Interrelationship Between Estimates of Adiposity and Body Fat Distribution With Metabolic and Hemostatic Parameters in Obese Children

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Adiposity in childhood is often associated with metabolic abnormalities and accompanied by a dysregulation of the coagulation and fibrinolytic systems. We studied the interrelationship of metabolic and hemostatic parameters and explored their relationship with measures of adiposity and fat distribution in obese children. In 34 obese boys (mean age, 11.7 years) and 57 obese girls (12.1 years), blood samples were determined for insulin, glucose, triglycerides, fibrinogen, plasminogen activator inhibitor-1 (PAI-1), and tissue-type plasminogen activator-antigen (tPA-Ag). Body composition was assessed by means of impedance. Waist (Wc) and hip circumference were measured. The thickness of subcutaneous adipose tissue-layers (SAT-layers) was measured at 15 different body sites (from 1-neck to 15-calf) by means of the optical device, Lipometer. Overall subcutaneous fatness (SAT) was calculated and SAT-distribution was estimated by means of factor analysis. Significant correlations were found between different measures of adiposity and Wc with metabolic parameters. Fibrinogen was mainly associated with upper body subcutaneous fatness (factor 1) in boys. In girls, hemostatic parameters were associated with nearly all measures of adiposity and also with factor 1 and SAT. Regression analysis showed that factor 1 together with PAI-1 (both $P < .0001$) contribute to fibrinogen (adjusted [adj], $R^2 = .30$). PAI-1 together with trigylcerides (both $P < .0001$) and age ($P < .04$) were main determinants for tPA-Ag (adj, $R^2 = .41$). tPA-Ag ($P < .0001$) together with glucose ($P < .001$, negative slope), fibrinogen ($P < .001$, negative slope), and percentage fat mass (%FM) ($P < .01$) contributed to PAI-1 (adj, $R^2 = .54$). These results favor the concept of an interrelationship between metabolic and hemostatic parameters resulting from increased adiposity, perhaps influenced by pubertal development of children. Although upper body subcutaneous fatness was found to be a main correlate of metabolic and hemostatic parameters, it remains to be investigated whether this type of subcutaneous fat distribution is involved in the expression of metabolic and hemostatic risk factors and participates in the dysregulation of the hemostatic system in the state of childhood obesity.

OBESITY IS OFTEN accompanied by related metabolic disorders and by a dysregulation of the coagulation and fibrinolytic systems. Some of these metabolic abnormalities, ie, hyperinsulinemia and changes in the lipoprotein profile are already present in the state of childhood and juvenile obesity[1] and may contribute to later health outcomes.[2]

A defect in the fibrinolytic system appears to be a risk factor for the development of cardiovascular disease mainly characterized by increased plasma levels of an inhibitor of fibrinolysis the plasminogen activator inhibitor-1 (PAI-1).[3] PAI-1 levels are elevated in the common syndrome of insulin resistance[4,5] as it is encountered in obese adults[6,7] and obese children.[8] Plasma levels of PAI-1 are related to insulinemia in cross-sectional studies, and insulin stimulates PAI-1 in vitro and in vivo.[9-12]

Adipose tissue itself is a main source of PAI-1,[13-16] but not all body fat depots contribute to PAI-1 in an equal manner. Visceral fat is a main determinant for PAI-1,[17-20] whereas recent findings indicated that subcutaneous adipose tissue secreted a greater amount of PAI-1 than visceral adipose tissue from the same obese individuals.[21]

In obese boys and girls, visceral fat and fat-free mass (FFM) were significant predictors of PAI-1,[22] but also total body fatness was shown to contribute to PAI-1 in obese children.[23] However, the possible relationship between overall subcutaneous fatness and subcutaneous fat distribution on plasma hemostatic factors has not been investigated in obese children. We determined whether hemostatic and metabolic risk factors are interrelated and independently associated with different estimates of adiposity and body fat distribution. Because men were shown to have a 2 times higher plasma PAI-1 activity than women due to gender differences in waist to hip ratio,[24] we also investigated whether any relationship between hemostatic parameters and subcutaneous fat distribution also depends on the sex of obese children.

