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Possible Role of Adiponectin and Insulin Sensitivity in Mediating the Favorable Effects of Lower Body Fat Mass on Blood Lipids

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Aims: The objective of this study was to investigate the role of insulin sensitivity and serum adiponectin concentration as determinants, in middle-aged men, of the relationship between lower body fat and blood lipids after truncal fat has been accounted for.

Methods: Men (443) aged 39–65 yr, body mass index 18–43 kg/m^2, participated in the study. The following variables were measured: regional body fat distribution as assessed by dual-energy x-ray absorptiometry, maximal oxygen uptake, physical activity, fasting levels of serum adiponectin, triglycerides, and high-density lipoprotein- and total cholesterol. Plasma glucose and serum insulin were measured in the fasting state and after an oral glucose load.

Results: Lower body fat mass was inversely associated with serum triglycerides and total cholesterol and positively with serum high-density lipoprotein-cholesterol after adjustment for age, lean tissue mass, truncal fat mass, weight history, maximal oxygen uptake, and the level of physical activity ($P < 0.0005$). Serum adiponectin level and Matsudas insulin sensitivity index were positively intercorrelated, and both were positively correlated to lower body fat mass. When including adiponectin and insulin sensitivity in the analyses, the relationships between lower body fat mass and serum lipids were partly explained.

Conclusion: For a given level of truncal fat mass, a large lower body fat mass is associated with an advantageous blood lipid profile, which may be partially mediated by the relationships to both insulin sensitivity and serum adiponectin level. **(*J Clin Endocrinol Metab* 91: 1698–1704, 2006)**

IT IS WELL established that a high waist to hip ratio is associated with an atherogenic blood lipid profile independently of body fatness even in healthy younger men (1) and women (2). This may partly be explained by a large waist circumference representing a great amount of visceral fat accumulation that may be responsible for high serum levels of triglyceride and total cholesterol and a low level of high-density lipoprotein (HDL)-cholesterol (3, 4). However, there is good evidence that an association exists between peripheral fat and an advantageous blood lipid profile after central fat has been accounted for (5–8). This association may contribute to the relationship between waist to hip ratio and blood lipids.

Insulin resistance is well acknowledged as a key player in the association between intraabdominal fat accumulation and dyslipidemia (9), and a low circulating adiponectin level may be an important factor in this relationship. A promoting impact of plasma adiponectin on insulin sensitivity has been emphasized by many experimental and observational studies (10). A high level of visceral fat accumulation for a given whole-body adiposity is associated with low plasma levels of adiponectin (11, 12). Moreover, high plasma concentrations of adiponectin were found to be related to an advantageous blood lipid profile independently of adiposity and fat distribution (13, 14).

Plasma levels of insulin and adiponectin may also mediate the apparent beneficial effect of lower body fat on blood lipids. When truncal fat mass is accounted for, a large lower body fat accumulation appears to be associated with a high insulin sensitivity (7) and, consequently, a healthy lipid profile. A low waist to hip ratio has been reported to be associated with high levels of plasma adiponectin independently of body fat percentage (15). Furthermore, an investigation based on the same population as the present study found a positive association between lower body fat mass and plasma concentrations of adiponectin (16).

In the present study, we confirmed the association between a large lower body fat mass and an advantageous blood lipid profile after truncal fat is accounted for. We investigated the role of insulin sensitivity and serum adiponectin as possible explanatory factors behind this as-

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Abbreviations: BMI, Body mass index; CV, coefficient(s) of variation; DXA, dual-energy x-ray absorptiometry; EOOG, early onset obese group; FTM, fat tissue mass; HALS, HIV-associated lipodystrophy syndrome; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LTM, lean tissue mass; NEFA, nonesterified fatty acid; OGTT, oral glucose tolerance test; RSG, randomly selected group; VLDL, very low-density lipoprotein; VO_2max, maximal oxygen uptake.

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sociation in a very wide range of adiposity of middle-aged men.

