Contribution of Visceral Fat Mass to the Insulin Resistance of Aging

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Recent studies have shown that central obesity (increased waist to hip ratio [WHR]) is related to insulin resistance and aging. Furthermore, in central-obesity states, the intraabdominal fat (IAF) depot has been postulated to contribute most to the development of insulin resistance. Therefore, the observed insulin resistance of aging may be related more to changes in body composition than to aging per se. The purpose of this study was to explore the association of IAF with age and insulin sensitivity (S_I) after controlling for obesity. We examined 60 healthy nondiabetic subjects (normal 75-g oral glucose tolerance test, aged 23 to 83, 15 men and 45 women). We chose subjects so that those ≤125% and greater than 125% of ideal body weight were equally represented in each age decade. We quantified total and subcutaneous abdominal fat and IAF at the umbilicus using a validated magnetic resonance imaging (MRI) scanning technique and determined S_I using a modified minimal model. IAF correlated significantly with age ($r = .49$, $P = .0001$) in the group as a whole, as well as in men ($r = .58$, $P = .022$) and women ($r = .48$, $P = .0008$) separately. In all subjects, S_I was significantly related to IAF ($r = -.50$, $P < .0001$) but was not related to age ($r = .00$, $P = .98$). In multivariate analysis for various combinations of age, sex, and measures of fat distribution, WHR accounted for 28% and IAF for 51% of the variance in S_I, whereas age, sex, and interactions of age and sex accounted for only 1%. In conclusion, IAF mass, which has been postulated to be the most metabolically active of the adipose depots, correlates significantly with insulin resistance and age in healthy nondiabetic individuals regardless of gender and after controlling for obesity.

AGING HAS TRADITIONALLY been associated with a decline in glucose tolerance and an increased likelihood of developing type II diabetes.[1-3] This observation of a deterioration in glucose tolerance with age is believed to be due to the development of peripheral-tissue insulin resistance rather than to a defect in insulin secretion. As such, many studies using the glucose clamp technique have demonstrated that the rate of peripheral-tissue glucose disposal at physiologic insulin concentrations is lower in younger as compared with older subjects.[4-6] However, recent data have suggested that the insulin resistance noted secondary to the aging process may not be related to aging per se, but may be more related to changes in body composition (eg, an increase in total body fat or central obesity, ie, elevated waist to hip ratioi [WHR]).[7] In these recent studies, the waist and waist/hip circumference has been reported to account for the majority of the variance in peripheral-tissue insulin action, whereas age has explained only a small percentage of the total variance when waist/hip circumference was statistically controlled.[8,9] These results suggest that insulin resistance is more associated with the abdominal obesity accompanying aging per se. The waist circumference represents two fat depots, subcutaneous fat and intraabdominal (eg, visceral) fat (IAF).[9] Specifically, accumulation of visceral fat has been reported to be more closely associated with the clinical syndrome of insulin resistance (eg, glucose intolerance, hyperlipidemia, and hypertension).[10-12] Therefore, the purpose of this study was to investigate visceral fat mass in a cross-sectional study of healthy, aging individuals, and relate quantitative visceral fat mass to both age and insulin sensitivity (S_I).

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SUBJECTS AND METHODS

Subjects

Studies were performed in 60 healthy, community-dwelling subjects (aged 23 to 83 years, 15 men and 45 women). Participants underwent a standardized interview to obtain demographic data and information documenting eligibility. All subjects were fully ambulatory and normally active, and took no medications known to affect glucose metabolism, blood pressure, or lipids. Participants were considered healthy as determined by medical history, physical examination, ECG, complete blood cell counts, routine blood and urine chemistries, and thyroid function tests. The study was designed to evaluate equal numbers of subjects in each decade who were ≥ 125% and less than 125% of ideal body weight. All subjects provided written informed consent to participate in this study, which was approved by the Clinical Research Practices Committee of Bowman Gray School of Medicine.

Quantification of IAF Mass

Total abdominal, intraabdominal (visceral), and subcutaneous abdominal fat masses were quantified using magnetic resonance imaging (MRI). MRI examinations were performed on a Picker Vista HPQ (Picker International, Cleveland, OH) MRI scanner operating at a field strength of 1.5 T. The inversion recovery protocol used was first described by Seidell et al[13] and subsequently validated on our system.[14] The imaging parameters were as follows: TI = 300 ms, TR = 833 ms, and TE = 30 ms. A 256 × 256 image matrix was acquired with two signals averaged. The field of view varied with individual patient size.