SUBJECTS AND METHODS

Subjects

A total of 34 obese boys ([mean and standard deviation]; age, 11.7 ± 2.6 years; body mass index [BMI], 27 ± 4.9) and 57 obese girls (age, 12.1 ± 1.9 years; BMI, 27.8 ± 5.2) were investigated. Obesity was defined as a BMI (kg/m^2) ≥ 90th percentile for age and sex. All anthropometric, metabolic, and fibrinolytic characteristics are shown in Table 1.

Laboratory Methods

Venous blood samples were taken between 8 AM and 8:30 AM after an overnight fast. Blood samples for the measurements of fibrinolytic parameters were drawn into plastic tubes containing 0.1 mol/L sodium citrate. The plasma was separated by centrifugation at 3,000 × *g* for 10 minutes at 4°C and stored at −70°C. Tissue-type plasminogen activator-antigen (tPA-Ag) and plasminogen activator inhibitor-1-antigen

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Submitted August 8, 2000; accepted November 19, 2000.

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0026-0495/01/5006-0024$35.00/0
doi:10.1053/meta.2001.22562

(PAI-1-Ag) were determined by means of enzyme-linked immunosorbent assay (ELISA) (Kabi, Vienna, Austria). Fibrinogen was assayed by a thrombin time method according to Clauss.[25]

Insulin (μlU/mL) was measured by means of radioimmunoassay (RIA) (Linco Research, St Charles, MO) with an intra- and interassay coefficients of variation $<7\%$ and $<8.5\%$ in our laboratory, respectively.

Glucose (mmol/L) was measured by means of the hexokinase/glucose 6-phosphate-dehydrogenase method using a commercial kit (Boehringer, Mannheim, Germany). Insulin resistance was calculated through the fasting insulin resistance index (FIRI): [fasting glucose (mmol/L) $\times$ fasting insulin (μlU/mL)]/25.[26]

Triglycerides (mmol/L) were measured by means of hydrolysis with subsequent determination of liberated glycerol by colorimetry (Boehringer).

Assessment of Body Composition

FFM was estimated[27] by means of bioelectrical impedance (BIA, Akern-RJL 101/S, Clinton, MI) with an applied current of 0.8 mA at 50 kHz in the fasting state. Fat mass (FM) was calculated as the difference between body weight and FFM. Percentage fat mass (%FM) was expressed as the relative amount of FM for a given body weight. The equation used to predict FFM[27] has been established for the pediatric age range (3.9 to 19.3 years) by validating FFM predicted by BIA against potassium-dilution technique. However, those equations have not been evaluated for our study group because no impedance predictions for Austrian normal-weight and obese children exist.

Assessment of Abdominal Fat Distribution

Waist (Wc) and hip circumference (Hc) were measured to the nearest 0.5 cm in triplicate and the median was taken. The waist-to-hip ratio (WHR) was calculated as Wc/Hc.

Measurement of Subcutaneous Adipose Tissue

The thickness of subcutaneous adipose tissue-layers (SAT-layers in mm) were determined by means of the optical device, Lipometer (Moeller Mebtechnik, Graz, Austria),[28] as described previously.[29,30] The Lipometer uses light-emitting diodes, which illuminate the interesting subcutaneous fatty layer, forming certain geometrical patterns varying in succession. A photodiode measures the corresponding light intensities back scattered in the subcutaneous adipose tissue. These light signals are amplified, digitized, and stored on computer. Measurements of SAT-layers were performed at 15 specified body sites, from 1-neck to 15-calf, on the right side of the body (Fig 1) in the standing position. The coefficients of variation of SAT-layers ranged between 1.9% for SAT-layer 5-front chest and 12.2% for SAT-layer 13-rear thigh.[30] To give a proxy estimate of overall subcutaneous adipose tissue (SAT, in mm), linear addition was performed for all 15 SAT-layers (Table 1).

Children were judged as healthy by medical examination, and written informed consent was given by the parents. The study was approved by the local ethical committee.

