Age-Related Increase in Visceral Adipose Tissue and Body Fat and the Metabolic Risk Profile of Premenopausal Women

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OBJECTIVE — Age-related differences in body fat and, more specifically, in the accumulation of abdominal visceral adipose tissue (AT) were examined as potential covariates of the age-related difference in the metabolic profile predictive of cardiovascular disease (CVD) risk observed in young, as compared with middle-aged, premenopausal women.

RESEARCH DESIGN AND METHODS — Body composition, AT distribution, plasma lipoprotein-lipid levels, glucose tolerance, and plasma insulin concentrations were assessed in a sample of 122 young women (27.4 ± 7.5 years, mean ± SD) and compared with a sample of 52 middle-aged premenopausal women (49.5 ± 5.3 years) who still had a normal menstrual cycle.

RESULTS — Middle-aged women were characterized by elevated levels of total abdominal and visceral AT and greater body fat mass and waist circumference, as well as by higher plasma levels of total cholesterol, LDL cholesterol, apolipoprotein (apo)B, and LDL-apoB compared with younger women. Furthermore, middle-aged women showed a greater glycemic response to a 75-g oral glucose load than young women ($P < 0.01$). In both young and middle-aged subjects, visceral AT accumulation was significantly correlated with plasma triglyceride, apoB, and LDL-apoB levels and with the cholesterol/HDL cholesterol ratio, as well as with plasma glucose, insulin, and C-peptide levels measured in the fasting state and after the oral glucose load, and negatively correlated with HDL cholesterol levels ($-0.41 \leq r \geq 0.65, P < 0.05$). When variables were adjusted for levels of visceral AT and fat mass, age-related differences that were initially found in plasma apoB and LDL-apoB levels, as well as in fasting glycemia and glucose tolerance, were eliminated.

CONCLUSIONS — Results of the present study suggest that even before the onset of menopause there is an age-related deterioration in the metabolic risk profile and an increase in visceral AT deposition in middle-aged women compared with young control subjects. Furthermore, our results provide support for the notion that the age-related increase in visceral AT accumulation is a significant factor involved in the deterioration of the CVD risk profile noted in premenopausal women with age.

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The risk of cardiovascular disease (CVD) is known to increase with age, partly through the deterioration of metabolic risk factors such as plasma lipoprotein levels (1,2). Plasma cholesterol, LDL cholesterol, and triglyceride (TG) levels have been reported to increase with age, whereas discordant results have been reported regarding age-related changes in HDL cholesterol concentrations, some studies showing a trend for a decrease in HDL cholesterol levels over time (3–5), whereas others reported either an increase (6) or no change in HDL cholesterol levels (7).

Obesity, and especially abdominal obesity, is associated with metabolic disturbances that contribute to increase the risk of CVD (8), supporting the early clinical observations of Vague (9), who first documented in the 1940s that regional adipose tissue (AT) distribution was an important determinant of the health hazards of obesity (9). Studies using imaging techniques such as computed tomography (CT) have shown that visceral AT is associated with an increased risk of type 2 diabetes and CVD, namely through alterations in indices of plasma glucose-insulin homeostasis and through a dyslipidemic profile (10–13). In this regard, age is a major correlate of visceral AT accumulation, as the size of this depot increases with age in both men and women (14–17). In women, the menopause-induced estrogen deficiency has been shown to be associated with an acceleration of visceral AT accumulation (17–19), although the molecular mechanisms responsible for this phenomenon remain speculative (20). Although protective effects have been attributed to estrogen in women (18,19), no study has, to the best of our knowledge, investigated the effect of age on visceral AT accumulation in premenopausal women.

Thus, the purpose of the present study was to investigate the age-related changes in body fat mass and visceral AT and in the metabolic risk profile in a group of premenopausal women. To achieve this objective, we have studied a sample of 52 middle-aged women (mean age ± SD: 49.5 ± 5.3 years) who still had a normal menstrual cycle and compared them with a

group of 122 young adult women (27.4 ± 7.5 years) for body composition, AT distribution, plasma lipoprotein-lipid levels, glucose tolerance, and plasma insulin concentrations. We have also examined the relationships of visceral AT accumulation to metabolic risk variables in the two age-groups. Furthermore, we have verified whether an adjustment for total body fat mass and visceral AT area would have any effect on the age-related differences in the metabolic risk profile.