According to the MRI protocol reported by Seidell et al,[13] the inversion recovery time is selected so that the expected signal from muscle tissue will be at zero crossing, thus producing no signal. Since the spin-lattice time of muscle is much longer than that of

adipose tissue, the fat signal will recover substantially with a relatively strong signal.

Using the described protocol, four 10-mm thick slices were obtained with 5 mm between slices. The four images generated from each scan were stored on magnetic tape and transferred to a research computer for analysis. The third slice was centered at the umbilicus (3rd lumbar vertebra) and was used to quantify fat areas, since it has been shown to correlate highly with the mean of all four slices (r = .985, n = 157; J.R. Crouse and J.G. Terry, unpublished observations, May 1994).

In all subjects, body mass index (BMI) was calculated as body weight in kilograms divided by height in meters squared. WHR was measured as the ratio of the minimal circumference of the abdomen to the circumference of the buttock at the maximal gluteal protuberance.

Oral Glucose Tolerance Test

Glucose tolerance was determined for all subjects using a 75-g oral glucose tolerance test (World Health Organization criteria) performed after a 12-hour fast.[15] Blood samples for determination of glucose and insulin were taken before and 30, 60, 120, and 180 minutes after glucose ingestion. Plasma glucose levels were measured by a glucose oxidase method (Beckman Instruments, Brea, CA), and insulin concentrations were measured by radioimmunoassay (IncStar, Stillwater, MN), as previously described.[16] Subjects demonstrating a diabetic response according to World Health Organization criteria were excluded from further study.

S_I

S_I was determined using the frequently sampled intravenous tolerance test (minimal model),[17] with a modification using exogenous insulin administration.[18,19] Studies were initiated in the morning after an overnight fast. Two 18-gauge intravenous catheters were placed in each forearm and kept patent by a controlled flow of saline infusion. Each line was equipped with a three-way stopcock. One line was used for intravenous administration of test substances, and the other was used for blood samples. Blood samples of 1 mL for insulin and glucose were drawn from the line at −15 minutes, −5 minutes, and immediately (0 minutes) before the glucose solution was injected. Glucose solution (300 mg/kg) was injected intravenously and flushed with 3 mL saline solution at 0 minutes. Blood samples of 1 mL were drawn at 2, 3, 4, 5, 8, 10, 12, 14, 16, 18, and 20 minutes. Regular insulin (Humulin Regular; Eli Lilly, Indianapolis, IN) was injected as an intravenous bolus of 0.03 U/kg at 20 minutes. Blood withdrawals continued at 22, 24, 28, 32, 40, 45, 50, 60, 70, 80, 90, 100, 110, 120, 140, 160, and 180 minutes. Samples were centrifuged immediately, and plasma was placed on ice. Glucose determinations were made immediately after centrifugation using the glucose oxidase method on a Beckman Glucose Analyzer (intraassay coefficient of variation, 2%). Insulin was assayed within 1 week from frozen plasma by radioimmunoassay (IncStar; intraassay coefficient of variation, <5%). At each time point, glucose and insulin measurements were determined in duplicate. S_I and glucose effectiveness were determined from the minimal model, as previously described.[17,18]

Statistical Analyses

Data were analyzed using the descriptive statistics and multivariable regression facilities of JMP Version 2.03 (SAS Institute, Cary, NC). For hypothesis testing, effects were considered significant with P less than .05. In the regression models, S_I and IAF were examined both with and without transformation. Both natural-log and square-root transformations were evaluated for best linear fit.

RESULTS

In this study, we had the opportunity to compare circumference-derived fat distribution (WHR) with BMI and with MRI-derived direct measures of total, intraabdominal, and subcutaneous fat (Table 1). WHR appeared to correlate better with other anthropometric parameters in women than in men, was least well-correlated with BMI, but correlated about equally well with total, intraabdominal, and subcutaneous fat.

