

Independent Effect of Visceral Adipose Tissue on Metabolic Syndrome in Obese Adolescents

Céline Druet^{a,b} Véronique Baltakse^c Didier Chevenne^d Sophie Dorgeret^e
Isabelle Zaccaria^f Ying Wang^g Claire Levy-Marchal^{a, b}

^aINSERM, U690; ^bUniversité Paris 7; ^cPediatric Clinic, ^dLaboratoire d'Hormonologie,
^eDepartment of Pediatric Radiology, ^fINSERM CIE 5 Unit of Clinical Epidemiology; AP-HP, and
^gClinical Investigation Unit, Hôpital Robert Debré, Paris, France

Key Words

Obesity and overweight · Children · Insulin resistance ·
Metabolic syndrome · Visceral fat

Abstract

Background/Aims: Obesity is linked to metabolic complications, even in children, but the role of the distribution of adiposity is unclear. We aimed to assess which compartment of fat mass – total (TFM), visceral (VFM) or subcutaneous (SCFM) – is related to metabolic complications in overweight and obese children and adolescents. **Design:** Analyses were conducted in 159 overweight or obese children and adolescents (median body mass index 4.0 SD). TFM was measured by dual-energy x-ray absorptiometry. Distribution of abdominal fat was assessed by MRI. Insulin resistance (IR) was determined using a homeostatic model assessment. The definition of metabolic syndrome (MS) was derived from National Cholesterol Education Program ATP III. **Results:** A parental history of obesity was positively and significantly associated with fat content of the three compartments (TFM: $\beta = 2.22$; VFM: $\beta = 0.17$; SCFM: $\beta = 0.12$, respectively). VFM was also associated with gender ($\beta = -0.29$) and ethnicity ($\beta = -0.54$). TFM was a significant and independent determinant of IR ($\beta = 0.02$) whereas IR and VFM only were significantly

related to MS (OR = 3.55 and 3.66 respectively). **Conclusion:** Our data indicate that even in overweight children VFM was influenced by several factors such as sex and ethnicity and that a relationship was evidenced between the amount of VFM and MS.

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Introduction

Overweight and obesity are rapidly increasing among children and adolescents around the world including countries in Europe [1]. Obesity is linked to serious metabolic complications in adults developing as early as in childhood [2]. Moreover, an obese child is at risk of remaining an obese adult. An American study has shown that body mass index (BMI) at an age of 13 years is a good predictor of overweight at 35 years [3]. Consequently, an obese child is at risk of developing metabolic complications in adulthood [4]. Several metabolic complications are clustered into the so-called metabolic syndrome (MS) and MS is strongly associated with insulin resistance (IR) including in children [2, 5, 6]. In overweight and obese children, MS is as frequent as 30% at least in Hispanic children with a family history for type 2 diabetes [5] or

50% in severely obese children [2]. In a previous study, we showed that among 308 overweight and obese children and adolescents, 15.9% presented with MS. As expected, abdominal obesity was the most frequent feature (95.8%), followed by IR (71.8%) and elevated systolic blood pressure (28.6%). Hypertriglyceridaemia was found in 22.4%, and 22.1% had a low high-density lipoprotein cholesterol (HDL-C) level. Moreover, we showed that the frequency of MS was significantly influenced by the degree of abdominal obesity, assessed by waist circumference (WC) [6].

Beside total fat mass, abdominal fat may play a crucial role in the development of the metabolic complications. In obese adults, abdominal obesity is associated with an increased cardiovascular risk and risk factors such as IR, hypertension, disorders of glucose tolerance and dyslipidaemia [7, 8]. This association is well known in adults but not in children. Furthermore, it has been suggested that puberty is a sensitive period for the development of central obesity [9]. At the same time, the clustering of blood pressure and lipids profile with insulin sensitivity appears even in non-obese children [10].