RESEARCH DESIGN AND METHODS

Subjects

A total of 122 young adult women (mean age ± SD: 27.4 ± 7.5 years) and 52 middle-aged but premenopausal women (49.5 ± 5.3 years) involved in the Québec Family Study (QFS) (21), were used for the present analyses. The QFS, which is an ongoing family study aimed at a better understanding of the genetic aspects of obesity and related metabolic complications, has been approved by the Medical Ethics Committee of Laval University. All participants signed an informed-consent document to volunteer for this study. Women with diabetes or CVD or on medication known to affect carbohydrate or lipid metabolism were excluded from the present analyses. Premenopausal status was ascertained by self-report on the basis of regularity of the menstrual cycle at physical examination.

Anthropometric measurements

The hydrostatic weighing technique (22) was used to measure body density which was obtained from the mean of six measurements. Pulmonary residual volume was measured before immersion in the hydrostatic tank, using the helium dilution method of Meneely and Kaltreider (23). Percent body fat was derived from body density using the equation of Siri (24). Height, body weight, and waist and hip circumferences were measured according to the procedures recommended at the Airlie Conference (25), and the waist-to-hip ratio was calculated.

Physical activity journal

Activity records were completed using a physical activity journal as previously described (26). The evaluation of mean daily energy expenditure with this activity diary has been shown to provide values comparable to those obtained with the doubly labeled water technique (27). This

Table 1—*Physical characteristics of young and middle-aged premenopausal women*

	Young women	Middle-aged women
n	122	52
Age (years)	27.4 ± 7.5	49.5 ± 5.3*
BMI (kg/m²)	25.7 ± 6.8	27.1 ± 6.5
Body fat mass (kg)	21.3 ± 12.6	26.9 ± 11.7†
Waist circumference (cm)	78.0 ± 14.2	83.9 ± 15.7‡
Waist-to-hip ratio	0.77 ± 0.06	0.80 ± 0.08‡
CT abdominal AT area (cm²)		
Total	358.9 ± 219.5	452.9 ± 196.3†
Visceral	63.7 ± 40.9	116.1 ± 67.5*
Subcutaneous	295.2 ± 86.0	336.7 ± 143.8
Daily energy expenditure (kJ/24 h)	11,981.3 ± 3,254.2	12,477.7 ± 2,711.7