Subjects and Methods

Subjects

The study population consisted of two groups of men sampled from different parts of a large population of young men examined at the draft boards at around age 20 yr. A group of early onset obese group (EOOG) was recruited by selection of all cases that were obese at draft board [body mass index (BMI) $\geq$ 31 kg/m^2]. The other group of men, the randomly selected group (RSG), was established by randomly selecting every 200th draftee from the same population and at the same time period as the EOOG men were sampled. This recruitment procedure resulted in a study population with a 200-fold relative oversampling of the obese subjects, which allowed for a better statistical accuracy in the upper part of the adiposity distribution. The two different groups were recruited for this study to achieve a great range of adiposity in our population. Thus, the purpose of the study was not to compare the two groups representing different levels of adiposity but to analyze the two groups combined in attempt to clarify general linear relationships.

The present study, which was performed during 1998–2000, was the most recent of a series of follow-up studies on these two cohorts (17). Due to death, emigration, disappearance, major illness, or refusal to participate, the number of participants in both groups was lower in this study than the original groups. Furthermore, only subjects who were less than 65 yr of age and reported to be healthy and not to take any medicine regularly were invited to participate in the present follow-up study. In some subjects, we failed to perform successful measurements of body composition, oral glucose tolerance test (OGTT), or maximal oxygen uptake test. The number of men included in EOOG and RSG included in the study was 174 and 269, respectively. Subject characteristics for the two study groups are shown in Table 1. The men included in the EOOG and RSG differed as expected with regard to present BMI. However, the average BMI of the men in RSG also exceeded 25 kg/m^2 (Table 1). Despite a large difference in average BMI between the RSG and EOOG, a substantial overlap was seen between the two groups (Table 1). The study was approved by the Ethical Committee for Copenhagen and Frederiksberg. All participants signed a written consent before participation.

Methods

Body weight was obtained by weighing the subjects in underwear on an electronic scale. Subjects' height was measured without shoes. Body composition was measured by dual-energy x-ray absorptiometry (DXA) using a Lunar DPX-IQ DXA scanner (LUNAR Radiation Corporation, Madison, WI). Subjects who had extremities that could not be placed inside the scanning area were excluded from the study. Due to each subject's supine position during the scanning, the panniculus tended to move sideward rather than to cover the lower body segment. Moreover, if the panniculus was large, a Velcro belt was tied around the abdomen to fix it. In this way, we further ensured that the panniculus was not included in the lower body segment. Lean tissue mass (LTM; grams) and fat tissue mass (FTM; grams) were obtained for the whole body, head, arms, lower body region, and trunk. The lower body and truncal regions were separated by a diagonal line passing through the middle of the femoral neck, which meant that a part of the gluteal region was included in the lower body region (16).

TABLE 1. Present characteristics of the RSG and EOOG

	RSG	EOOG
No.	269	174
No. of current smokers	107	68
Age (yr)	49.6 ± 5.9	47.5 ± 5.0
Weight (kg)	82.9 ± 12.6	112.2 ± 18.0
Height (cm)	178.5 ± 6.0	178.8 ± 6.8
BMI (kg/m^2)	26.0 ± 3.6	35.1 ± 5.3
BMI (kg/m^2) at draft board	21.6 ± 2.5	33.0 ± 2.3
Total fat mass (kg)	19.1 ± 8.2	37.0 ± 11.6
Lower body FTM (kg)	5.6 ± 2.4	10.9 ± 4.5
Truncal FTM (kg)	10.3 ± 4.9	19.9 ± 6.0
Upper body FTM (kg)	2.2 ± 1.0	4.7 ± 1.5
VO_2max (liters/min)	2.6 ± 0.6	2.8 ± 0.6

Mean ± SD.