Table 2 lists descriptive statistics by sex and age groups. Overall, there was no relationship of age to S_I for men or women (Fig 1A, Table 2), nor did weight or BMI increase with age in this cohort (Table 2, Fig 1B). Although BMI did not increase with age, WHRs, which were greater in men (mean ± SD, .95 ± .08; range, .81 to 1.13) than in women (mean ± SD, .90 ± .10; range, .69 to 1.05), tended to increase with age in both (r = .43 and P = .11 for men; r = .31 and P = .039 for women; and r = .29 and P = .03 overall). IAF, expressed as total area or total area per kilogram body weight, increased significantly with age in both men and women (Fig 1C, Table 2). Significance levels for the association of age with IAF were much greater than for age with WHR. There was no association of age with subcutaneous fat or total fat. Glucose tolerance (area under the curve [AUC]) was significantly related to age in men (r = .60, P = .019), approached significance in women (r = .29, P = .056), and was significantly related to age in the group as a whole (r = .36, P = .005). Insulin AUC was not related to age in the entire cohort (r = .02, P = .87) or in men (r = .007, P = .98) or women (r = .028, P = .86) considered separately.

Table 3 lists the association of specific anthropometric measures with metabolic parameters in men and women. Associations of IAF with S_I were significant in both men and women (Table 3, Fig 2), whereas associations of S_I with WHR were only significant in women. We also evaluated the relationship of the IAF to subcutaneous fat ratio to S_I. There was no correlation of the IAF to subcutaneous fat ratio to S_I in either women (r = .04, P = NS) or men (r = .35, P = NS). IAF also was significantly associated with the glucose AUC in both men and women, whereas WHR was only significantly associated with glucose AUC in women.

Table 4 lists statistical models of S_I for various combinations of sex, age, and measures of fat distribution. As shown, in univariate analysis, WHR and log (IAF) were both highly correlated with S_I (R^2 = .25 and .31, models 4

Table 1. Anthropometric Correlations in Men, Women, and Both Groups Together

	WHR					
	Men		Women		All Subjects	
	r	P	r	P	r	P
Total fat (cm²)	.62	.015	.73	.0001	.62	.0001
IAF (cm²)	.56	.031	.62	.0001	.60	.0001
SubQ (cm²)	.49	.067	.61	.0001	.49	.0001
BMI	.48	.068	.55	.0001	.51	.0001

Abbreviation: SubQ, subcutaneous abdominal fat.

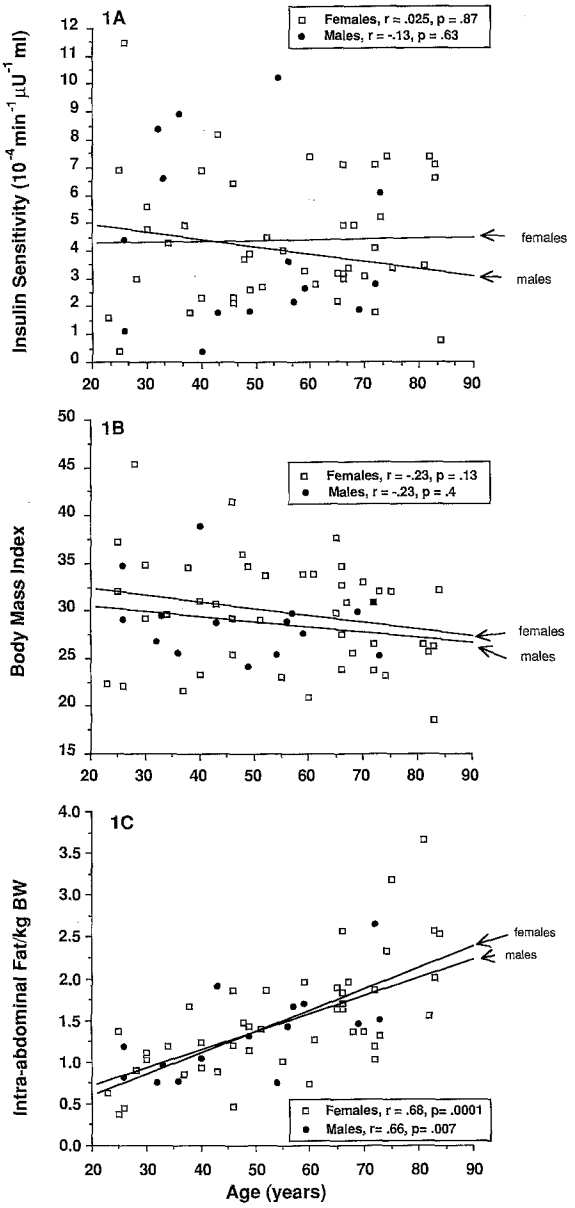

Fig 1. Correlation of age with S_I (A), BMI (B), and IAF (C).