Data on body composition in overweight children are scanty in European populations. The aims of the present study were: to describe and to identify determinants of total fat mass (TFM), visceral fat mass (VFM) and subcutaneous fat mass (SCFM) and to assess which compartment of fat mass: TFM, VFM or SCFM is related to metabolic complications in overweight and obese children and adolescents.

Subjects and Methods

Study Population

Study subjects were part of an established cohort of 442 French overweight and obese children consecutively recruited in the paediatric clinics for obesity of three university hospitals. One of the three centres was able to perform an MRI. In the present study, only those subjects (159) were included in whom abdominal adiposity had been studied by MRI.

Subjects were eligible if they were aged between 7 and 18 years, and had a BMI (weight in kilograms divided by the square of the height in meters) above the value that predicted a BMI ≥ 25 kg/m² in adulthood according to the definition of overweight and obesity by the International Obesity Task Force (IOTF) [11]. Exclusion criteria were the use of any medication interfering with glucose homeostasis or any concomitant chronic illness. Written informed consent from parents and written assent from children and adolescents were obtained. The study protocol was reviewed and approved by the Ethical Committee of the Paris-St Louis University.

Study Protocol

Children were admitted in the morning after an overnight fast. Parent's BMI was recorded from interviews with the parents. Two ethnic groups were defined, Caucasian and non-Caucasian, according to the country of birth of the parents. Body weight was measured with a portable scale and height with a wall-mounted stadiometer. WC was measured at the level of the umbilicus. Pubertal development was assessed by physical examination according to Tanner staging [12, 13]. Blood pressure was measured in the right arm of seated subjects after a 30-min rest using an automated device (Dinamap, Critikon, Neully Plaisance, France) and a cuff of recommended size for the mid-upper arm circumference. Three measurements were made at 1-min intervals and the average of the last two measurements for systolic (SBP) and diastolic (DBP) readings was used in the analysis.

A fasting blood sample was obtained for the determination of plasma glucose, serum insulin, cholesterol, HDL-C and triglyceride levels. The degree of IR was determined using a homeostatic model assessment (HOMA) calculated as fasting insulin (mIU/l) \times fasting glucose (mmol/l)/22.5 [14].

TFM was measured by dual-energy x-ray absorptiometry (DEXA) using a LunaR Prodigy DXP (GE Medical Systems, Madison, Wisc., USA; Software version 1.35) and was expressed in kilograms. Abdominal VFM and SCFM were measured by MRI. Images were acquired on a Philips Gyroscan 1.5 T on a slice thickness of 10 mm between L4 and L5. The images were then transferred to a work station, and specialized software was used to determine SCFM and VFM area for each slice. These areas were estimated with a pixel density technique by standardizing the signal intensity of fat on a representative area and circumscribing the entire image to obtain direct measures of VFM and SCFM on each slice. There were expressed in square centimetres.

Analytical Methods

Plasma glucose, total cholesterol, HDL-C and triglyceride concentrations were measured by enzymatic methods. Serum insulin concentrations were determined by an immunoradiometric assay (Bi-Insulin IRMA, CIS Bio international, Gif-sur-Yvette, France). Cross-reactivity with proinsulin and des31,32 proinsulin was $<1\%$. The detection limit is 0.2 mIU/l and intra- and inter-assay coefficients of variations were, respectively, 3.8 and 8% at 8 mIU/l and 2.4 and 4.8% at 50 mIU/l.

Definitions

The definition of MS was derived from the National Cholesterol Education Program ATP III [15] with the presence of at least three of the following abnormalities: abdominal obesity, hypertriglyceridaemia, low HDL-C, fasting hyperglycaemia and elevated blood pressure.

Abdominal obesity was defined as WC ≥ 75 th percentile for age and sex, using French reference values from the Fleurbaix Laventie Ville Santé Study [16]. As described earlier, overweight and obesity were defined according to the definition of IOTF, and BMI was expressed in Z-score for the distribution for age and sex according to the French reference distributions established in children [17]. Hypertriglyceridaemia was defined as a value ≥ 90 th percentile for the distribution for age, sex and ethnicity [18]. Low HDL-C for all ages and both genders was defined as a value ≤ 1.03 mmol/l. Elevated SBP or DBP was defined as a value ≥ 90 th percentile for age and sex [19]. IR was defined as a value of

HOMA \geq 75th percentile for the distribution for age and sex recently established in a representative sample of children and adolescents from Quebec [20]. Impaired fasting glycaemia was defined as a value \geq 6.1 mmol/l according to the WHO criteria [21].