The subjects were requested to avoid vigorous exercise on the day before and on the day of examination. Blood was sampled from an antecubital vein. Serum lipids were analyzed in the fasting subject. Total serum cholesterol was analyzed using an enzymatic end-point analysis with a Monotest Cholesterol kit (Roche Diagnostics, Mannheim, Germany) and using the cholesterol oxidase-phenol aminoantipyrine method. Serum HDL-cholesterol was analyzed using a homogenous enzymatic colorimetric test with a HDL-C plus kit (Boehringer Roche Diagnostics). Serum triglyceride was analyzed using an enzymatic, colormetric end-point analysis with MPR2 Triglycerides (Roche Diagnostics) and the glycerol phosphate oxidase-phenol aminoantipyrine method. Serum low-density lipoprotein (LDL)-cholesterol concentration was calculated from serum total cholesterol, HDL-cholesterol, and triglyceride concentrations according to Friedewalds formula. OGTT was performed according to the 1999 World Health Organization guidelines (18) with 75 g glucose administered after a 12-h fast and after a daily intake more than or equal to 150 g carbohydrate during the preceding 3 d. Two preload samples were drawn with 5-min interval, and the average was used as the baseline values. Postload samples were taken at min 15, 30, 45, 60, 90, and 120 for analysis of glucose and insulin. The equation $10{,}000/(FG \times FI \times \text{mean } G \times \text{mean } I)^{1/2}$, where FG is baseline plasma glucose concentration, FI is baseline serum insulin concentration, mean G is mean plasma glucose concentration during the OGTT, and mean I is mean serum insulin concentration during the OGTT, was applied as an index of whole-body insulin sensitivity. This index (Matsudas index) has been demonstrated to correlate better with whole-body insulin sensitivity as assessed by hyperinsulinemic euglycemic clamp than HOMA insulin resistance index and other proposed indices both in normal, impaired glucose tolerance, and type 2 diabetic individuals (19). Plasma glucose was determined by the hexokinase/glucose-6-phosphate dehydrogenase method [interassay coefficient of variation (CV) $<$ 0.02]. Serum insulin was measured by an ELISA method with a narrow specificity excluding des-31, des-32, and intact proinsulin (interassay CV $<$ 0.06). Adiponectin was assessed from baseline serum by a RIA kit purchased from LINCO Research Inc. (St. Charles, MO) using rabbit antiadiponectin antibodies (interassay CV $<$ 0.10).

Nonesterified fatty acids (NEFAs) were measured in full blood at baseline and at min 15, 30, 45, and 60 after the glucose load on COBAS MIRA (Roche Diagnostics) using an enzymatic analysis with acyl-coenzyme A synthetase and acyl-coenzyme A with a Wako NEFA C test kit (interassay CV $<$ 0.04). As a measure of the antilipolytic effect of the glucose load, the decline rate of the blood NEFA level from min 15–60 during the OGTT was determined as individual linear regression slope of concentrations *vs.* time.

Maximal oxygen uptake (VO_2max) was estimated by a progressive bicycling test. After a 5-min conditioning period, the load was increased by 20 W/min until voluntary exhaustion. The subject was instructed to pedal at a constant rate of 70 min^{-1}, but the ergometer adjusted the load to maintain external work effect irrespective of pedaling rate. Oxygen uptake was measured by a breath by breath system (Oxycon Champion, Jaeger, Würzburg, Germany). The subjects were instructed to complete questionnaires about their weekly leisure time and occupational physical activity, both of which were divided into four categories with a score from 1 to 4: leisure time, almost passive or light activity for less than 2 h (1); light activity such as strolling or gardening for 2–4 h (2); light activity for more than 4 h or heavy activity such as fast walking or bicycling or heavy gardening or gymnastics with sweating and breathlessness for 2–4 h (3); and heavy activity for more than 4 h or regular hard physical training several times per week (4).