Data are means ± SD. For body fat mass, n = 120 in young women and n = 48 in middle-aged women. Daily energy expenditure was estimated from a physical activity journal: n = 113 in young women and n = 49 in middle-aged women. Significant difference between young versus middle-aged women: *$P < 0.0001$, †$P < 0.01$, ‡$P < 0.05$.
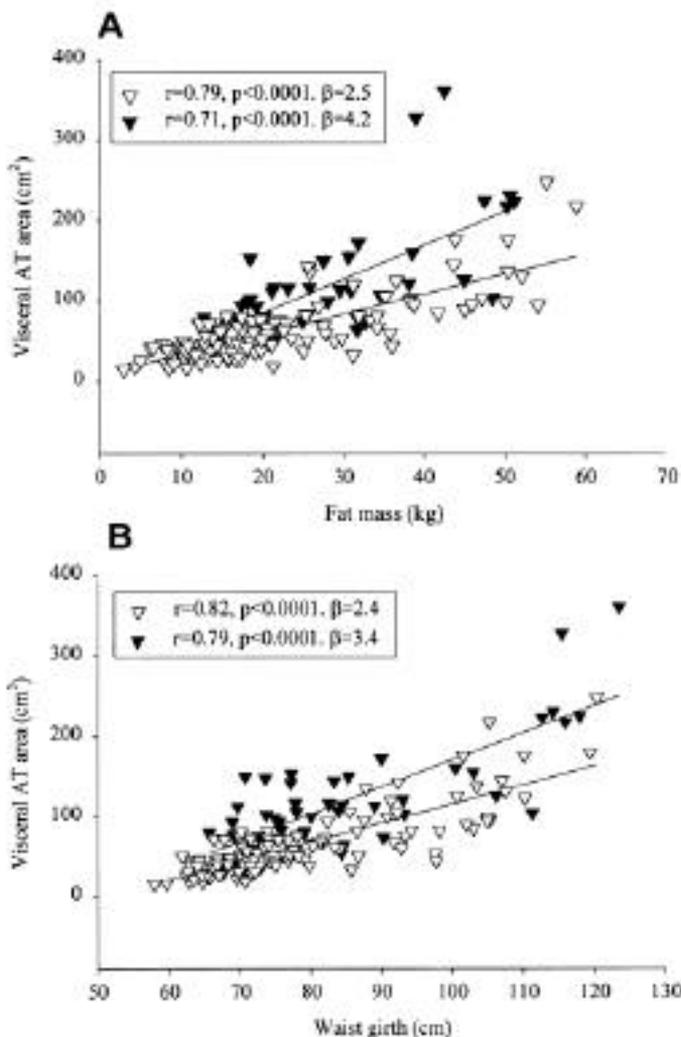
Figure 1—*Relationships of abdominal visceral adipose tissue area to body fat mass in 120 young ($\triangledown$) and 48 middle-aged ($\blacktriangledown$) women (A) and to waist circumference in 122 young ($\triangledown$) and 52 middle-aged women ($\blacktriangledown$) (B). The regression slope (β) in middle-aged women was significantly steeper than that in younger women (P < 0.0001).*

Table 2—*Metabolic risk profile of young and middle-aged premenopausal women*

	Young women	Middle-aged women
n	122	52
Cholesterol (mmol/l)	4.67 ± 1.03	5.40 ± 0.99*
Triglycerides (mmol/l)	1.23 ± 0.55	1.29 ± 0.62
LDL cholesterol (mmol/l)	2.83 ± 0.92	3.39 ± 0.89*
HDL cholesterol (mmol/l)	1.30 ± 0.30	1.44 ± 0.37†
Cholesterol/HDL cholesterol	3.75 ± 1.06	3.99 ± 1.23
ApoB (g/l)	0.89 ± 0.22	1.01 ± 0.22†
LDL-apoB (g/l)	0.80 ± 0.20	0.91 ± 0.21†
Fasting glucose (mmol/l)	4.88 ± 0.44	5.07 ± 0.48†
Fasting insulin (pmol/l)	68.7 ± 54.0	54.8 ± 42.0
Fasting C-peptide (pmol/l)	647.8 ± 294.7	609.8 ± 240.5

Data are means ± SD. $n = 102$ young women and 35 middle-aged women for apoB and LDL-apoB. Significant difference between young versus middle-aged women: *$P < 0.0005$, †$P < 0.05$.
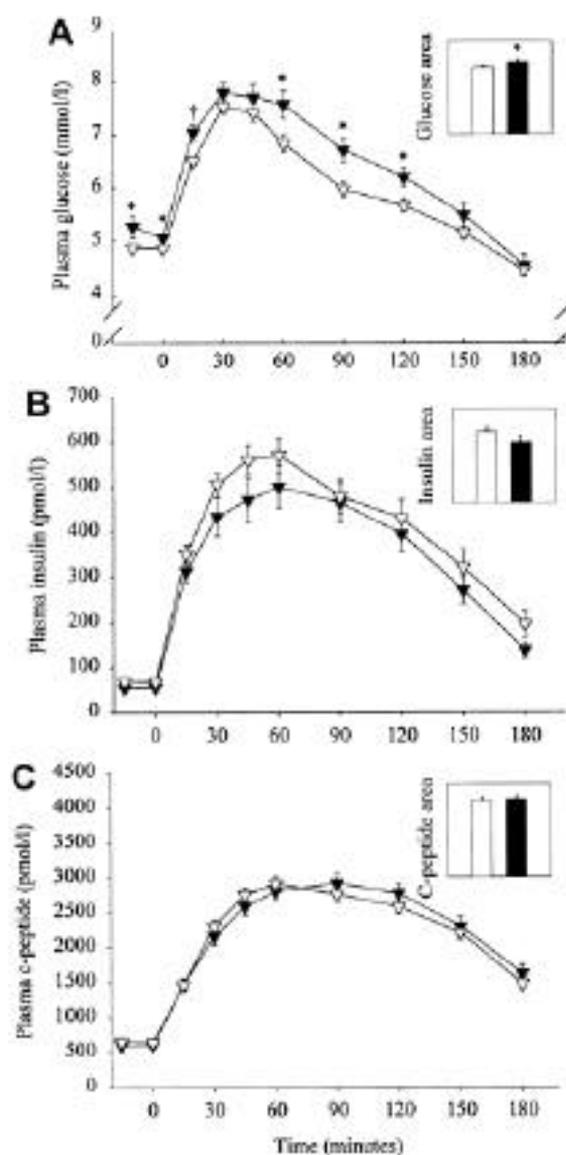

