Familial Aggregation of Abdominal Visceral Fat Level: Results From the Quebec Family Study

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The purpose of this study was to investigate the importance of familial aggregation in abdominal visceral fat (AVF) level as assessed by computed tomography (CT). Four measures of abdominal adipose tissue, obtained from an abdominal scan between the fourth and fifth Lumbar vertebrae (L4-L5) taken in 366 adult subjects from 100 French-Canadian nuclear families, were considered in this study. Total abdominal fat, AVF, subcutaneous abdominal fat, obtained by computing the difference between total and AVF tissue areas, and the visceral to total abdominal fat ratio were measured. Spouses, parent-offspring, and sibling correlations were computed by maximum likelihood methods after adjustment of the four phenotypes for age and for age and total fat mass (FM) derived from underwater weighing. Significant familial aggregation was found for all phenotypes, whether adjusted or not for body FM. However, after adjustment of data for body FM, in addition to age, all spouse correlations became nonsignificant, suggesting that the familial aggregation of abdominal fat is primarily genetic. Heritability estimates reached 42% and 56% for subcutaneous fat and AVF, respectively. These results suggest that genetic factors are major determinants of the familial aggregation observed in the amount of abdominal fat, irrespective of total body fat content, and that AVF seems more influenced by genetic factors than abdominal subcutaneous adipose tissue. These findings imply that some individuals are more at risk than others to exhibit the various metabolic complications associated with upper-body obesity because of their inherited tendency to store abdominal fat in the visceral depot rather than in the subcutaneous depot.

IT IS NOW widely recognized that regional distribution of body fat is an important variable to consider in the assessment of the health hazards of obesity. Several studies have shown that a centralized distribution of body fat was associated with several metabolic disturbances considered as risk factors for cardiovascular diseases such as insulin resistance, hyperinsulinemia, glucose intolerance and type II diabetes,[1] dyslipidemias,[2-4] and hypertension.[5] Excess amount of abdominal visceral fat (AVF) appears to be an important component of this cluster of metabolic disturbances that have been referred to as the metabolic syndrome.[6]

Distribution of body fat is generally assessed from anthropometric measures using sums or ratios of various skinfold thicknesses, waist girth, or the ratio of waist to hip circumferences. Based on these indicators, a stronger genetic effect is generally found for regional fat distribution (30% to 50%) than for total amount of body fat (25%).[7-9] Despite its critical role in the metabolic abnormalities associated with upper-body obesity, little is known about the contribution of genetic factors in AVF level compared with total body fat or other regional fat distribution phenotypes. The only evidence for a role of genetic factors in abdominal fat assessed by computed tomography (CT) comes from the long-term overfeeding and negative energy balance experiments conducted with monozygotic twins.[10,11] Following overfeeding, surface areas of both subcutaneous and visceral depots were found to increase significantly, but gains in abdominal fat were not randomly distributed among genotypes. Results indicated that after adjustment for the gain in total fat mass (FM), there were about four and six times more variance between pairs than within pairs for gains in abdominal subcutaneous and visceral fat depots, respectively.[10] Comparable results were obtained in seven pairs of identical twins who were exposed to 93 days of regular exercise with daily energy intake clamped at baseline level in order to generate an energy deficit of approximately 53,000 kcal below the cost of weight maintenance.[11] These results demonstrate that some individuals are more responsive than others in terms of changes in body fat in the abdominal region when challenged with extra calories or an energy deficit and suggest that genetic factors play an important role in this phenomenon.

Visceral fat can only be assessed by imaging techniques such as CT or nuclear magnetic resonance that are difficult to use on a large-scale basis. For that reason, familial correlations for AVF have never been reported. In the Quebec Family Study (QFS), abdominal subcutaneous and visceral fat levels were measured by CT in 366 individuals from 100 nuclear families. We report familial correlations for total abdominal fat, for abdominal subcutaneous and visceral fat depots, and for the visceral to total abdominal ratio in this cohort of families.

METHODS

Population

Between 1978 and 1981 (phase 1) a total of 1,630 individuals from 375 randomly ascertained families of French descent living in the Quebec city area were recruited to participate in the QFS, a population-based study of the genetics of physiological fitness and body composition. In 1989, a follow-up study (phase 2) of a subset of families from the original cohort was initiated to investigate the genetics of causes and consequences of obesity.[12] Among subjects participating in phase 2 of QFS, CT-assessed abdominal adipose tissue was available in a total of 366 subjects distributed in 100 nuclear families. All individuals used in the analyses were at least

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18 years of age. Characteristics of the subjects of these families are listed in Table 1.