Statistics

Data not normally distributed were $\log_{10}$ transformed (fibrinogen, insulin, glucose, FIRI, and triglycerides). Analysis of variance was used to compare parameters between groups. In the case of a significant difference, the Student-Newman-Keuls test was used. When variances were not normally distributed, Kruskal-Wallis test was used. Correlations between variables of interest were calculated using Pearsons correlations and Spearmans rank sum test. Partial correlation was performed to adjust for the influence of confounding variables. To estimate subcutaneous fat distribution and to reduce the number of correlations, factor analysis was used for 15 SAT-layers. To give an easy way to calculate the resulting factors (see Results), a linear addition was performed for those SAT-layers, which belong to the extracted factors. The independence and significance of variables was tested by stepwise, multiple regression analysis based on results of the univariate correlations.

A maximum of 4 independent variables in each regression model were allowed to enter the equation. Because maturity levels were not assessed in obese children, chronologic age was used as a surrogate for sexual maturation in the regression models. The significance level of *P* values was set at 5%. Data are given as mean and standard deviation unless otherwise indicated.

RESULTS

No signifcant sex-differences were found for metabolic and hemostatic parameters (Table 1). Wc was not different between boys and girls, but girls had a greater Hc, and WHR was greater in boys.

Factor analysis for measured SAT-layers extracted 3 factors, which were the same in boys and in girls (not shown). Therefore, data were collapsed and factor analysis was used for the whole study group. Factor 1 had an Eigenvalue of 5.0 and

Table 1. Anthropometric, Metabolic, and Fibrinolytic Parameters of Obese Children

Parameters	Boys (n = 34)	Girls (n = 57)	*P*
Age (yr)	11.7 ± 2.6	12.1 ± 1.9	.40
Body mass (kg)	67.55 ± 22	69.1 ± 17.5	.71
BMI	27 ± 4.9	27.8 ± 5.2	.51
WC (cm)	90.5 ± 13.5	90.6 ± 13.5	.98
HC (cm)	91.25 ± 12.1	98.45 ± 12.4	.01
WHR	0.99 ± 0.05	0.92 ± 0.07	<.0001*
FM (kg)	31.55 ± 13.7	32.7 ± 12.75	.69
%FM	45.65 ± 6.5	45.9 ± 7.5	.86
Factor 1 (mm)	117.5 ± 27.4	116.9 ± 30.3	.93
Factor 2 (mm)	51.2 ± 12.1	45 ± 11.7	.018
Factor 3 (mm)	62.3 ± 13.3	56.8 ± 13	.053
SAT (mm)	231.1 ± 41.3	218.75 ± 40.9	.17
Fibrinogen	286.4 ± 89.4	287.5 ± 74.3	
Log_{10} fibrinogen	2.44 ± 0.12	2.45 ± 0.1	.785
t-PA-Ag	3.86 ± 1.56	4 ± 1.6	.68
PAI-1 Ag	66.9 ± 28.4	66.2 ± 28.8	.915
Insulin (μlU/mL)	15.3 ± 15.2	15.2 ± 10.1	
Log_{10} insulin	1.06 ± 0.3	1.1 ± 0.24	.415
Glucose (mmol/L)	4.2 ± 1	3.95 ± 1.2	
Log_{10} glucose	0.61 ± 0.09	0.58 ± 0.11	.15
FIRI	2.43 ± 2.38	2.6 ± 2.4	
Log_{10} FIRI	0.255 ± 0.31	0.29 ± 0.32	.63
Triglycerides (mmol/L)	1.02 ± 0.69	0.88 ± 0.35	
Log_{10} triglycerides	−0.06 ± 0.23	−0.086 ± 0.17	.56

NOTE. Data are presented as mean ± SD. *P* accounts for differences between boys and girls (by means of ANOVA). Factor 1 (summed SAT-layers from 1-neck to 6-lateral chest), factor 2 (summed SAT-layers from 11-front thigh to 15-calf), factor 3 (summed SAT-layers from 7-upper abdomen to 10-hip). SAT (overall subcutaneous adiposity; summed SAT-layers from 1-neck to 15-calf.

