	7.6 ± 1.5	0.0001
Women				
n	823	365	329	—
Fasting glucose (mg/dl)	89.8 ± 8.5	94.6 ± 9.8	146.9 ± 55.1	0.0001
Fasting insulin (pmol/l)	7.5 ± 4.4	9.2 ± 6.0	—	0.0001
2-h glucose (mg/dl)	106 ± 20.8	161.8 ± 16	—	0.0001
HbA$_{1c}$ (%)	5.9 ± 0.5	6.0 ± 0.6	7.6 ± 1.6	0.0001

Data are means ± SD. *P* values reflect differences across the three groups determined by ANOVA. Data for fasting insulin and 2-h glucose are not reported in subjects with type 2 diabetes (see RESEARCH DESIGN AND METHODS).

Table 3—*Mid-thigh muscle attenuation and distribution of AT in subjects with NGT, IGT, and type 2 diabetes*

	NGT	IGT	Type 2 diabetes	*P*
Men				
n	815	235	397	—
Muscle area (cm²)	131.2 ± 21.5	134.3 ± 23.5	135.5 ± 23.5†	0.01
Muscle attenuation (HU)	38.0 ± 6.2	36.5 ± 6.7*	36.8 ± 6.6	0.003
Mid-thigh AT (cm²)				
Subcutaneous	46.8 ± 20.0	50.3 ± 22.5	46.8 ± 19.6	0.06
Intermuscular	9.21 ± 5.9	10.3 ± 5.8*	11.2 ± 9.4†	0.0001
Abdominal AT (cm²)				
Visceral	144.9 ± 65.9	163.0 ± 72.5*	172.2 ± 79†	0.0001
Subcutaneous	221.2 ± 87.1	244.6 ± 94.1*	245.7 ± 93.8†	0.0001
Women				
n	823	365	329	
Muscle area (cm²)	90.2 ± 16.6	93.7 ± 17.6*	99.8 ± 23.5†‡	0.0001
Muscle attenuation (HU)	34.7 ± 6.5	33.7 ± 7.2	33.0 ± 7.2†	0.02
Mid-thigh AT (cm²)				
Subcutaneous	104.0 ± 44.6	110.6 ± 52.1	107.7 ± 45.2	0.32
Intermuscular	9.4 ± 5.3	10.9 ± 6.5*	12.1 ± 6.1†‡	0.0001
Abdominal AT (cm²)				
Visceral	116.1 ± 54	140.8 ± 60.3*	162.2 ± 65.5†‡	0.0001
Subcutaneous	322.4 ± 120.4	345.6 ± 135.4*	370.0 ± 127†	0.0001

Data are means ± SD. Overall *P* values reflect differences across the three groups determined by ANOVA. A multiple comparison procedure was performed using a Bonferoni correction to determine specific group differences in the various regional fat distribution characteristics. *P* values <0.016 are considered significant in multiple comparisons; *NGT vs. IGT, †NGT vs. type 2 diabetes, ‡IGT vs. type 2 diabetes. The Kruskal-Wallis test with χ^2 approximation, a nonparametric one-way ANOVA by ranks, was used in the case of data that were not normally distributed.

fat content, the cross-sectional areas of mid-thigh muscle fat infiltration, intermuscular thigh AT, and the area of AT surrounding the muscle (or subcutaneous AT) is presented in Table 3. The size (area) of the mid-thigh muscle was not different between men with IGT and men with type 2 diabetes, although the size of the muscle was slightly smaller in men with NGT (Table 3). Muscle area was greater in type 2 diabetic women than in women with IGT and NGT and was greater in women with IGT than in women with NGT. The mean attenuation coefficient of mid-thigh skeletal muscle was lower (*P* < 0.01) in men and women with IGT and type 2 diabetes than in subjects with NGT (Table 3), differences reflective of a greater muscle lipid content in subjects with IGT and type 2 diabetes (16). Men and women with IGT and type 2 diabetes also had more fat interspersed within muscle measured as AT visible beneath the fascia lata. Moreover, these differences in intermuscular fat among the NGT, IGT, and type 2 diabetic groups remained significant after adjusting for percent body fat. However, there was a

similar amount of subcutaneous thigh AT as well as total thigh fat among the three groups. Thus, the composition of the mid-thigh was different with respect to IGT and type 2 diabetes. Overall, subjects with IGT and type 2 diabetes had similar amounts of subcutaneous AT and slightly greater amounts of muscle tissue. However, their muscle composition reflected greater muscle lipid content and a greater amount of AT located beneath the muscle fascia.