Figure 2—*Plasma glucose* (A), *insulin* (B), *and C-peptide* (C) *concentrations in the fasting state and after the oral glucose load in 50 middle-aged* (▼) *and 119 young* (▽) *women. Bar charts show plasma glucose* (mmol · l^{-1} · min^{-1}) × 10^{-3} *and insulin and C-peptide areas* (pmol · l^{-1} · min^{-1}) × 10^{-3}. *Significant differences between the two age-groups:* *$P < 0.05$, †$P < 0.005$.*

method has also been shown to be characterized by a high level of reliability (26).

Computed tomography
CT was performed on a Siemens Somatom DRH scanner (Siemens, Erlangen, Germany) using procedures previously described (28). Briefly, subjects were examined in the supine position with both arms stretched above the head. The CT scan was performed at the abdominal level between L4 and L5 vertebrae using a radiograph of the skeleton as a reference to establish the position of the scan to the nearest millimeter. Total abdominal AT area was calculated by delineating the surface with a graph pen and then computing the AT surface using an attenuation range of −190 to −30 Hounsfield units (28). Abdominal visceral AT area was measured by drawing a line within the muscle wall surrounding the abdominal cavity. The abdominal subcutaneous AT area was calculated by subtracting the amount of abdominal visceral fat from the total abdominal AT area.

Plasma lipoprotein-lipid
Blood samples were collected from an antecubital vein into vacutainer tubes containing EDTA after a 12-h overnight fast for the measurement of plasma lipid and lipoprotein levels. Cholesterol and TG levels were determined in plasma and lipoprotein fractions using an Analyzer Technicon RA-500 (Bayer, Tarrytown, NY) and enzymatic reagents were obtained from Randox (Crumlin, U.K.). Plasma VLDL (density < 1.006 g/ml) were isolated by ultracentrifugation (29). The HDL fraction was obtained after precipitation of LDL in the infranatant (density > 1.006 g/ml) with heparin and $MnCl_2$ (30). The cholesterol and TG content of the infranatant were measured before and after the precipitation step. ApoB concentration was measured in plasma and in the LDL fraction by the rocket immunoelectrophoretic method of Laurell (31) as previously described (32). Lyophilized serum standards for apoB measurements were prepared in our laboratory, calibrated with reference standards obtained from the Centers for Disease Control and Prevention (Atlanta, GA) and the results validated against external quality controls for apoB (Canadian Reference Laboratory [1996], Vancouver, British Columbia, Canada).