Assessment of Abdominal Fat by CT

Cross-sectional abdominal adipose tissue areas were assessed by CT using a Siemens Somatom DRH scanner (Erlanger, Germany) as described in detail elsewhere.[13] Briefly, an abdominal scan was obtained between the fourth and fifth lumbar vertebrae (L4-L5) with subjects in a supine position with arms stretched above the head. A radiograph of the skeleton was used as reference to determine the position of the scan to the nearest millimeter. Total and visceral adipose tissue areas were delineated with a graph pen and then computed using an attenuation range of −190 to −30 Hounsfield units.[14] AVF area was determined by drawing a line within the muscle wall surrounding the abdominal cavity. The area of abdominal subcutaneous fat was obtained by computing the difference between total and visceral adipose tissue areas. The fraction of total abdominal fat found in the abdominal cavity was assessed by computing the visceral to the total abdominal fat ratio. The intraclass reliability coefficients for CT-derived abdominal fat measurements are good and usually greater than 0.9.[14]

Body Composition Measurements

Total body FM was determined with the Siri equation[15] from density measurements obtained by underwater weighing, as previously described.[16] These measures were used as concomitant variables in the regression procedures described later to take into account the effects of body FM in the variation of abdominal fat level.

Statistical Analysis

Familial correlations were computed after adjustment of the abdominal fat phenotypes for concomitants using regression equations performed separately in each sex and generation group. Two different adjustments were performed on each of the four abdominal fat phenotypes: first, they were adjusted for age (up to a cubic polynomial in age) and, second, for age and for the linear effects of FM. To obtain regression equations not unduly affected by extreme observations, individuals with phenotype values beyond ±4 SD from the mean of their sex- and generation-specific group were identified and temporarily set aside. Three outliers in the distribution of AVF were identified according to this criteria: they were two obese women (body mass index [BMI] of 38 and 45) and one obese man (BMI of 37). After each sex- and generation-specific equation had been obtained, the outliers were added back to the sample and the residual scores were calculated and used as phenotypes for computation of familial correlations. Two other concomitant variables that could affect AVF are smoking and menopause. Since only 16% of the subjects were smokers, this variable was not included in the adjustment procedures. The adjustment for age performed separately in each sex and generation groups accounts for the effects of menopause on AVF levels.

The familial correlation model involves four types of individuals (f = fathers, m = mothers, s = sons, d = daughters) leading to eight correlations within three familial classes (1 spouse [fm], four parent-offspring [fs, fd, ms, md], and three siblings [ss, dd, sd]). Familial correlations were estimated by fitting the general model (all eight correlations) directly to family data under the assumption of multivariate normality by using the maximum likelihood method. A series of reduced models to assess sex and generation differences and the significance of the correlations were tested using the likelihood ratio test (minus twice the difference in the log-likelihoods obtained under the general and the reduced model hypothesis), which is asymptotically distributed as a χ^2, with the degrees of freedom being the difference in the number of estimated correlations between the two models. A significant χ^2 value indicates that the hypothesis tested is rejected. Nonnested models were compared using Akaike's[17] information criterion (AIC), which is minus twice the log-likelihood plus twice the number of estimated correlations. The best model was the one with the smallest AIC. The computer program SEGPATH[18] was used to estimate the familial correlations.

The specific hypotheses tested for each phenotype were conducted as follows. Sex and generation differences in correlations were first considered by testing the hypotheses of no sex difference in offsprings ($ss = dd = sd$, $fs = fd$, $ms = md$, $df = 4$), no sex differences in offsprings or parents ($ss = dd = sd$, $fs = fd = ms = md$, $df = 5$), and no sex nor generation differences ($ss = dd = sd = fs = fd = ms = md$, $df = 6$). The hypotheses of no spouse correlations ($fm = 0$, $df = 1$), no parent-offspring correlations ($fs = fd = ms = md = 0$, $df = 4$), no sibling correlations ($ss = sd = dd = 0$, $df = 3$), no parent-offspring and sibling correlations ($ss = sd = dd = fs = fd = ms = md = 0$, $df = 7$), and no familial correlations at all ($fm = ss = sd = dd = fs = fd = ms = md = 0$, $df = 8$) were then successively tested. The most parsimonious model, ie, the one that best fitted the data with the fewest parameters estimated, was derived by combining all nonrejected hypotheses into a single test.