Statistical Analysis

All analyses were performed using SAS Software, version 9.01 (SAS, Cary, N.C., USA). Descriptive statistics were expressed as median (1st–3rd quartiles: Q1–Q3) for quantitative variables and as count (percentages) for qualitative variables. Variables with skewed distributions (HOMA, VFM and SCFM) were log-transformed. The relationship of TFM, VFM and SCFM with basic, anthropometric and parental variables was assessed using simple linear regression. Determinants of TFM, VFM and SCFM were assessed by multiple linear regressions, including as independent variables: age, sex, ethnicity, parental history of obesity. WC was added in the model for TFM, and TFM in models for VFM and SCFM.

Multivariate linear regression analysis was also conducted to investigate predictors of IR, expressed by log HOMA (age, sex, ethnicity, parental history of obesity, TFM, log VFM and log SCFM). A multivariate logistic regression analysis was performed to test for independent predictors of MS (age, sex, log HOMA, parental history of obesity, TFM, log VFM and log SCFM). In those two models, we introduced three measures of fat mass: TFM, log VFM, log SCFM; we tested their multicollinearity by calculating the variance inflation factor which was >0.10 and allowed us to keep them in the models. The results were expressed as the ORs with their 95% CIs. A p value <0.05 was considered statistically significant.

Results

Characteristics of the Study Population

As shown in table 1, 27 overweight and 132 obese children and adolescents (86 girls and 73 boys) were included with a median age of 11.5 years (Q1–Q3: 9.9–12.9). The median BMI was 28.5 kg/m² (Q1–Q3: 26.1–32.5) or 4.0 SD (Q1–Q3: 3.4–4.7). Approximately half of the population was prepubertal (47.8%). Caucasians represented 63.5% of the study population. Among the non-Caucasians, 43% were Africans, 48% were Caribbeans and 9% were from others origin. Parental history of obesity was reported positive for 51.6% of the cases. Frequency of IR was 63.5% (n = 101) and 20.7% (n = 33) of the subjects had MS.

Description of TFM, VFM and SCFM

Table 2 shows the relationship of TFM, VFM and SCFM to demographic, anthropometric and parental variables. Age, BMI, even after adjustment for age and sex, and WC were positively and significantly related to TFM, VFM and SCFM. TFM and SCFM were also sig-

Table 1. Characteristics of the study population (n = 159)

Age, years (n = 159)	11.5 (9.9–12.9)
Sex (n = 159)	
Male	73 (45.9%)
Female	86 (54.1%)
Puberty (n = 159)	
I	76 (47.8%)
II, III, IV, V	83 (52.2%)
BMI, kg/m ² (n = 159)	28.5 (26.1–32.5)
BMI, SD (n = 159)	4.0 (3.4–4.7)
Degree of obesity (n = 159)	
Overweight	27 (17.0%)
Obese	132 (83.0%)
TFM, kg (n = 158)	29.9 (21.6–35.9)
TFM, % (n = 158)	44.9 (40.8–47.7)
VFM, cm ² (n = 159)	51.6 (36.7–80.2)
SCFM, cm ² (n = 158)	379.8 (278.7–481.8)
Parental history of obesity (n = 139)	
Yes	82 (51.6%)
No	57 (35.8%)
Caucasian (n = 159)	
Yes	101 (63.5%)
No	58 (36.5%)
IR (n = 156)	
Yes	101 (63.5%)
No	55 (34.6%)
MS (n = 159)	
Yes	33 (20.7%)
No	126 (79.3%)