Abdominal fat

Abdominal AT areas in men and women with NGT, IGT, and type 2 diabetes are also presented in Table 3. Visceral and subcutaneous abdominal AT areas were both higher in men and women with IGT and type 2 diabetes (Table 3). The proportion of total abdominal AT comprised of visceral AT was remarkably similar across the groups. For men, the proportion of visceral AT was 40–41% across the three groups. Although this proportion was consistently lower in women, it was similar in women with NGT and IGT (26%), albeit slightly higher in women

with type 2 diabetes (30%). Interestingly, men with NGT had ~25% more visceral AT than women with NGT, but visceral AT in type 2 diabetic men was only 7% higher than that in type 2 diabetic women. Consistent with the findings for intermuscular fat, differences in visceral fat among these three groups of glucose tolerance or diabetes status remained different after adjusting for the proportion of total body fat.

**Associations between body fat depots and fasting insulin and glucose tolerance**

Across the entire cohort, omitting participants with known type 2 diabetes, there were positive associations between total body fat and fasting insulin in men (*r* = 0.49) and women (*r* = 0.47) and between total body fat and 2-h glucose values in men (*r* = 0.16) and women (*r* = 0.16), after adjusting for age and race (all *P* < 0.01). In addition, there were significant associations between regional AT depots and fasting insulin that had intriguing interactions with obesity, or lack thereof. To determine whether fat distribution was related to insulin resistance in normal-weight individuals, the associations of regional body fat depots measured by CT with fasting insulin and glucose tolerance were examined separately in normal-weight (BMI 15.0–24.9 kg/m²), overweight (BMI 25.0–29.9 kg/m²), and obese (BMI >29.9 kg/m²) men and women (Fig. 1), adjusting for race.

Men and women with type 2 diabetes were excluded from the regression analyses because of the potentially confounding influence of exogenous insulin or other oral antidiabetic medication, which may spuriously increase fasting insulin levels. Subjects with NGT and IGT were combined in these race-adjusted multivariate models so that relationships between body composition and fasting insulin, a marker of insulin resistance, could be examined in normal-weight, overweight, and obese subjects. Figure 1 illustrates the relative magnitude of these associations by the standardized β coefficients for each fat depot stratified by BMI groups. In normal-weight men and women, intermuscular thigh fat and both compartments of abdominal fat were positively associated with fasting insulin, and subcutaneous thigh fat was also positively correlated with fasting insulin, but only in normal-weight men. Interestingly, except

for visceral fat, there was no association between any of these fat depots and fasting insulin in men and women with a BMI >29.9 kg/m^2. Apart from the apparently greater magnitude for the association between visceral fat and fasting insulin than that for intermuscular thigh fat in normal-weight subjects, the other remarkable observation was that the association between intermuscular thigh fat and fasting insulin was more robust than for subcutaneous thigh fat. The scatterplots in Fig. 2 also demonstrate the relative strength of the associations of intermuscular thigh fat and visceral fat with fasting insulin. The associations between both of these fat depots and fasting insulin are clearly weaker in the highest BMI groups despite their higher range of values for intermuscular and visceral fat. A race interaction was found between subcutaneous abdominal fat and fasting insulin only in overweight men; white men had higher fasting insulin values after adjusting for abdominal subcutaneous fat. No other interactions of any other body composition characteristics with race were observed in association with fasting insulin. Similar associations were observed among subjects with the highest proportion of body fat determined by DEXA.