Oral glucose tolerance test (OGTT)
A 75-g OGTT was performed in the morning after an overnight fast. Blood samples

Table 3—Correlations between fat mass, visceral AT area, and metabolic risk variables in young versus middle-aged premenopausal women

	Young women (n = 122)		Middle-aged women (n = 52)	
	Visceral AT	Fat mass	Visceral AT	Fat mass
Lipoprotein-lipid variables				
Cholesterol	0.33*	0.13	0.23	0.16
TG	0.53*	0.39*	0.35†	0.39†
HDL cholesterol	−0.41*	−0.46*	−0.37†	−0.48*
Cholesterol/HDL-cholesterol	0.61*	0.52*	0.48*	0.52*
ApoB	0.38*	0.20†	0.36†	0.29
LDL-apoB	0.38*	0.22†	0.36†	0.25
Insulin-glucose homeostasis				
Fasting insulin	0.57*	0.60*	0.65*	0.61*
Fasting glucose	0.48*	0.42*	0.33†	0.46‡
Fasting C-peptide	0.50*	0.51*	0.58*	0.66*
Insulin area	0.52*	0.51*	0.45‡	0.36†
Glucose area	0.45*	0.35*	0.40‡	0.21
C-peptide area	0.43*	0.36*	0.38†	0.31†

n = 102 for young women and 35 for middle-aged women for apoB and LDL-apoB. n = 119 for young women and 50 for middle-aged women for all data under insulin-glucose homeostasis. *P < 0.0005, †P < 0.05, ‡P < 0.005.

were collected in EDTA-containing tubes (Miles Pharmaceuticals, Rexdale, Ontario, Canada) through a venous catheter placed in an antecubital vein at −15, 0, 15, 30, 45, 60, 90, 120, 150, and 180 min for the determination of plasma glucose, insulin, and C-peptide concentrations. Plasma glucose was measured enzymatically (33), whereas plasma insulin was measured by radioimmunoassay with polyethylene glycol separation (34). Plasma C-peptide levels were measured by a modification of the method of Heding (35), with polyclonal antibody A-4741 from Ventrex (Portland, ME) and polyethylene glycol precipitation (34). The total glucose, insulin, and C-peptide areas under the curve during the OGTT were determined with the trapezoid method.

Statistical analyses

An unpaired Student's *t* test was performed to compare young and middle-aged women. Pearson correlation coefficients were calculated to quantify the univariate associations among variables. Regression equations with visceral AT area as the dependent variable and either waist girth or fat mass as the independent variables were computed within each age-group. Stepwise multiple regression analyses were computed within each age-group to sort the contribution of fat mass, visceral AT area, and age to the variance of metabolic variables. Finally, covariance analyses were

used to evaluate the effect of visceral AT accumulation and total body fat mass on the age-related differences found in the metabolic risk profile of young and middle-aged women. All these analyses were performed on the SAS statistical package (SAS Institute, Cary, NC).

RESULTS — Table 1 shows physical characteristics of young and middle-aged

women. Middle-aged women had higher body fat mass, waist circumference, and waist-to-hip ratio and higher total abdominal and visceral AT areas than younger women (*P* < 0.05). Figure 1 shows that for any level of body fat mass or waist girth, middle-aged women were characterized by higher levels of visceral AT compared with young women (regression slopes were significantly different between the two age-groups, *P* < 0.0001).

Plasma cholesterol, LDL cholesterol, apoB, LDL-apoB, and HDL cholesterol as well as fasting glucose were all significantly higher in middle-aged versus young women (*P* < 0.05), whereas no significant difference was found between the two groups for TG levels, the total cholesterol/HDL cholesterol ratio and for fasting insulin and C-peptide concentrations (Table 2).

Figure 2 shows that an increased glycemic response to the glucose load was found in middle-aged premenopausal women compared with young women (*P* < 0.05). However, no difference was found in the insulin and C-peptide responses between the two age-groups.

When univariate correlation coefficients were computed, it was found that, overall, increased levels of body fat mass as well as of visceral AT were associated with altered plasma lipoprotein-lipid and glucose-insulin concentrations in both age-groups (Table 3). In addition, subcutaneous AT

Table 4—Multivariate regression analysis showing independent contributions of age, visceral AT, and fat mass to the variance of indices of plasma insulin glucose homeostasis and lipid-lipoprotein levels in young and middle-aged women