RESULTS

As shown in Table 1, mean levels of total FM are higher in parents than in offsprings and, within each generation, higher values are observed in females as compared with males. The same trend was observed for total and subcutaneous fat levels. Male subjects of both generations exhibited higher amounts of AVF, which resulted in a significantly higher visceral to total abdominal fat ratio for males

Table 1. Physical Characteristics of the Subjects

Variable	Parents		Offspring	
	Male (N = 93)	Female (N = 104)	Male (N = 85)	Female (N = 84)
Age (yr)	55.5 ± 6.4	53.3 ± 6.2	25.6 ± 4.7	25.5 ± 4.8
BMI (kg/m2)	27.8 ± 4.5	26.0 ± 5.4	24.6 ± 4.0	24.2 ± 5.4
FM (kg)*	22.8 ± 9.0	24.7 ± 9.3	15.1 ± 9.5	19.1 ± 10.7
Abdominal adipose tissue areas (cm^2)				
Total	401.7 ± 166.9	432.2 ± 175.9	253.2 ± 163.0	319.6 ± 187.3
Subcutaneous	233.5 ± 106.7	311.5 ± 126.1	177.7 ± 127.1	263.8 ± 158.4
Visceral	168.2 ± 81.7	120.7 ± 65.3	75.5 ± 44.8	55.8 ± 33.5
Visceral/total	0.42 ± 0.09	0.28 ± 0.07	0.32 ± 0.09	0.18 ± 0.05

NOTE. Values are means ± SD.

*For this variable, N = 85, 86, and 84 for male parents, female parents, and male offspring, respectively.

as compared with females, with values of 42% versus 28%, and 32% versus 18% in parents and offsprings, respectively.

The effects of age (results not shown) were generally not significant for total and subcutaneous abdominal fat levels (0% to 10%) and tended to be higher for AVF and for the ratio of visceral to total abdominal fat (9% to 17%). However, the effects of age and FM were highly significant and accounted for approximately 60% to 90% of the variance for total, subcutaneous, and visceral abdominal fat levels. For the visceral to total abdominal fat ratio, the effects of age and FM were much smaller, ranging from approximately 10% to 25%.

Table 2 summarizes the results of the various models tested for each of the four phenotypes under both adjustments methods, ie, age-adjusted data and age- and FM-adjusted data. Table 2 indicates whether or not the model tested is rejected ($P < .05$) and gives the corresponding AIC. Since all hypotheses related to sex and generation differences could not be rejected (except for age- and FM-adjusted total abdominal fat, $P = .049$), the corresponding models are not presented in Table 2.

For total, subcutaneous, and AVF levels adjusted for age, correlations were all significant. In each case, the parsimonious model (by likelihood ratio and by AIC) corresponded to the no sex nor generation differences model ($ss = dd = sd = fs = ms = md$). For the visceral to total abdominal fat ratio, only parent-offspring correlations were significant. The model with no sex or generation differences, and no spouse and no sibling correlations, was retained as the most parsimonious.

For age- and FM-adjusted phenotypes, the spouse correlation was not significant for any of the phenotypes, which suggests that common familial environment is not a major determinant of the familial resemblance observed in visceral fat adjusted for body FM. For total abdominal fat, the model (results not shown) that includes no sex differences in offspring ($ss = dd = sd, fs = fd, ms = md$) was rejected ($P = .049$; AIC = 17.5). However, since the model for no spouse correlations (AIC = 14.1) fits better than the one with no sex differences in offspring (AIC = 17.5), the former was retained as the most parsimonious model. Taken together, these results are highly suggestive of a significant genetic effect for abdominal fat, independently of overall body fatness.

Table 3 gives the maximum likelihood estimates of the correlations under the most parsimonious models for each of the four phenotypes under the two adjustment schemes. The familiality estimate (t^2) is derived under the parsimonious models by simply doubling the average sibling correlation or the parent-offspring correlation when sibling correlations are not significant. When spouse correlations are significant, as found for total, subcutaneous, and visceral fat levels adjusted for age, the familiality includes both genetic heritability (h^2) and familial environmental (c^2) sources of variance. However, when the spouse correlations are not significant, the familial estimate is assumed to represent primarily genetic heritability, provided there is random mating.