The 2-h glucose concentrations after an oral glucose challenge were significantly correlated with intermuscular fat, muscle attenuation, and visceral fat in women within the lowest BMI strata but not in the lowest BMI strata of men (data not shown). Notably, in men within the highest BMI strata, none of the body fat depots were related to 2-h glucose concentration, whereas in the highest BMI category for women, only visceral fat was associated with this measure of glucose tolerance. Among the overweight women, white women had higher 2-h glucose values than black women, even after adjusting for subcutaneous thigh fat, subcutaneous abdominal fat, and total body fat.

CONCLUSIONS — Although the prevalence of type 2 diabetes is increasing across the entire range from adolescents upward (2,20), the highest prevalence remains among the elderly, in whom a combined prevalence of IGT and type 2 diabetes is ~45% (2). However, the prevalence of obesity, at least by BMI criteria, is lower in the elderly than among middle-aged adults (4). This prevalence raises the question of whether obesity is a strong
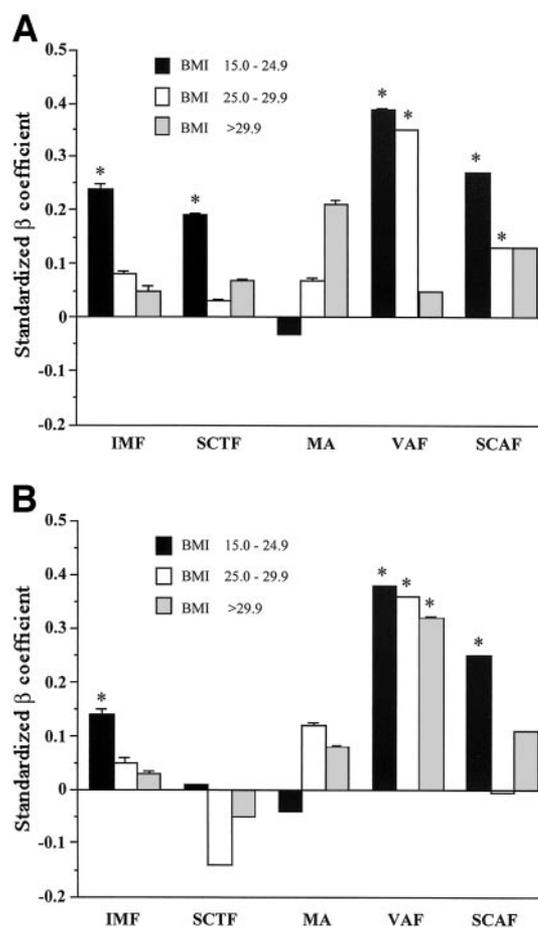

Figure 1—*Standardized β coefficients depicting body fat depots by CT scan in association with fasting insulin levels in normal-weight (BMI 15.0–24.9 kg/m^2), overweight (BMI 25.0–29.9 kg/m^2), and obese (BMI >29.9 kg/m^2) men (A) and women (B) adjusted for race and age. Subjects with type 2 diabetes were excluded from the analysis. IMF, intermuscular fat; MA, muscle attenuation; SCAF, subcutaneous abdominal fat; SCTF, subcutaneous thigh fat; VAF, visceral abdominal fat. *Significant associations, P < 0.01.*

determinant of type 2 diabetes in the elderly, an association of undisputed strength among middle-aged and younger adults and even adolescents (1). It might be the case that among the elderly, β-cell defects in insulin secretion assume an even greater role in the pathogenesis of type 2 diabetes and that obesity-related insulin resistance is less of a factor. Yet there is an alternative hypothesis—one that was examined in the current study—that proposes that an individual might manifest the metabolic perturbations of obesity, including insulin resistance, despite having either a normal or only modestly increased BMI. In this concept of the "metabolically obese, normal-weight individual," it is posited that in addition to generalized obesity, regional AT distribution is a key determinant of insulin resistance and altered glucose homeostasis. Supporting this concept are individuals who accumulate a relative preponderance of visceral AT despite only modest overall increases in weight and who are insulin resistant and at a greater risk for type 2 diabetes (5,7).