Statistical analysis

No interactions with study group (EOOG or RSG) were found in the relationships between lower body FTM and any of the serum lipid variables; therefore, the groups were pooled in the analyses of variance. Relationships between the serum lipid variables (as independent variables) and lower body FTM were tested by analyses of covariance with study group as a fixed factor and lower body FTM together with age,

LTM, truncal FTM, weight changes since the time of recruitment, leisure time and occupational physical activity, and VO_2max as covariates. In the analyses of these data, the effect of truncal FTM as an independent factor is equivalent to the effect of total body fat in analyses of covariance, which also include lower body FTM, because the sum of truncal FTM and lower body FTM explains 99.8% of the variation in total body fat by univariate linear regression. Preliminary interactions between study group and all the covariates were allowed for in the models, but only statistical significant interactions were entered into the final models. When testing serum triglyceride, logarithmic transformation and exclusion of cases with triglyceride values more than 3.99 mmol/liter (corresponding to mean + 2 SD) as outliers were required to achieve a normal distribution in the residuals of the model. To test the role of insulin sensitivity and serum adiponectin as cofactors, the analyses were repeated with the inclusion of Matsudas index and/or serum adiponectin as additional covariates.

Results

Table 2 shows concentrations of fasting serum lipid and adiponectin and plasma glucose and Matsudas index in the two study groups. Serum triglyceride, total cholesterol, and LDL-cholesterol concentrations were inversely and serum HDL-cholesterol positively related to lower body FTM, independent of truncal FTM, VO_2max, reported physical activity, and age (Table 3 and Figs. 1 and 2). The associations between serum lipids and lower body FTM were present also without the inclusion truncal FTM in the analyses ($P < 0.05$, data not shown), although they were weakened due to the fact that truncal and lower body FTM are positively related, whereas truncal FTM is associated with blood lipids in the opposite direction as lower body FTM.

In a multivariate model including truncal, but not lower body FTM, Matsudas index showed associations with all measured blood lipids in the same directions as lower body FTM (Table 4). Serum adiponectin concentration also demonstrated associations with serum triglyceride and HDL-cholesterol concentrations in the same direction as lower body FTM (Table 4). Serum adiponectin concentration was positively related to the Matsudas index by simple regression analysis ($P < 0.0005$).

The relationships between lower body fat and blood lipid concentrations persisted although with reduced slopes after inclusion of Matsudas index or serum adiponectin concentration or both factors (Table 3). Matsudas index correlated positively with lower body FTM after accounting for truncal FTM in both study groups ($P < 0.005$). This was also the case for serum adiponectin concentration after accounting truncal FTM, LTM, age, and fitness estimates ($P < 0.0005$). These positive covariations between Matsudas index and serum adiponectin concentration on one hand and lower body FTM on the other in concert with the correlations of these factors with blood lipids explained their ability to reduce the strength of the relationships between lower body FTM and blood lipids.

Blood NEFA concentration declined rapidly after min 15 after glucose administration (Fig. 3), and the decline rate was positively related to serum adiponectin concentration, whereas there was no association between fasting blood NEFA concentration and serum adiponectin concentration (Table 4). There were no relationships between Matsudas index and fasting blood NEFA concentration or the blood NEFA decline rate after the glucose load (Table 4).

Serum adiponectin concentration was positively related to the Matsudas index by simple regression analysis ($P < 0.0005$).

Discussion

The present finding in middle-aged men with a wide range of body fat showed that a large lower body FTM was related to a low cardiovascular risk profile, after truncal fat mass was accounted for, corroborates observations in previous studies. In men with a large variation in total body fatness, peripheral skinfolds were negatively associated with serum total serum cholesterol level after accounting for the variation in intra-abdominal and sc abdominal fat as measured by computed tomography (5). Several other studies have found that hip (20, 21) or thigh (22) circumference was negatively associated with plasma triglyceride and positively associated with serum HDL-cholesterol both in men and women, after waist circumference was adjusted for. Studies with direct measurement of different fat depots by DXA like the present, or by computed tomography, support the anthropometric studies with regard to a possible advantageous impact of lower body fat (6–8). Finally, in the SOS study, based on 2450 severely obese men and women, a large thigh circumference was a marker of low cardiovascular risk (23), suggesting a cardioprotective role of femoral fat.