Abbreviations: tPA-Ag, tissue-type plasminogen activator-antigen; PAI-1-Ag, plasminogen activator inhibitor-1-antigen; FIRI, fasting insulin resistance index (fasting glucose [mmol/L] $\times$ fasting insulin [μlU/mL]/25).

* By means of Kruskal-Wallis test.

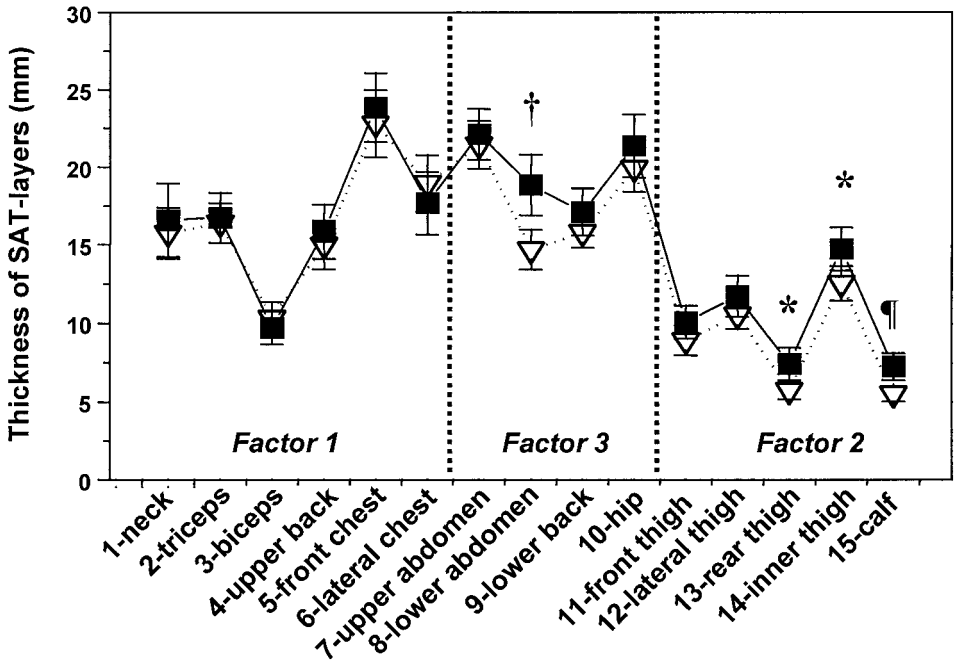

Fig 1. Pattern of SAT-layers (in mm) in obese boys (■ and solid line) and obese girls (▽ and dotted line). Values are given as mean and 95% confidence interval of the mean. Superscripts denote a significant difference in the thickness of SAT-layers between boys and girls (*$P < .05$, ¶$P < .01$, †$P < .001$). Factor 1 (upper body subcutaneous adiposity, from 1-neck to 6-lateral chest), factor 2 (lower body subcutaneous adiposity, from 11-front thigh to 15-calf), factor 3 (abdominal subcutaneous adiposity, from 7-upper abdomen to 10-hip). See also Methods and Results.

included 6 SAT-layers from the upper body (from 1-neck to 6-lateral chest). Factor 2 had an Eigenvalue of 3.42 and included 5 SAT-layers from the lower extremities (from 11-front thigh to 15-calf). Factor 3 had the lowest Eigenvalue (1.23) and included 4 SAT-layers from the abdominal region (from 7-upper abdomen to 10-hip). Linear addition was performed for factor 1-related SAT-layers (upper body subcutaneous adiposity), for factor 2-related SAT-layers (lower body subcutaneous adiposity), and for factor 3-related SAT-layers (abdominal subcutaneous adiposity) (Fig 1).

Boys had a greater value of factor 2 ($P = .018$) and factor 3-related SAT-layers ($P = .053$) than girls. Factor 1 and overall subcutaneous fatness (SAT) were not different between boys and girls (Table 1).