and 10). This analysis included both men and women. However, when multivariate analysis was performed including sex and the respective sex-fat interaction (models 12 and 15), the model containing log(IAF) explained 13% more of the variance in S_I than the model containing WHR (38% *v* 25%). A model including sex and log (total fat) and the respective sex-fat interaction (model 13) also performed well. When models included sex, age, fat measurement, and sex-age interactions, the model including IAF (model 18) accounted for 51% of the variance in S_I, whereas no variable achieved statistical significance in the comparable model including WHR. Age (which accounted for only 1% of the variance in S_I in multivariate analysis including age, sex, and age-sex interactions) was not shown to be significantly related to S_I in either univariate or multivariate models including sex or direct measures of abdominal fat (total, intraabdominal, or subcutaneous fat) (models 2, 11, and 16 to 18).

DISCUSSION

Our data indicate that aging is associated with changes in body composition reflected by an increase in WHR but more notably by the accumulation of IAF. This accumulation of IAF occurred despite controlling for the association of body weight and BMI with age in this study. In addition, the major finding of this study is that measures of body composition such as WHR and IAF accounted for 28% and 51%, respectively, of the variance in S_I, whereas age accounted for approximately 1% of the variance.

Past studies have found aging to be associated with a progressive decline in glucose tolerance and development of compensatory hyperinsulinemia.[1,2,20,21] The impairment in glucose tolerance secondary to aging has been attributable to an increased peripheral-tissue (ie, skeletal muscle) resistance to insulin action.[4-6,22,23] It has been debated over the recent past whether this deterioration in glucose tolerance is secondary to the aging process per se or to other factors such as abdominal obesity, an increase in total adiposity, or sedentary life-style. As such, Zavaroni et al[21] found that the effect of aging on glucose tolerance was either eliminated or markedly attenuated after adjusting for the effects of obesity and physical activity. Additional

Table 2. Descriptive Statistics by Sex and Age

	Women					Men				
	20-40 Years (n = 12)	40-60 Years (n = 11)	60-80 Years (n = 22)	Age Correlation		20-40 Years (n = 6)	40-60 Years (n = 6)	60-80 Years (n = 3)	Age Correlation	
				r	*P*				*r*	*P*
S_I	4.3 ± 3.0	3.9 ± 2.0	4.2 ± 2.0	.025	.87	6.2 ± 5.0	3.4 ± 3.3	3.4 ± 2.2	−.13	.63
Weight (kg)	80.4 ± 19.9	85.4 ± 14.9	74.8 ± 13.5	.28	.061	93.4 ± 18.4	95.7 ± 19.3	84.4 ± 4.4	.22	.43
BMI	29.7 ± 7.2	30.5 ± 5.9	28 ± 4.9	−.23	.13	29.7 ± 4.8	28.8 ± 5.5	28.1 ± 3	−.23	.40
WHR	0.86 ± 0.13	0.88 ± 0.09	0.93 ± 0.07	.31	.039	0.93 ± 0.11	0.95 ± 0.08	1.00 ± 0.04	.43	.11
TOTFAT (cm^2)	453.1 ± 299.7	532.2 ± 153.3	529.4 ± 136.1	.08	.62	411.1 ± 203.9	443.8 ± 164.4	395.2 ± 55.7	.05	.86
SubQ (cm^2)	376 ± 199.6	423.7 ± 127	391.2 ± 125.3	.10	.54	333 ± 176	271.2 ± 64.7	243.4 ± 23.3	.28	.32
IAF (cm^2)	77.1 ± 39.7	109.2 ± 46.8	138.3 ± 48.8	.48	.0008	78.8 ± 26.4	160.7 ± 94.2	149.4 ± 36.4	.58	.022

NOTE. Data are the mean ± SD.

Abbreviations: TOTFAT, total abdominal fat; SubQ, subcutaneous abdominal fat.