One of the questions being addressed in this study is therefore to which extent variations in serum adiponectin levels may explain the association between body fat distribution and blood lipids because body fat distribution appears to be a strong determinant of plasma adiponectin concentration (14). The amount of abdominal fat has been found

TABLE 2. Fasting circulating levels of biochemical variables and Matsudas insulin sensitivity index in the RSG and EOOG

	RSG	EOOG	*P*
n	269	174	
F-s-triglycerides (mmol/liter)	1.41 ± 0.87	1.91 ± 1.55	<0.0005
F-s-total cholesterol (mmol/liter)	5.75 ± 1.05	5.57 ± 1.05	0.08
F-s-HDL-cholesterol (mmol/liter)	1.23 ± 0.28	1.06 ± 0.25	<0.0005
F-s-adiponectin (μg/ml)	11.4 ± 10.3	10.6 ± 7.8	0.01
F-p-glucose (mmol/liter)	5.69 ± 0.62	6.34 ± 1.96	<0.0005
2-h p-glucose (mmol/liter)	6.68 ± 2.02	8.06 ± 3.64	<0.0005
F-blood-NEFA (μmol/liter)	359 ± 142	393 ± 161	0.02
F-s-insulin (pmol/liter)	38.5 ± 27.6	68.7 ± 51.0	<0.0005
2-h s-insulin (pmol/liter)	196.4 ± 185.0	335.0 ± 409.2	<0.0005
Matsudas index	7.59 ± 4.41	4.78 ± 3.32	<0.0005

Mean ± SD. *P* values obtained by Student's *t* test. F-, Fasting; s-, serum; p-, plasma.

TABLE 3. Independent relationships between fasting serum (f-s) lipid concentrations and lower body FTM with and without Matsudas index and serum adiponectin concentrations included in the models

	Matsudas index not included, f-s-adiponectin not included		Matsudas index included, f-s-adiponectin not included		Matsudas index not included, f-s-adiponectin included		Matsudas index included, f-s-adiponectin included	
	B × 10^5	*P*	B × 10^5	*P*	B × 10^5	*P*	B × 10^5	*P*
F-s-triglyceride (mmol/liter)[a]	−2.28 (−3.16 to −1.41)	<0.0005	−1.64 (−2.53 to −0.76)	<0.0005	−2.03 (−2.92 to −1.15)	<0.0005	−1.47 (−2.36 to −0.57)	0.001
F-s-HDL-cholesterol (mmol/liter)	3.40 (2.23 to 4.57)	<0.0005	2.87 (1.65 to 4.09)	<0.0005	2.97 (1.78 to 4.15)	<0.0005	2.54 (1.32 to 3.77)	<0.0005
F-s-total cholesterol (mmol/liter)	−9.16 (−14.45 to −3.87)	<0.001	−7.82 (−13.20 to −2.43)	0.005	−10.27 (−15.62 to −4.93)	<0.0005	−8.05 (−13.54 to −2.57)	0.004
F-s-LDL-cholesterol (mmol/liter)[b]	−9.07 (−13.87 to −4.27)	<0.0005	−7.34 (−12.34 to −2.33)	0.004	−8.71 (−13.63 to −3.80)	0.001	−7.46 (−12.56 to −2.36)	0.004

Parameter estimates (B), their 95% confidence intervals, and *P* values were obtained by analyses of covariance with study group as fixed factor and age, total LTM (kilograms), lower body (FTM) (grams), truncal FTM (kilograms), weight changes since the time of recruitment (kilograms), VO_2max (liters per minute), leisure time physical activity, and occupational physical activity entered as independent variables.

[a] Thirteen subjects with a fasting serum triglyceride level > 3.99 mmol/liter were excluded, and triglyceride data were logarithmisized to obtain normality in residuals.

[b] Calculated by Friedewalds formula.