	Young women		Middle-aged women	
Dependent variable	Independent variables	Partial (R² × 100)	Independent variables	Partial (R² × 100)
Fasting insulin	Fat mass	36.46*	Visceral AT	44.02*
Fasting glucose	Visceral AT	20.38*	Fat mass	21.61†
Insulin area	Visceral AT	27.54*	Visceral AT	20.31†
Glucose area	Visceral AT	19.97*	Visceral AT	21.18†
Fasting C-peptide	Visceral AT	25.74*	Fat mass	43.29*
C-peptide area	Visceral AT	18.90*	Visceral AT	14.23‡
ApoB	Visceral AT	12.81*	Visceral AT	12.83‡
LDL-apoB	Visceral AT	14.04*	Visceral AT	13.06‡
			Age	12.25‡
Cholesterol	Visceral AT	4.84‡	Age	21.12†
LDL cholesterol	Visceral AT	7.22†	Age	15.20‡
Cholesterol/HDL cholesterol	Visceral AT	32.27*	Visceral AT	27.13*
TG	Visceral AT	22.13*	Visceral AT	17.79†
HDL cholesterol	Fat mass	21.17*	Fat mass	23.24*

*P < 0.0005, †P < 0.005, ‡P < 0.05.

Table 5—Physical characteristics and metabolic risk profile of young and middle-aged pre-menopausal women after adjustment for age-related differences in visceral AT accumulation and total body fat mass

	Young women	Middle-aged women
n	122	52
Body fat mass (kg)	22.9	22.9
Waist circumference (cm)	79.9 ± 4.8	78.3 ± 5.2
CT abdominal AT area (cm²)		
Visceral	77.1	77.1
Subcutaneous	309.3 ± 58.1	287.8 ± 63.0*
Cholesterol (mmol/l)	4.68 ± 0.90	5.18 ± 0.98†
TG (mmol/l)	1.26 ± 0.47	1.10 ± 0.51
LDL cholesterol (mmol/l)	2.85 ± 0.82	3.18 ± 0.89*
HDL cholesterol (mmol/l)	1.27 ± 0.29	1.51 ± 0.31‡
Cholesterol/HDL cholesterol	3.84 ± 0.90	3.57 ± 0.98
ApoB (g/l)	0.90 ± 0.22	0.94 ± 0.24
LDL-apoB (g/l)	0.82 ± 0.20	0.85 ± 0.22
Fasting glucose (mmol/l)	4.91 ± 0.42	4.97 ± 0.46
Fasting insulin (pmol/l)	73.0 ± 40.3	38.4 ± 44.0‡
Fasting C-peptide (pmol/l)	672.7 ± 243.2	525.5 ± 271.0†

Data are means ± SD. Significant difference between young versus middle-aged women: *$P < 0.05$, †$P < 0.005$, ‡$P < 0.0005$; $n = 102$ for young women and $n = 35$ for middle-aged women, for apoB and LDL-apoB. $n = 119$ for young women and $n = 50$ for middle-aged women, for fasting glucose, insulin, and C-peptide.

area followed exactly the same pattern of correlation with metabolic variables as body fat mass (data not shown).

Multiple regression analyses were conducted to sort out the contribution of age, body fatness, and visceral AT accumulation to the variance in metabolic risk variables. As shown in Table 4, visceral AT made the largest contribution to the variance of most of the metabolic variables in young women. Only fasting insulin and HDL cholesterol levels were better explained by fat mass than by visceral AT. In middle-aged women, visceral AT was also the most important predictor of several metabolic variables, whereas age made a contribution to the variance in cholesterol and LDL cholesterol.

Finally, to investigate further the contribution of visceral AT area and fat mass to age-related differences in the metabolic risk profile, covariance analyses were performed (Table 5). Adjustment for fat mass and visceral AT eliminated the age-related differences initially found for waist circumference, whereas this analysis yielded residual differences in abdominal subcutaneous AT area between the two age-groups. Differences initially found in plasma apoB and LDL-apoB, and in fasting glucose as well as in the glycemic response to the oral glucose load (Fig. 3), were also eliminated after adjustment for visceral AT area and total body fat mass. However, plasma cholesterol and LDL cholesterol as well as HDL cholesterol remained significantly higher in middle-aged than in young women. Furthermore, fasting plasma insulin and the insulin response to the glucose load (insulin area) were found to be significantly lower in middle-aged than in younger women whereas C-peptide levels during the oral glucose load at −15, 0, 30, 45, and 60 min were also significantly lower in middle-aged than in younger women (Fig. 3).