Table 3. Correlations of Anthropometric Characteristics With Metabolic Parameters

	Total Fat						IAF						SubQ						WHR					
	Men		Women		All Subjects		Men		Women		All Subjects		Men		Women		All Subjects		Men		Women		All Subjects	
	r	*P*	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*
Glucose AUC	.38	.16	.28	.06	.28	.029	.52	.048	.44	.0026	.45	.0004	.23	.40	.16	.31	.16	.22	.34	.19	.42	.004	.39	.002
Insulin AUC	.44	.10	.43	.003	.39	.002	.44	.10	.32	.033	.34	.009	.33	.23	.38	.011	.32	.011	.16	.54	.35	.019	.25	.06
S_I	−.70	.004	−.58	.0001	−.57	.0001	−.68	.005	−.44	.0024	−.50	.0001	−.53	.04	−.50	.0005	−.46	.0002	.35	.18	.57	.001	−.49	.0001

studies also found that a decline in glucose tolerance from young to middle age may be explained by changes in body composition and activity level, but that age remained a significant independent risk factor for the glucose intolerance observed with aging. However, recent studies have disputed the role of aging as an independent factor in altering S_I. Coon et al[7] evaluated 36 older and 13 young nondiabetic individuals, and determined S_I with hyperinsulinemic euglycemic clamps. Glucose disposal rate correlated significantly with WHR and percent body fat and positively with maximum oxygen consumption ($\dot{V}O_2max$), but was not related to age. Using multiple regression analysis, only WHR was independently correlated with glucose disposal.[7] In addition, their data indicated that in older men with normal glucose tolerance, WHR was inversely related to S_I and accounted for more than 50% of the variance in glucose disposal.

In a second study, Kohrt et al[8] evaluated 67 older subjects (34 men and 33 women) and 17 younger subjects (11 men and six women) and determined glucose tolerance, body fat composition, $\dot{V}O_2max$, and glucose disposal by hyperinsulinemic euglycemic clamps. In men, waist circumference accounted for 43% of the variance in glucose disposal rate, and the remaining independent contributions of age, $\dot{V}O_2max$, total adiposity, and WHR were not significant. In women, waist circumference alone accounted for 50% of the variance in insulin action, which increased to 60% when WHR was added. In women, the remaining partial correlations of age, $\dot{V}O_2max$, and body fat percentage were not significant. In a third study, Franssila-Kallunki et al[24] found no correlation between age and total glucose disposal in 40 men and women ranging in age from 21 to 80 years. Finally, O'Shaughnessy et al[25] evaluated both premenopausal and postmenopausal obese and non-obese women and concluded that aging does not appear to intensify the insulin resistance of obese states when both coexist in the same individual.

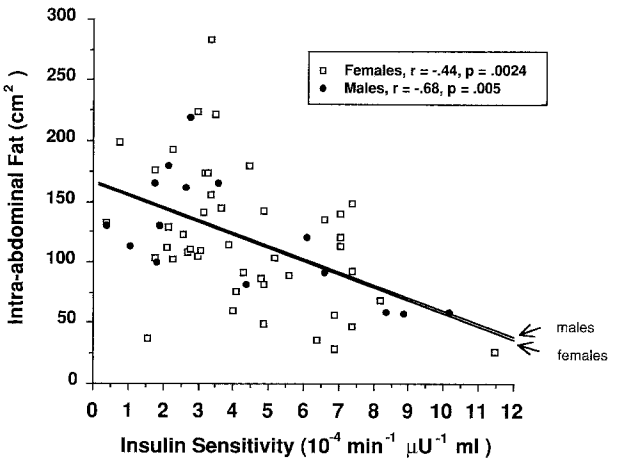

Fig 2. Correlation of S_I with IAF in both men and women.

Table 4. Statistical Models of Insulin Sensitivity

Model	Effects	R^2	*P*
1	Sex	.00	.781
2	Age	.00	.976
4	WHR	.25	<.001
5	Total fat	.32	<.001
6	Log(total fat)	.35	<.001
7	SubQ fat	.22	<.001
8	Log(subQ fat)	.24	<.001
9	IAF	.25	<.001
10	Log(IAF)	.31	<.001
11	Age	.01	.643
	Sex		.604
	Age · sex		.520
12	Sex	.25	.940
	WHR		.001
	Sex · WHR		.984
13	Sex		.062
	Log(total fat)	.43	<.001
	Sex · log(total fat)		.050
14	Sex		.367
	Log(subQ fat)	.29	<.001
	Sex · log(subQ fat)		.308
15	Sex		.013
	Log(IAF)	.38	<.001
	Sex · log(IAF)		.013
16	Age		.909
	Log(total fat)	.36	.065
	Age · log(total fat)		.945
17	Age		.567
	Log(subQ fat)	.25	.055
	Age · log(subQ fat)		.574
18	Sex		.002
	Age		.585
	Log(IAF)	.51	<.001
	Sex · age		.478
	Sex · log(IAF)		.005
	Age · log(IAF)		.276
19	Sex		.889
	Age		.614
	WHR	.28	.243
	Sex · age		.728
	Sex · WHR		.966
	Age · WHR		.674