As shown in Table 3, approximately 70% of the variance in age-adjusted levels of visceral fat could be explained by familial factors transmitted from parents to offspring. This familiality includes some portion due to the familial environment since spouse correlations are significant. On the other hand, the estimates for the FM-adjusted phenotypes are assumed to be entirely genetic in origin, as spouse correlations were not significantly different from zero. For total abdominal fat, the expected familialities were 69% (twice the average of *fs* and *ss* correlations) for males, 76% (twice the average of *md* and *dd* correlations) for females, and 57% (twice the average of *fd*, *ms*, and *sd* correlations) for

Table 2. Summary of Hypotheses Testing for Familial Correlations in Abdominal Adipose Tissue Areas

	Total		Subcutaneous		Visceral		Visceral/Total	
Model	Reject	AIC	Reject	AIC	Reject	AIC	Reject	AIC
Age-adjusted data								
General	—	16.0	—	16.0	—	16.0	—	16.0
No spouse	Yes	21.3	No	17.2	Yes	26.1	No	14.1
No parent-offspring	Yes	35.8	Yes	34.4	Yes	37.5	Yes	17.9
No sibling	Yes	34.1	Yes	35.3	Yes	28.0	No	13.0
No parent-offspring and sibling	Yes	46.8	Yes	46.9	Yes	42.4	No	14.9
No familial resemblance at all	Yes	52.6	Yes	48.8	Yes	51.6	No	12.9
Parsimonious*	No	6.8	No	7.2	No	11.2	No	9.9
Age- and FM-adjusted data								
General	—	16.0	—	16.0	—	16.0	—	16.0
No spouse	No	14.1	No	14.9	No	14.3	No	14.2
No parent-offspring	Yes	23.9	Yes	19.0	Yes	21.5	No	17.1
No sibling	Yes	34.7	Yes	25.4	Yes	19.5	No	12.0
No parent-offspring and sibling	Yes	39.7	Yes	27.0	Yes	32.6	No	13.0
No familial resemblance at all	Yes	37.9	Yes	25.6	Yes	30.7	No	11.4
Parsimonious†	No	14.1	No	8.5	No	9.2	No	6.3

*Parsimonious models for age-adjusted data are: (1) no sex nor generation differences for total, subcutaneous, and visceral fat; (2) no sex nor generation differences, and no spouse and no sibling correlations for visceral/total.

†Parsimonious models for age and fat mass adjusted data are: (1) no spouse correlation for total fat; (2) no sex nor generation differences and no spouse correlation for subcutaneous and visceral fat; (3) no sex nor generation differences, and no spouse and no sibling correlations for visceral/total.

Table 3. Maximum Likelihood Correlations (±SE) Under the Most Parsimonious Model for Various Abdominal Adipose Tissue Areas

Phenotype/ Correlation	Total	Subcutaneous	Visceral	Visceral/ Total
Age-adjusted data				
fm	.30 ± .09	.21 ± .10	.36 ± .09	[0]
fs	.35 ± .05	.34 ± .05	.34 ± .06	.12 ± .05
fd	[.35]	[.34]	[.34]	[.12]
ms	[.35]	[.34]	[.34]	[.12]
md	[.35]	[.34]	[.34]	[.12]
ss	[.35]	[.34]	[.34]	[0]
dd	[.35]	[.34]	[.34]	[0]
sd	[.35]	[.34]	[.34]	[0]
Familiality (t^2)	70%	68%	68%	0%-24%
Age- and FM-adjusted data				
fm	[0]	[0]	[0]	[0]
fs	.25 ± .12	.21 ± .05	.28 ± .05	.15 ± .05
fd	.42 ± .11	[.21]	[.28]	[.15]
ms	.23 ± .11	[.21]	[.28]	[.15]
md	.12 ± .12	[.21]	[.28]	[.15]
ss	.44 ± .17	[.21]	[.28]	[0]
dd	.64 ± .11	[.21]	[.28]	[0]
sd	.21 ± .12	[.21]	[.28]	[0]
Familiality (t^2)	57%-76%	42%	56%	0%-30%

NOTE. Values in brackets are fixed to 0 or to the value of a preceding parameter.

cross-sex pairs. For the visceral to total abdominal fat ratio, significant parent-offspring correlations suggest that a familial hypothesis cannot be ruled out; however, the lack of sibling correlations suggest that a simple model is unlikely.