Spearmans Rank Correlation Between Estimated Parameters in Boys and Girls

In boys, insulin was significantly associated with different estimates of adiposity, ie, body mass, BMI, FM, and %FM (Table 2). Insulin was also correlated to Wc, but not correlated to SAT and its distribution (factor 1, factor 2, and factor 3). The same was observed for FIRI and triglycerides. However, triglycerides were positively correlated to factor 1 ($P < .05$). Fibrinogen was correlated only to factor 1 ($P = .001$) and SAT ($P = .016$). tPA-Ag was not correlated to any of the different estimates of adiposity or subcutaneous fat distribution. PAI-1 was correlated to body mass, FM, %FM, and Wc.

In girls, insulin and FIRI were significantly associated with all estimates of adiposity and were also related to Wc, WHR, factor 1, and SAT. Triglycerides were correlated to BMI, %FM, Wc, and WHR. Triglycerides were also associated with factor 1 ($P = .004$) and SAT ($P = .014$). Fibrinogen was correlated to almost all estimates of adiposity and also to factor 1 ($P = .005$) and SAT ($P = .006$). However, in contrast to obese boys, tPA-Ag was significantly correlated to FM, %FM, Wc, WHR, factor 1 ($P < .0001$), and SAT ($P = .003$). PAI-1 was correlated to %FM only.

Crude and Partial Correlations Between Metabolic and Hemostatic Parameters

Bivariate correlations were calculated to see whether metabolic and hemostatic parameters are interrelated (Table 3). To judge the influence of adiposity on outcome measures, partial correlation was performed using BMI as a confounding variable.

In boys, insulin and FIRI were significantly correlated to trigylcerides. When adjusted for adiposity, the magnitude of these relationships was reduced. Glucose was in inverse relationship with PAI-1, and this association was strengthened after control for adiposity. Triglycerides were significantly associated with tPA-Ag independent of adiposity. The same independence was obtained for the relationship between tPA-Ag and PAI-1. However, the magnitude of the inverse relationship between PAI-1 and fibrinogen was slightly increased after adjustment for adiposity.

In girls, insulin, glucose, and FIRI were related to triglycerides and fibrinogen independent of adiposity. However, the relationship between insulin and fibrinogen was blunted after control for BMI. Nothwithstanding, the relationship between insulin and FIRI with tPA-Ag was not substantially influenced by the degree of adiposity. The same was found for the inverse relationship between glucose and PAI-1, which persisted after control for BMI. Triglycerides were related to tPA-Ag, and fibrinogen was inversely related to PAI-1, with the latter being in signifcant relationship to tPA-Ag. Again, the magnitude of these relationships remained fairly constant after controlling for BMI.

Table 2. Crude Correlations Between Estimates of Adiposity, Body Fat Distribution, and Metabolic and Fibrinolytic Parameters in Obese Boys and Girls

Parameters	Body Mass	BMI	FM	%FM	Waist	WHR	Factor 1	Factor 2	Factor 3	SAT
Boys (N = 34)										
Insulin	0.59*	0.735†	0.61†	0.35‡	0.64†	0.25	0.22	−0.26	−0.31‡	0.03
Glucose	0.33‡	0.36‡	0.23	−0.03	0.25	−0.23	0.18	−0.19	−0.08	0.07
FIRI	0.56*	0.71†	0.54*	0.21	0.60†	0.12	0.15	−0.17	−0.24	0.05
Triglycerides	0.57*	0.59*	0.62†	0.43§	0.60†	0.31‡	0.33‡	−0.22	−0.23	0.225
Fibrinogen	0.01	0.23	0.11	0.24	0.12	0.245	0.50*	0.07	0.20	0.38‡
t-PA-Ag	0.14	0.21	0.21	0.17	0.27	0.20	0.06	0.10	0.01	0.13
PAI-1	0.315‡	0.29	0.43§	0.41‖	0.35‡	0.15	−0.12	0.01	−0.21	−0.07
Girls (N = 57)										
Insulin	0.51†	0.65†	0.53†	0.47*	0.64†	0.28‡	0.53†	−0.21	−0.03	0.325‡
Glucose	0.19	0.20	0.13	0.0	0.23‡	0.06	0.11	−0.1	−0.06	0.08
FIRI	0.43*	0.59†	0.46*	0.40§	0.62†	0.255‡	0.495†	−0.18	0.02	0.34§
Triglycerides	0.18	0.35§	0.19	0.30‡	0.34§	0.32§	0.35§	0.03	0.215	0.29‡
Fibrinogen	0.23‡	0.33§	0.23‡	0.18	0.37§	0.20	0.34§	0.15	0.15	0.33§
t-PA-Ag	0.11	0.22	0.255‡	0.42*	0.23‡	0.26‡	0.48†	−0.09	0.15	0.36§
PAI-1	0.05	0.11	0.16	0.33§	0.025	0.11	0.18	−0.03	0.10	0.12