Qualitative variables are described as n (%) and quantitative variables as median (Q1–Q3: 1st quartile to 3rd quartile).

nificantly associated with puberty; pubertal adolescents having more TFM and SCFM than prepubertal ($\beta = 11.32$, 95% CI 8.35–14.29 and $\beta = 0.27$, 95% CI 0.15–0.38 respectively) and VFM was also significantly associated with ethnicity ($\beta = -0.49$, 95% CI -0.66 to -0.31): Caucasians had more VFM than non-Caucasians. TFM and VFM tended to be higher in subjects with parental history of obesity while SCFM was significantly associated with parental history of obesity ($\beta = 0.19$, 95% CI 0.07–0.31).

Determinants of TFM, VFM and SCFM

Independent associations of TFM with age, sex, ethnicity, parental history of obesity and WC are shown in table 3A. The significant predictors in the model, with a positive effect, were age ($\beta = 1.96$, 95% CI 1.36–2.56), WC ($\beta = 0.48$, 95% CI 0.38–0.57) and parental history of obesity ($\beta = 2.22$, 95% CI 0.02–4.43).

Table 2. Description of total (TFM), visceral (VFM) and subcutaneous (SCFM) fat mass according to characteristics of subjects

Explanatory variable	TFM, kg		log VFM, cm ²		log SCFM, cm ²	
	β (95% CI)	p	β (95% CI)	p	β (95% CI)	p
Age, years	3.46 (2.83; 4.09)	<0.0001	0.09 (0.05; 0.13)	<0.0001	0.09 (0.06; 0.11)	<0.0001
Sex (girls vs. boys)	1.79 (-1.67; 5.26)	0.3	-0.20 (-0.38; -0.02)	0.03	0.06 (-0.06; 0.18)	0.3
Puberty (pubertal vs. prepubertal)	11.32 (8.35; 14.29)	<0.0001	0.15 (-0.03; 0.33)	0.1	0.27 (0.15; 0.38)	<0.0001
BMI, kg/m ²	1.85 (1.66; 2.05)	<0.0001	0.06 (0.04; 0.08)	<0.0001	0.06 (0.05; 0.06)	<0.0001
SD	3.55 (1.79; 5.31)	0.0001	0.17 (0.07; 0.26)	0.0007	0.14 (0.08; 0.20)	<0.0001
Waist circumference (cm)	0.63 (0.55; 0.72)	<0.0001	0.02 (0.02; 0.03)	<0.0001	0.02 (0.02; 0.03)	<0.0001
Ethnicity (non-Caucasian vs. Caucasian)	-1.2 (-4.79; 2.38)	0.5	-0.49 (-0.66; -0.31)	<0.0001	-0.11 (-0.23; 0.02)	0.09
Parental history of obesity (yes vs. no)	2.95 (-0.67; 6.56)	0.1	0.16 (-0.04; 0.37)	0.1	0.19 (0.07; 0.31)	0.002

Table 3. Multivariate linear regression models showing determinants of total (TFM) (A), log visceral (VFM) (B) and log subcutaneous (SCFM) fat mass (C)

	A TFM, kg		B log VFM, cm ²		C log SCFM, cm ²	
	β (95% CI)	p	β (95% CI)	p	β (95% CI)	p
Age	1.96 (1.36; 2.56)	<0.0001	-0.02 (-0.07; 0.03)	0.3	-0.01 (-0.03; 0.02)	0.7
Sex (girls vs. boys)	1.84 (-0.40; 4.08)	0.1	-0.29 (-0.45; -0.13)	0.0005	-0.01 (-0.10; 0.08)	0.8
Ethnicity (non-Caucasian vs. Caucasian)	1.05 (-1.24; 3.34)	0.4	-0.54 (-0.71; -0.37)	<0.0001	-0.08 (-0.18; 0.01)	0.09
Parental history of obesity (yes vs. no)	2.22 (0.02; 4.43)	0.05	0.17 (0.01; 0.33)	0.04	0.12 (0.03; 0.21)	0.01
Waist circumference (cm)	0.48 (0.38; 0.57)	<0.0001				
TFM, kg			0.03 (0.01; 0.03)	<0.0001	0.02 (0.02; 0.03)	<0.0001