FIG. 1. Fasting serum triglyceride concentrations (millimoles per liter) adjusted for differences in study group, age, total LTM, truncal FTM, weight changes since the time of recruitment, VO_2max, leisure time physical activity, and occupational physical activity against lower body FTM.

to be negatively associated with plasma adiponectin. In one study, visceral but not sc abdominal fat was reported to relate inversely to plasma adiponectin in healthy women (24). However, in another study performed in men, posterior sc abdominal adipose tissue was the best negative predictor of plasma adiponectin (25). As the assessment of fat distribution was performed by DXA in our study, we were unable to distinguish between the different compartments of abdominal adipose tissue.

Studies assessing adiponectin gene expression have found that it is lower in visceral compared with sc abdominal adipose tissue (26, 27). Moreover, a borderline significant inverse relationship between the amount of visceral fat and adiponectin gene expression has been reported in obese women (28), suggesting an antagonizing impact of intraab-

FIG. 2. Fasting serum HDL-cholesterol concentrations (millimoles per liter) adjusted for differences in study group, age, total LTM, truncal FTM, weight changes since the time of recruitment, VO_2max, leisure time physical activity, and occupational physical activity against lower body FTM.

TABLE 4. Independent relationships of fasting serum (f-s) lipid and blood NEFA concentrations with Matsudas insulin sensitivity index and fasting serum adiponectin concentrations without the inclusion of lower body fat in the models, and independent relationships of fasting blood NEFA concentrations and NEFA decline rate during the OGTT between min 15 and 60 postload *vs.* Matsudas insulin sensitivity index and fasting serum adiponectin concentrations

	vs. Matsudas index[a]		*vs.* F-s-adiponectin concentration[b]		*vs.* F-s-adiponectin concentration	
	B × 10^5	*P*	B × 10^5	*P*	B × 10^5	*P*
F-s-triglyceride (mmol/liter)[c]	−1533 (−2027 to −1038)	<0.0005	−425 (−646 to −204)	<0.0005	−331 (−546 to −116)	0.003
F-s-HDL-cholesterol (mmol/liter)	1527 (836 to 2217)	<0.0005	718 (419 to 1017)	<0.0005	628 (330 to 926)	<0.0005
F-s-total cholesterol (mmol/liter)	−6149 (−9171 to −3127)	<0.0005	−674 (−2003 to 656)	0.32	−238 (−1563 to 1086)	0.72
F-s-LDL-cholesterol (mmol/liter)[d]	−3928 (−6716 to −1140)	0.006	−652 (−1873 to 569)	0.29	−389 (−1617 to 839)	0.53
Fasting blood NEFA (mmol/liter)	150 (−287 to 587)	0.50	112 (−74 to 297)	0.24	101 (−85 to 288)	0.29
NEFA decline rate (mmol/liter/min)	7.6 (−3.7 to 18.9)	0.19	9.6 (4.9 to 14.4)	<0.0005	9.3 (4.5 to 14.0)	<0.0005

Parameter estimates (B), their 95% confidence intervals and *P* values were obtained by analyses of covariance with study group as fixed factor and Matsudas index, age, total LTM (kg), truncal FTM (kg), weight changes since the time of recruitment (kg), VO_2max (liters per minute), leisure time physical activity, and occupational physical activity entered as independent variables.

[a] Fasting serum adiponetic concentration not included in the model.

[b] Matsudas index not included in the model.

[c] Thirteen subjects with a fasting serum triglyceride level > 3.99 mmol/liter were excluded, and triglyceride data were logarithmisized to obtain normality in residuals.

[d] Calculated by Friedewalds formula.

dominal fat on adiponectin production. The present study now suggests an independent positive role of lower body FTM on adiponectin. Accordingly, a study in patients with HIV-associated lipodystrophy syndrome (HALS) found that limb fat deposition was positively related with plasma adiponectin and that this association cancelled visceral fat as a predictor for plasma adiponectin in a multivariate analysis (29). Proinflammatory cytokines produced in varying quantities by the different adipose tissue compartments may play a role in the overall production of adiponectin. The above study reported that a 52% reduction in adiponectin gene expression in sc abdominal adipose tissue in HALS patients was accompanied by an increased adipose tissue gene expression of TNF-α, IL-6, and IL-8 when compared with HIV-infected subjects without HALS (29). Accordingly, TNF-α gene expression in adipose tissue shoved inverse associations with adiponectin gene expression and plasma levels of adiponectin in nondiabetic subjects (30). That these cytokines may exert an inhibitory effect on adiponectin gene expression has been demonstrated by incubation experiments in isolated adipose tissue fragments (26, 29). To our knowledge, no studies have compared lower body or limb fat with different abdominal fat depots with regard to the production of substances that potentially may affect adiponectin production.