NOTE. The crude correlations between different estimates of adiposity, body fat distribution, and metabolic parameters were calculated in obese boys and girls separately.

* $P < .001$.
† $P < .0001$.
‡ $P < .05$.
§ $P < .01$.
‖ $P = .01$.

Multiple Regression Analysis With Fibrinogen, t-PA-Ag, and PAI-1 as Dependent Variables

Calculations were performed on the basis of the univariate correlations (Table 2) and partial correlations (Table 3). Sex and age were held constant in all regression models as independent variables. Multiple regression was performed to test for interdependence of investigated parameters, and stepwise regression was conducted to extract main determinants for the variability of the dependent variable (Table 4).

When fibrinogen served as the dependent variable, only PAI-1 reached a level of significance ($P < .0001$), but factor 1 together with PAI-1 explained 30% of the variation in fibrinogen.

PAI-1 ($P < .0001$), log triglycerides ($P < .0001$), and also

Table 3. Crude and Partial Correlations With BMI as Confounding Variable Between Metabolic and Hemostatic Parameters in Obese Boys and Girls

Parameters	Insulin	Glucose	FIRI	Triglycerides	Fibrinogen	t-PA-Ag	PAI-1
Boys (N = 34)							
Insulin	—	0.37* [0.28]	0.95† [0.93]	0.70† [0.41]	0.17 [0.37]	0.19 [−0.15]	0.04 [−0.30]
Glucose	—	—	0.60‡ [0.62]	0.28 [0.22]	0.21 [0.17]	−0.09 [−0.17]	−0.45§ [−0.58]
FIRI	—	—	—	0.68† [0.35]	0.16 [0.20]	0.19 [−0.17]	−0.02 [−0.30]
Triglycerides	—	—	—	—	0.13 [0.03]	0.46§ [0.47]	0.14 [0.06]
Fibrinogen	—	—	—	—	—	0.01 [−0.16]	−0.35* [−0.45]
t-PA-Ag	—	—	—	—	—	—	0.48§ [0.41]
Girls (N = 57)							
Insulin	—	0.49† [0.52]	0.95† [0.93]	0.63† [0.54]	0.25* [0.17]	0.42‡ [0.34]	0.12 [0.0]
Glucose	—	—	0.70† [0.79]	0.31* [0.37]	0.45‡ [0.43]	−0.12 [−0.07]	−0.47‡ [−0.44]
FIRI	—	—	—	0.61† [0.54]	0.37§ [0.31]	0.30* [0.26]	−0.02 [−0.17]
Triglycerides	—	—	—	—	0.14 [0.12]	0.39§ [0.36]	0.18 [0.11]
Fibrinogen	—	—	—	—	—	−0.04 [−0.03]	−0.40§ [−0.43]
t-PA-Ag	—	—	—	—	—	—	0.55† [0.60]

NOTE. Crude correlations and partial correlation with BMI as confounding variable between metabolic and hemostatic parameters in obese boys and girls separately. The coefficients of partial correlations are given in brackets.

* $P < .05$.
† $P < .0001$.
‡ $P < .001$.
§ $P < .01$.