Table 3B shows associations of VFM and age, sex, ethnicity, parental history of obesity and TFM. All these parameters except age were independently and positively associated with VFM. Interestingly, after adjustment for age, sex, ethnicity, parental history of obesity and TFM, boys had significantly more VFM than girls ($\beta = -0.29$, 95% CI -0.45 to -0.13) and ethnicity remained significantly associated with VFM ($\beta = -0.54$, 95% CI -0.71 to -0.37): Caucasians had more VFM than non-Caucasians.

Table 3C shows associations of SCFM and age, sex, ethnicity, parental history of obesity and TFM. The significant factors in the model were ethnicity ($\beta = -0.08$, 95% CI -0.18 to -0.01), parental history of obesity ($\beta = 0.12$, 95% CI 0.03-0.21), and TFM ($\beta = 0.02$, 95% CI 0.02-0.03).

Relationship between Adipose Tissues and Metabolic Complications

In a multiple regression model, TFM was a significant and independent determinant of IR ($\beta = 0.02$, 95% CI 0.01-0.04) (table 4A) whereas IR and VFM were only significantly related to MS (OR = 3.55, 95% CI 1.53-8.22 and OR = 3.66, 95% CI 1.21-11.07 respectively) (table 4B).

Discussion

First we described the TFM and its distribution in overweight and obesity in a study sample of French adolescents. Among obese or overweight children, all fat compartments were strongly associated with age and a parental history of obesity and the two components of abdominal fat mass were influenced by TFM. Boys accumulated more VFM than girls and Caucasians had more VFM than non-Caucasians.

Then we determined the effect of fat mass and its distribution on metabolic complications of obesity. Our findings show that high TFM is a risk factor for IR whereas high VFM is associated with MS.

In our study population, Caucasian children had more VFM than non-Caucasians. Ethnicity differences in body fat distribution are clearly evidenced in adults where lower VFM is found in Blacks compared with Whites [22]. The same difference is also described in obese children [23]. Among obese adolescents, Blacks had approximately 30% less VFM than Whites [24]. Greater VFM in Caucasians, evidenced as early as in childhood, might be a

Table 4. Multivariate regression models showing association of fat mass and metabolic complications: IR (log HOMA) (**A**) and the MS (**B**)

A	log HOMA		
	β (95% CI)	p	
Age	0.02 (-0.05; 0.09)	0.6	
Sex (girls vs. boys)	-0.07 (-0.29; 0.15)	0.5	
Ethnicity (non-Caucasian vs. Caucasian)	0.13 (-0.12; 0.38)	0.3	
Parental history of obesity (yes vs. no)	-0.08 (-0.31; 0.14)	0.5	
TFM, kg	0.02 (0.01; 0.04)	0.02	
log VFM, cm ²	0.13 (-0.12; 0.39)	0.3	
log SCFM, cm ²	0.32 (-0.14; 0.78)	0.2	

B	MS			
	with MS (n = 33)	without MS (n = 126)	OR (95% CI)	p
Age	11.8 (10.3–12.8)	11.4 (9.9–12.9)	0.83 (0.62; 1.14)	0.3
Sex				
Female	14 (42.4)	72 (57.1)	1.00	0.3
Male	19 (57.6)	54 (42.9)	0.60 (0.22; 1.58)	
log HOMA	0.9 (0.7–1.3)	0.6 (0.2–1.0)	3.55 (1.53; 8.22)	0.003
Parental history of obesity				
Yes	17 (51.5)	65 (51.6)	1.00	0.9
No	12 (36.4)	45 (35.7)	1.06 (0.38; 2.95)	
TFM, kg	32.7 (24.9–38.3)	28.5 (21.4–34.8)	0.98 (0.92; 1.07)	0.7
log VFM, cm ²	4.4 (3.9–4.7)	3.9 (3.5–4.3)	3.66 (1.21; 11.07)	0.02
log SCFM, cm ²	6.1 (5.8–6.3)	5.9 (5.6–6.1)	0.35 (0.05; 2.63)	0.3

Values are n (%) or median (Q1–Q3).

factor contributing to the greater frequency of metabolic features in obese Caucasian children [25].