Entirely consistent with information from the general population of elderly individuals (2,3), the prevalence of type 2 diabetes within the Health ABC cohort was quite high at 24%, and an additional 21% had IGT as determined by oral glucose challenge testing. Thus, the Health ABC cohort provides an excellent opportunity to test the hypothesis of whether certain aspects of the obesity phenotype, more specifically visceral adiposity and other novel components of regional fat disposition, contribute to the risk for type 2 diabetes. These findings strongly support this hypothesis and reveal that the concept of the metabolically obese, normal-weight individual is likely to be of great importance in understanding the risk factors that drive the heightened risk of type 2 diabetes in relation to aging.

With respect to the most simple of body composition determinations, that of BMI, in the Health ABC cohort, men and women with IGT and type 2 diabetes did have a significantly greater BMI. Yet, the differences are not striking, and there was a substantial overlap in the range of BMI

A

B
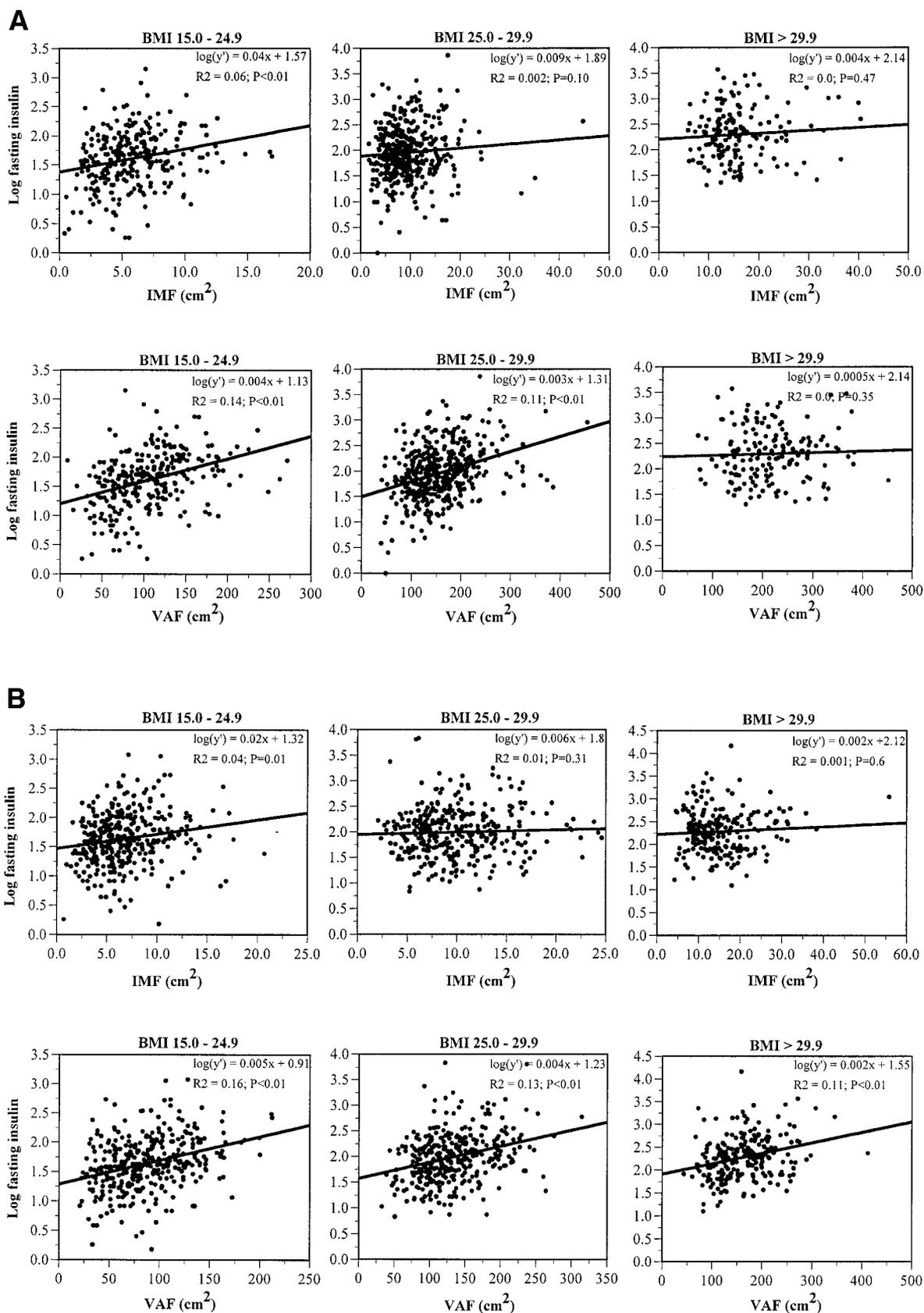
Figure 2—*Associations of fasting insulin with intermuscular fat (IMF) and visceral abdominal fat (VAF) in normal-weight (BMI 15.0 –24.9 kg/m²), overweight (BMI 25.0 –29.9 kg/m²), and obese (BMI >29.9 kg/m²) men (A) and women (B). Note the different scales reflecting the different ranges of values for the three BMI groups. Subjects with type 2 diabetes were excluded from the analysis.*