Table 4. Multiple and Stepwise Regression Analyses With Log Fibrinogen, tPA-Ag, and PAI-1 as Dependent Variables in Obese Children

Multiple Regression				Stepwise Regression			
Independent Variables	95% CI	β	P	Independent Variables	95% CI	β	P
Dependent variable							
Log fibrinogen							
Sex	±0.043	−0.006	.77	Factor 1	±0.00064	0.0016	<.0001
BMI	±0.008	0.0062	.14	PAI-1	±0.00067	−0.00135	.00013
WC	±0.0035	−0.0007	.67	Intercept, 2.33; adj R^2 = .30, P < .0001			
Factor 1	±0.0019	0.001	.29				
SAT	±0.0012	0.00014	.81				
PAI-1	±0.0007	−0.0014	<.0001				
Log insulin	±1.06	0.037	.48				
Age	±0.01	−0.0074	.17				
Dependent variable							
tPA-Ag							
Sex	±0.50	−0.33	.20	PAI-1	±0.0087	0.023	<.0001
%FM	±0.041	0.039	.08	Log triglycerides	±1.163	2.99	<.0001
Log insulin	±1.26	−0.46	.47	Age	±0.11	−0.12	.037
Log triglycerides	±1.45	3.11	<.00011	Intercept, 3.89; adj R^2 = .41, P < .0001			
PAI-1	±0.0092	0.02	<.0001				
Age	±0.11	−0.14	.014				
Dependent variable							
PAI-1							
Sex	±9.02	5.15	.26	tPA-Ag	±2.80	7.85	<.0001
%FM	±1.0	1.12	.03	Log glucose	±40.96	−80.5	.0002
WC	±0.56	−0.07	.805	Log fibrinogen	±44.02	−76.95	.0008
Log glucose	±43.84	−85.59	.00022	%FM	±0.68	1.105	.0019
Log fibrinogen	±46.57	−69.2	.0041	Intercept, 221.17; adj R^2 = .54, P < .0001			
tPA-Ag	±2.86	8.11	<.0001				
Age	±2.38	1.18	.33				

NOTE. The P level of significance, the regression coefficient (β), and the 95% confidence interval (95% CI) for each independent variable is shown. The adjusted R^2 is given for each stepwise regression model.

age (P = .037) were found to contribute to tPA-Ag (adjusted [adj], R^2 = .41). tPA-Ag (P < .0001) together with log glucose (P = .0002, negative slope), log fibrinogen (P = .0008, negative slope) and %FM (P = .0019) contributed to PAI-1 (adj, R^2 = .54).

DISCUSSION

We studied the relationship of adiposity and measures of body fat distribution with hemostatic and metabolic parameters in obese boys and girls. No significant sex-dependent differences were found in metabolic and hemostatic parameters (Table 1). Only WHR as a common index of abdominal fat distribution was greater in boys because of the greater Hc in girls. However, there were significant differences in the thickness of some SAT-layers between boys and girls. The thickness of SAT-layer 8-lower abdomen was greater in obese boys as was the thickness of 3 SAT-layers from the lower extremities (Fig 1). Nevertheless, the sum of 15 SAT-layers (overall subcutaneous fatness, SAT) was not different between boys and girls. To reduce the complex information of 15 different SAT-layers, we performed a factor analysis followed by a simple linear addition for those SAT-layers, which belong to the 3 extracted factors (Results and Fig 1). Boys showed greater values of lower body subcutaneous adiposity (factor 2) and abdominal subcutaneous adiposity (factor 3) (Table 1), but upper body subcutaneous adiposity (factor 1) was not different between boys and girls.

Factor 1 was significantly correlated to triglycerides and fibrinogen in boys, as it was also correlated to insulin, FIRI, and tPA-Ag in girls (Table 2). With the exception of factor 3, which was inversely associated with insulin in boys (P < .05), factor 1 was the only measure of subcutaneous fat distribution, which was significantly related to metabolic and hemostatic parameters to some extent. Beside SAT, factor 1 was the only significant associate of fibrinogen in boys. It has been shown that fibrinogen is related to percentage body fat, abdominal subcutaneous adipose tissue,[22] and to ponderal index in children.[31] A possible explanation for this discrepancy between these studies and ours is that we investigated obese boys covering a broad range of age (from 4.5 to 17.5 years). It is likely that age-related changes in body composition and in the metabolic profile were responsible for this discrepancy. However, factor 1 was significantly related to other measures of adiposity, Wc, and also to subcutaneous abdominal fat, regardless of sex (data not shown). Therefore, factor 1 might not only reflect subcutaneous fat patterning, but percentage body fat, as well.[32]