CONCLUSIONS — There are, with age, notable changes in body composition and AT distribution (14,16). Indeed, an increase in body fat mass and a preferential accumulation of AT in the abdominal region have been reported with age in both men and women (15,17). Results of the present study are concordant with these findings inasmuch as a higher accumulation of abdominal visceral AT as well as of total body fat mass were observed in middle-aged compared with young women. However, no significant difference between the two age-groups was noted for abdominal subcutaneous AT accumulation assessed by CT. This increase in visceral AT is in accordance with earlier reports (14–17) showing that the selective accumulation of abdominal AT observed with age is due to a preferential deposition of AT in the abdominal cavity.

Results of the present study suggest that aging per se is associated with a preferential accumulation of visceral AT, as middle-aged women of the present study did not show clinical signs of menopause. However, it is possible that some women in our sample could have been in their perimenopausal years and this is a limitation of our study, as we did not measure any hormone levels. Menopause has been shown to be associated with a preferential deposition of visceral AT (36). In this regard, the age-related increase in visceral fat may have been a confounding factor in some studies, thereby contributing to the overestimation of the effect of menopause per se on visceral AT accumulation (19). Thus, even before menopause, an age-related increase in visceral AT deposition can be observed.

A progressive deterioration in the metabolic risk profile is also generally observed with age (3–5,37,38). In the present study, middle-aged women showed higher plasma cholesterol, LDL cholesterol, apoB and LDL-apoB levels, as well as increased HDL cholesterol concentrations, compared with young control subjects. With the exception of HDL cholesterol, these results are in agreement with previous epidemiological studies (3–5,37,38). The observation of increased HDL cholesterol levels in middle-aged women is not, however, an uncommon finding, inasmuch as it had already been reported that middle-aged women (45–59 years) had higher HDL cholesterol levels than young women (20–44 years) (6). Furthermore, the possibility that the higher HDL cholesterol levels in middle-aged women may be explained by a selection bias cannot be excluded. Middle-aged women were also characterized by higher fasting glucose and an increased glucose response to an oral glucose challenge. These results are also concordant with previous findings (39–45).

After adjustment for abdominal visceral AT accumulation and total body fatness, the amount of abdominal subcutaneous AT was significantly higher in young compared with middle-aged women. Thus, for similar levels of total body fat and abdominal visceral AT, young women had elevated levels of subcutaneous abdominal AT compared with middle-aged women, providing further support to the notion that there may be a selective reduction in abdominal subcutaneous fat with age.