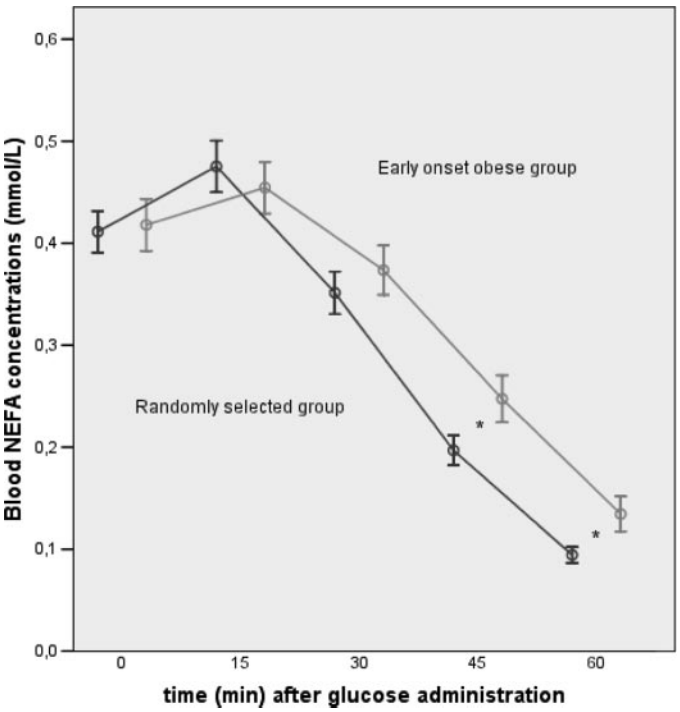

FIG. 3. Blood NEFA concentrations (mean ± 95% confidence interval) (millimoles per liter) during the first hour of the OGTT in the two recruitment groups. *, Significant differences ($P < 0.05$ by Student's *t* test) between the groups.

Both the present population (16) and a former study in older women (7) demonstrate that a larger lower body FTM for a given level of truncal FTM is associated with high insulin sensitivity. The present data demonstrate that the strength of the relationships between lower body FTM and serum triglyceride and HDL-cholesterol concentrations was somewhat reduced when the effect of adiponectin and/or Matsudas index was allowed for in the multivariate analyses. This suggests that plasma adiponectin and insulin sensitivity, to some extent, may be involved in the relationship between lower body FTM and blood lipid profile. Pertaining to adiponectin, previous studies have demonstrated an association between a high plasma level and an advantageous serum lipid profile independent of total body fat (13, 14, 31), intraabdominal fat (32), visceral fat (12), different abdominal adipose tissue compartments (33), and insulin sensitivity (13, 14, 24, 33, 34). Accordingly, in the present study, we found that serum adiponectin concentration was negatively related to serum triglyceride and positively related to serum HDL-cholesterol concentrations independent of body fat distribution and Matsudas index.

The liver is a major target organ for adiponectin. The activity of hepatic lipase that hydrolyzes triglyceride and phospholipids in HDL particles is an important factor to determine plasma level of HDL-cholesterol (35–38). An antagonizing effect by adiponectin on hepatic lipase may consequently increase plasma HDL-cholesterol level. The pres-