DISCUSSION

The results of this study show, for the first time, that the amount of abdominal fat assessed by CT strongly aggregates in families. Familial resemblance among biological relatives can be explained by genetic factors and/or shared family environment. Although it is difficult to discriminate between these two effects from correlations among family members, a consistent pattern of correlations, such as the one observed in the present study, provides support for the hypothesis of a contribution from genetic factors. The lack of significant spouse correlation, combined with significant parent-offspring and sibling correlations of the same magnitude, suggest that genetic factors are the major determinant of the familial aggregation. This is exactly what was found when data were adjusted for age and FM, suggesting that the amount of adipose tissue stored in the abdominal area is determined to a significant extent by genetic factors. In that situation, the familiality estimates (t^2) can be considered as equivalent to the heritability (h^2) of the phenotype. The heritabilities of abdominal fat are roughly estimated at 42% and 56% for subcutaneous and abdominal visceral fat levels, respectively. For the visceral to total abdominal fat ratio, the heritability is estimated at 30% based on parent-offspring correlations.

For total abdominal fat, the heritabilities were found to be slightly higher for females (76%) than for males (69%), based on the most parsimonious model presented in Table 3. An alternate parsimonious model that does not include sex differences and spouse correlation was found to fit the data better (AIC = 12.8) than the model for no spouse correlation alone (AIC = 14.1). Based on this alternate parsimonious model, parent-offspring and sibling correlations were estimated at 0.26, which translates into a heritability of 52% for total abdominal fat.

Familial aggregation of fat topography has already been reported.[19,20] Several heritability estimates of abdominal subcutaneous fat derived from various skinfolds measurements have also been reported.[7-9] For example, based on data from 173 monozygotic and 178 dizygotic male twin pairs, Selby et al[21] reported a heritability of 44% for the subscapular skinfold after adjustment for BMI, and concluded that central deposition of body fat was significantly influenced by genetic factors. Using data on more than 18,000 subjects from the Canada Fitness Survey, we have already shown that the total transmissible effect across generations reached approximately 40% for trunk skinfolds (sum of subscapular and suprailiac skinfolds), limb skinfolds (sum of triceps, biceps, and medial calf skinfolds), and the trunk to limb skinfolds ratio.[22] Based on data from QFS, we estimated that the heritability of the amount of subcutaneous fat in the truncal abdominal area after adjustment for total body fat and of the trunk to limb skinfolds ratio ranged from approximately 30%[19] to 50% depending on the phenotypes.[23] These heritability estimates are in the range of those found in the present study for the amount of total and subcutaneous abdominal fat.

With the use of CT it was possible to precisely determine the amount of fat in the various abdominal depots. It is relevant to point out that the importance of familial aggregation varies according to the abdominal fat depot considered. The results suggest a stronger genetic effect (h^2) for the amount of AVF compared with the amount of fat in the subcutaneous area, with heritability estimates of 56% and 42%, respectively. Thus, for a given level of body FM, the amount of fat stored in the visceral depot is significantly influenced by genetic factors. Given the importance of the visceral depot in the metabolic complications associated with obesity, this finding implies that the comorbidities of visceral obesity are largely dependent of the genotype.

The results of this study also reveal that different hypotheses regarding the role of genetic factors in the familial resemblance of abdominal fat are suggested depending on whether data are adjusted for body FM or not. When total and visceral fat were adjusted for the effects of age only, familial correlations were not generally compatible with a purely genetic hypothesis. However, after adjustment for FM in addition to age, the pattern of correlations clearly suggests a genetic hypothesis as the major determinant. This finding implies that the covariation between the amount of abdominal fat and total body fat contributes to the familial aggregation of abdominal fat. It also suggests that genes affecting abdominal fat level are different from those involved in determining total body FM.

Finally, when one looks at the correlations observed for the visceral to total abdominal fat ratio after adjustment for

age and FM, only parent-offspring correlations reached significance ($r = .15$), while the marital and sibling correlations were not significantly different from zero. Since parents and offsprings share, on average, 50% of their genes, the lack of a sibling correlation in the presence of a significant parent-offspring correlation is puzzling and needs to be evaluated further. The familial effect for the visceral to total abdominal fat ratio, if any, is probably low and not significant.

The results presented in this study reveal that CT-assessed abdominal fat level, independent of total body FM, strongly aggregates in families and that genetic factors are the major determinant of this familial aggregation. Moreover, a higher genetic effect was found for AVF than for abdominal subcutaneous fat with heritability estimates of 56% and 42%, respectively. These results suggest that some individuals are more at risk than others to exhibit the various metabolic alterations associated with upper-body obesity because of their inherited tendency to store abdominal fat in the visceral depot rather than in the subcutaneous depot. Identification of genes responsible for these genetic differences should become a high priority and is likely to increase our understanding of the biological mechanisms responsible for the metabolic disturbances associated with visceral obesity.

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