We also found that fibrinogen is inversely associated with PAI-1 in boys and girls independent of adiposity (Table 3). This relationship was also confirmed by regression analysis (Table 4), and both PAI-1 and factor 1 contributed to fibrino-

gen. However, as can be seen in Table 4, factor 1 was not significant ($P = .29$) when BMI, SAT, and Wc were considered in the multiple regression model. This might again indicate the above-mentioned interrelationship between other measures of adiposity and fat distribution. Whether this also implies that an influence of factor 1 on fibrinogen reflects the age-related increase in adiposity or suggests an adiposity-independent influence of upper body subcutaneous fat clearly remains to be demonstrated.

We found no significant relationship between any measure of adiposity and fat distribution with tPA-Ag in boys (Table 2). In girls, %FM and factor 1 were especially significantly correlated to tPA-Ag. The underlying reason for this gender-difference is unclear, but may be linked to gender differences in the relationship between tPA-Ag and markers of insulin resistance.[33] We found insulin and the FIRI significantly related to tPA-Ag only in girls (Table 3). Assuming that the mechanisms in the regulation of body fat distribution, ie, the enlargement in visceral fat and subcutaneous fat depends on sex and interfere with insulin resistance throughout puberty,[34,35] it is possible that some of these alterations lead to the observed sex-differences in the relationship between body fatness, fat distribution, insulin resistance, and tPA-Ag.

A small contribution of chronologic age as a surrogate of sexual maturation to explain the variability in tPA-Ag was found in the regression analysis (Table 4). In addition to age, PAI-1 and triglycerides, but not sex, retained as the main determinants for tPA-Ag (Table 4), further indicating the close relationship between PAI-1 and tPA-Ag.[23] Although trigylcerides were closely related to insulin and FIRI in a sex- and adiposity-independent manner (Table 3), their significant contribution to the variance of tPA-Ag might confirm the link between metabolic and hemostatic parameters in obesity.[36] However, these correlations cannot prove cause and effect, and we performed a cross-sectional study in a relatively small number of obese children. The longitudinal assessment of changes in body fat and insulin resistance and their possible interaction with regulatory pathways of the hemostatic system is therefore clearly warranted.

A strong indication of an interrelationship between metabolic and hemostatic parameters is confirmed by the finding that tPA-Ag, glucose, and fibrinogen contributed to PAI-1 (Table 4). Also %FM served as a main determinant in this regression model, which was expected because of the significant relationship between body composition and PAI-1 in boys and girls (Table 2). Interestingly, glucose and fibrinogen were inversely related to PAI-1 in boys and girls, and this relationship was rather independent of adiposity (Table 3). This inverse association was mirrored by the negative slopes of glucose and fibrinogen in the regression model (Table 4). However, the value of the negative slope for the regression between PAI-1 and fibrinogen (first model, Table 4) was small ($\beta = -0.00135$). Whether these differences in the magnitude of values of the slopes indicate some biologic relevance or not is unclear. However, a possible explanation for these differences is that a maturation-associated increase in adiposity and upper body subcutaneous fat (factor 1) leads to an increase in the expression of PAI-1 with a concomitant elevation of tPA-Ag[23] and fibrinogen (Table 4). As maturity proceeds, subtle changes in the metabolic state, perhaps mediated at the level of adipocytes from different fat depots due to the redistribution of body fat,[37] could affect the regulation of hemostatic factors. Unfortunately, we did not assess sexual maturation in these children and can, therefore, only speculate as to whether a critical window exists[38] in the development of risk factors for the thromboembolic complications of vascular diseases.

In conclusion, the results of the present study may favor the concept of an interrelationship between metabolic and hemostatic risk factors in obese children. These associations might be mediated by an increase in adiposity and, in particular, by an increase in upper body subcutaneous fatness. However, it remains to be shown whether sex-differences in the accumulation of certain fat depots throughout maturation, ie, differences in the enlargement and redistribution of visceral and subcutaneous adipose tissue affect the expression rate of hemostatic risk factors in distinct ways.

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