ence of such a mechanism is supported by findings of an inverse relationship between plasma adiponectin and hepatic lipase activity independent of BMI and plasma insulin (39). Furthermore, an insulin-amplifying effect of adiponectin on the liver may be an important mediator of the impact of adiponectin on blood lipids. An acute improvement of hepatic insulin sensitivity with adiponectin infusion has been demonstrated both by a euglycemic insulin clamp study in mice (40) and in isolated rat hepatocytes (41). However, adiponectin may also exert a more long-term effect on insulin sensitivity in the liver by lowering its lipid accumulation. Excessive hepatic lipid accumulation is associated with an impaired insulin sensitivity of the liver (42), which, in turn deteriorates its lipid metabolism (43). With insulin resistance, very low-density lipoprotein (VLDL)-triglyceride production in the liver is elevated due to an enhanced assembly of VLDL particles (44). This may further be amplified by an elevated circulatory supply of NEFA from insulin-resistant adipose tissue that provides substrate for triglyceride synthesis. Adiponectin is capable of reducing hepatic lipid content (45–48) probably mediated by stimulation of fat oxidation induced by activation of AMP-activated protein kinase (48). Apart from improving insulin sensitivity, a reduction in lipid deposition in the liver may directly reduce its production of VLDL-triglycerides. A high level of plasma triglycerides may contribute to a reduced plasma HDL-cholesterol level by exchanging cholesterol for triglyceride between HDL- and triglyceride-rich lipoproteins such as VLDL (49). The negative relationship between serum LDL-cholesterol and lower body FTM may be explained by a greater catabolism of the these particles due to a higher LDL-receptor activity associated with a higher insulin sensitivity in individuals with a large lower body FTM. However, other factors beyond variations in insulin action may be involved as the association persisted after allowing for differences in Matsudas in the analyses. Knowledge about LDL particle profile would have been more predictive in terms of cardiovascular risk.

Apart from the direct effects of adiponectin on the liver discussed above, the hormone may enforce the antilipolytic effect of insulin on adipose tissue. Hence, the present study confirms previous observations of an inverse association between plasma adiponectin level and postglucose serum NEFA concentrations that is independent of the insulin sensitivity in healthy subjects (13). This may result in a reduced hepatic exposure of NEFA from plasma. Plasma NEFA levels may further be reduced by an enhancing effect of adiponectin on skeletal muscle fat oxidation mediated by its stimulating impact on AMP-activated protein kinase (48).

In concert with the above-discussed studies, our data therefore suggest that part of the associations between serum adiponectin concentration and serum triglyceride and HDL-cholesterol concentrations is linked to the positive relationship between serum adiponectin and insulin sensitivity. On the other hand, the strong collinearity between serum adiponectin concentration and insulin sensitivity that is also found in our data may preclude the determination of the relative explicative power of adiponectin as an independent mediator of body fat distribution on blood lipids. Finally, an association between plasma adiponectin levels and postheparin lipoprotein lipase activity that was independent of insulin sensitivity and BMI has been reported in both diabetic and nondiabetic patients (50), which suggests another peripheral avenue for adiponectin to improve blood lipids.

An alternative hypothesis to lower body fat as the primary factor is that a gynoid fat distribution may be a consequence of an overall high insulin sensitivity promoting lower fat accumulation in favor of upper body fat accumulation. Furthermore, a gynoid fat distribution may improve serum lipid profile through other mechanisms than enhancement of serum adiponectin concentration and insulin sensitivity. Part of the association between lower body FTM and serum lipids persisted after the variation in both adiponectin and Matsudas index were accounted for, and this allows for the existence of additional mechanisms. However, the relative explicatory significance of some of the factors entered in regression models may be underestimated compared with their true impact because the true covariation with the other predictors may be closer than it appears in the models due to measuring errors or over-time variations. Hence, if serum adiponectin level and Matsudas index had been measured exactly and at the optimal time, less residual variation in lower body fat might have remained to be associated with serum lipids.

In conclusion, we found that a large lower body fat deposition in obese and nonobese middle-aged men was associated with a favorable serum lipid profile after variations in truncal fat deposition were accounted for. In concert with other reports, our findings suggest that both serum adiponectin level and insulin sensitivity have a mediating role between body fat distribution and blood lipids that may be manifested both in the liver and peripheral tissues.

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