Adjustment for abdominal visceral AT accumulation and total body fat mass abolished the age-related difference initially
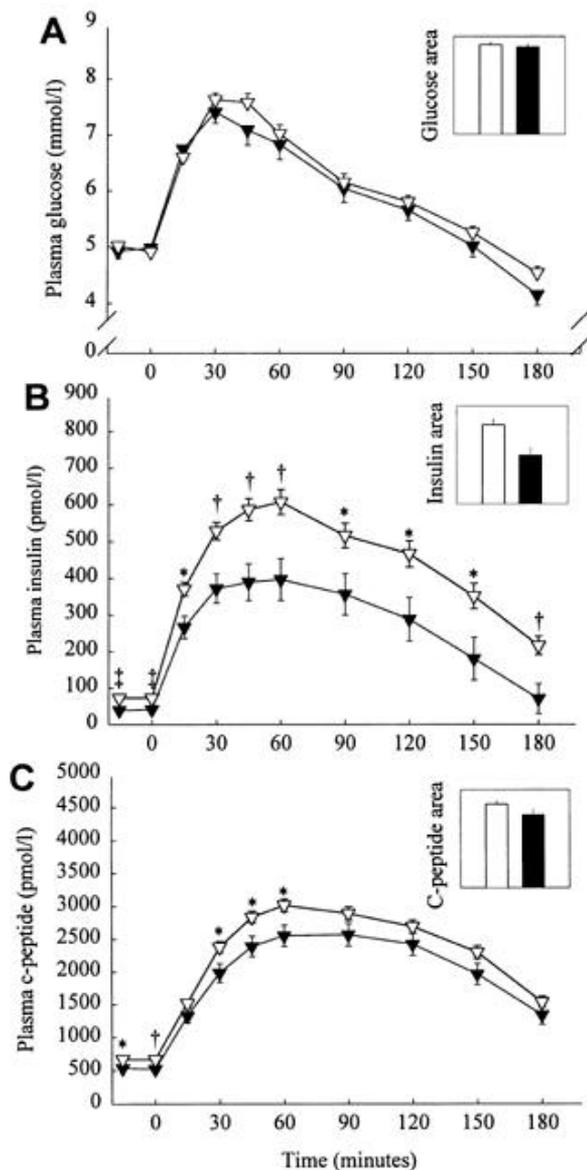
Figure 3—*Plasma glucose (A), insulin (B), and C-peptide (C) concentrations in the fasting state and after the oral glucose load in 50 middle-aged (▼) and 119 young (▽) women after adjusting subjects on the basis of their fat mass and visceral AT levels. Bar charts show plasma glucose (mmol · l⁻¹ · min⁻¹) × 10⁻³ and insulin and C-peptide areas (pmol · l⁻¹ · min⁻¹) × 10⁻³. Significant differences between the age-groups: *P < 0.05, †P < 0.005, ‡P < 0.0005.*

However, pairing or adjusting for visceral AT and body fatness levels did not have any effect on age-related differences in total cholesterol and LDL cholesterol levels, suggesting that the age effect on total and LDL cholesterol is largely independent from the increase in visceral AT. Similar results have been reported in men (7) and are consistent with the notion that excess visceral AT deposition is not a critical correlate of increased plasma cholesterol and LDL cholesterol levels (48).

It is well known that plasma insulin levels reflect, at least to a certain extent, insulin secretion, which has been related to subcutaneous fat (8,49,50). The higher relative abdominal subcutaneous AT accumulation observed in young compared with middle-aged women (after adjustment for fat mass and visceral AT), could, therefore, contribute to explain the higher insulinemic response found in younger compared with middle-aged women.

In summary, results of the present study show that middle-aged premenopausal women are characterized by an increased visceral AT accumulation and by some alterations in their metabolic risk profile compared with younger women. Thus, menopause is apparently not the only factor responsible for the metabolic deterioration observed with age in women. When young and middle-aged women with similar levels of abdominal visceral AT and total body fat mass were compared, some of the age-related differences in the metabolic profile (apoB and LDL-apoB levels as well as glucose tolerance) were eliminated, with the notable exception of plasma HDL cholesterol levels, which remained significantly higher in middle-aged than in young women. Thus, even in women who have not reached menopause, the age-related increase in visceral AT accumulation contributes to elevated apoB levels and to an impaired glucose tolerance. Finally, these results provide further support to the notion that the age-related increase in visceral AT is an important correlate of some of the alterations in plasma lipid-lipoprotein levels and in plasma glucose homeostasis that are observed with age in women.

found in plasma apoB and LDL-apoB levels and in glucose tolerance. These results provide further evidence that the variation in abdominal visceral fat and in total body fat contributes to the age-related increase in apoB and to the deterioration of glucose tolerance. Furthermore, results of multivariate analyses presented in Table 4 suggest that the deterioration in glucose tolerance as well as the increase in apoB levels found with age in women may be explained, at least to a large extent, by the concomitant increase in visceral AT. The hyperlipolytic state of visceral obesity (resulting from the excess lipolysis of portally drained adipocytes) is associated with an increased flux of free fatty acids to the liver, a factor which, along with the increased availability of glycerol for gluconeogenesis, may contribute to the increased hepatic glucose production found in this condition (43). The increased free fatty acid flux to the liver can also contribute to the increased production of TG rich lipoproteins by protecting apoB against its degradation (46,47), leading to an increased secretion of apoB.

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