In summary, the most recent results of studies reported by Kohrt et al,[8] Coon et al,[7] Franssila-Kallunki et al,[24] and O'Shaughnessy et al[25] suggest that insulin resistance is not a feature of aging per se, but may be more related to body composition changes, particularly changes in WHR or waist girth. These data support our findings and suggest that after controlling for the potential increase in BMI associated with age, aging is predominantly associated with an increase in IAF and not with diminished S_I in women, men, or in men and women together. Although insulin resistance is closely associated with changes in body composition with age (increased WHR and increased abdominal fat), our data suggest that controlling for BMI eliminates the association of insulin resistance with age, and raise the possibility that such an association reflects either an increase in total BMI with age or an interaction between BMI and IAF that results in age-associated increases in insulin resistance in populations uncontrolled for age-associated increases in BMI.

The relationship of adipose distribution to diabetes and hyperinsulinemia has been investigated extensively. Individuals with central obesity are more likely to have or to develop diabetes,[26,27] glucose intolerance,[28] and high insulin levels[28-30] in comparison to subjects who have peripheral obesity even after controlling for body weight. Adiposity in the central area can be described as consisting of two major fat depots: subcutaneous fat and IAF (visceral fat).[9] The accumulation of visceral fat has been postulated to be more closely linked to development of insulin resistance. Two hypotheses have been developed to explain the relationship of central obesity to carbohydrate metabolism. According to the first, an excess of highly metabolically active fats located within the peritoneal cavity leads to an abundance of free fatty acids in the portal circulation. Increased portal concentration of free fatty acids inhibits insulin clearance and degradation, and this allows more insulin to reach the peripheral circulation. The result is relative hyperinsulinemia.[31] The second hypothesis suggests that individuals with central obesity are more likely than those with peripheral obesity to have skeletal muscle cells with impaired S_I.[32] This has been suggested in studies showing that subjects with central obesity may have a muscle morphology consisting of more type IIB insulin-resistant fibers that are associated with a reduced glycogen synthesis.[33,34]

Quantitation of total abdominal fat into both visceral and subcutaneous fat areas was reported as early as 1983 with computed tomography scanning.[9] Visceral fat obesity has been more frequently accompanied by circulatory disorders such as left ventricular enlargement and hypertension than has subcutaneous fat obesity.[11,35] Visceral fat in both men and women, has been shown to correlate significantly with fasting plasma glucose, triglyceride, and cholesterol concentrations in obese individuals.[10-12] Furthermore, visceral fat also has been shown to correlate with total cholesterol, fasting plasma glucose, and triglyceride concentrations in normal-weight individuals.[12] Adipose distribution (WHR),[36] or specifically IAF,[12] has been correlated with coronary disease. From these findings, Matsuzawa et al[12] proposed a new clinical entity, "visceral fat syndrome," as a multi–risk-factor syndrome in which visceral fat accumulation, glucose intolerance, hypertension, and hyperlipidemia cluster to induce the occurrence of atherosclerosis. In their report, this syndrome is similar to the reported syndrome X or the "deadly quartet."

Matsuzawa et al[12] also found that aging is associated with visceral fat accumulation. They demonstrated, by computed tomography scanning, a close linear correlation between age and visceral fat volume in males, suggesting that visceral fat increases continually with age. This correlation also was present in female subjects and showed differences in slope between both premenopausal and postmenopausal subjects. However, the patients studied were considered obese. We studied both lean and obese individuals and eliminated age-associated increases in BMI by our study design. Yet our studies indicate that visceral fat accumulation continues with age in the entire cohort, as well as in men and women considered separately. Our research suggests that IAF increases with aging after controlling for BMI, and correlates closely with insulin resistance. Furthermore, in multivariate analysis with models that included age, sex, fat measures, and the respective interactions, we found that body composition changes, most notably an increase in WHR, account for 28% of the variance in S_I, whereas age accounted for approximately 1%. In addition, models including IAF were demonstrated to account for 51% of the variance in S_I.

In summary, we report on the relationship of IAF mass with aging. We found that aging is associated with the accumulation of IAF, after controlling for BMI. IAF mass was found to be highly correlated with S_I and accounted for more total variance in S_I than age.

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