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values between groups. What began to more clearly discriminate across the groups, at least with respect to body composition variables, was regional AT. Men and women with IGT and type 2 diabetes had substantially greater amounts of visceral abdominal AT than men and women with NGT. Visceral fat content, independent of total body obesity, is a particularly strong marker of insulin resistance and IGT in middle-aged (21,22) and elderly (11) adults. These results corroborate these findings and, further, suggest that the influence of visceral fat on insulin resistance is even stronger in normal-weight men and women than in overweight or obese men and women and that this association is not generally confounded by race. Thus, elderly men and women characterized by the metabolically obese but normal-weight phenotype appear to be specifically associated with excessive visceral fat accumulation.

Men and women with IGT and type 2 diabetes also had greater amounts of AT interspersed between the muscle of the legs, a modest but potentially important depot of AT with respect to insulin resistance that has been recently identified using novel methods of CT imaging analysis (18). In accounting for variance in fasting insulin among subjects with NGT and IGT, this being the surrogate for insulin resistance (23,24), the adverse effect of increased visceral and muscle AT was more clearly evident among the nonobese. Although the fat component within the thigh represents only ~5–10% of the total thigh fat content, the greater intermuscular fat content in these men and women was observed despite similar amounts of subcutaneous thigh fat. These results are in accord with previous findings of increased AT beneath the fascia of thigh muscle in middle-aged men and women with type 2 diabetes (18). Skeletal muscle attenuation on CT was lower in these elderly men and women with IGT and type 2 diabetes—a difference denoting an ~2% greater amount of lipid contained within their thigh muscle (16). This result is also in accord with prior observations of lower mean attenuation values for skeletal muscle in obese men and women, with and without type 2 diabetes (15,18). In addition, overall fat mass was strongly correlated with fasting insulin among subjects with NGT and IGT. However, the distribution of AT within muscle rather than the total

amount of thigh AT or the amount of skeletal muscle itself was a characteristic of elderly men and women with IGT or type 2 diabetes.

Our interpretation of these findings is that obesity does indeed contribute strongly to the risk for type 2 diabetes in the elderly. We cannot say whether obesity is a greater or lesser risk factor than impaired insulin secretion because this later determinant, known to be of crucial influence on the development of type 2 diabetes, was not measured. However, what can be learned is that the obesity phenotype that constitutes risk for IGT and type 2 diabetes in aging is a more complex phenotype of body composition than that reflected in weight or BMI. Instead, the obesity phenotype delineated by the Health ABC study that confers risk for IGT and type 2 diabetes in the elderly is strongly shaped by regional fat distribution.

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