We found that gender had an impact on the repartition of the excess of fat mass, boys having more VFM than girls after adjustment for age, ethnicity, family history of obesity and TFM. In adults, VFM was shown to be higher in obese men than in obese women [26]. It appears that this difference is already visible in childhood. This characteristic seems to be true only in obese children since no difference related to gender was observed in non-obese children [27, 28]. However, the hormonal environment seems to play an important role in determination of fat mass repartition [29]. Hormonal changes during puberty would contribute to the development of sexual differences and in determining fat mass repartition [9], but no longitudinal study has used imaging data to compare repartition of fat mass and concentration of sexual hormones.

Gender was found to have an effect on TFM even in childhood. A study has shown that girls aged 5–7 years

have significantly more TFM than boys [30]. We found no difference between TFM in girls and boys, the effect of gender was probably hidden by obesity.

Obesity, even in children and adolescents, is a major risk factor of IR, although relatively few studies have focused on the relation between IR and obesity distribution in children. We showed that IR in overweight and obese children is related to total adiposity and not to its distribution. Gower et al. [28] found the same results but in a population of prepubertal children, whereas other studies in severely obese children [31] or in obese Hispanics with a family history of type 2 diabetes [32] concluded of a predominant role of VFM on IR. It may be that VFM has a minimal effect on IR except under specific conditions which increase the risk of IR such as puberty, severe obesity or genetic risk of metabolic complications. From a new physiological point of view, a study shows that the contribution of visceral lipolysis to peripheral free fatty acids (FFA) is limited, even in obese adults, and is un-

likely to be a cause of IR in extrahepatic tissues, although it could contribute to hepatic IR. Upper body SCFM was by far the major contributor to systemic FFA in both lean and obese humans under postabsorptive conditions and seems to be a cause of IR in extrahepatic tissues [33]. Nevertheless, we found no effect of SCFM on IR; it could be explained by the fact that SCFM does not reflect upper body SCFM.

In our study, only MS was influenced but independently by visceral fat. For the same degree of obesity, children with more VFM were more at risk of developing MS. In non-obese subjects, VFM is correlated with TG, HDL-C, total cholesterol SBP and DBP [34]. It has been postulated that VFM has a direct adverse effect by releasing excess of FFA into the portal vein, thereby exposing the liver of viscerally obese persons to greater FFA concentrations [35] which is thought to result in an increased very low-density lipoprotein TG production [36]. VFM seems to be related to atherogenic criteria of MS, such as elevated blood pressure, hypertriglyceridaemia and hypo-HDL cholesterolaemia, it could then explain that obese children with high VFM are more at risk of developing MS. Interestingly, the effect of VFM on MS was independent of IR suggesting two separate mechanisms.

In clinical practice is not easy to measure VFM. Studies have shown that WC is a good marker of VFM in adults [8]. Moreover, WC is associated with cardiovascular risk in adults [37, 38] and in children [37]. Further studies are necessary to evaluate the association between WC and VFM in children in order to allow the clinician to use WC to reflect VFM in obese children and adolescents.

In conclusion, our data indicate that even in overweight children, VFM was influenced by several factors such as sex and ethnicity and that a relationship was evidenced between the amount of VFM and MS. Independent of TFM, VFM was found to be a predictor of MS.

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C.D. and C.L.M. designed the study. V.B. was involved with subject recruitment. C.D., S.D., D.C. and Y.W. collected the data. D.C. was involved in measurement of insulin and S.D. was involved in the measurement of fat mass. C.D. and I.Z. analyzed the data. C.L.M. was the principal investigator of the study. C.D. prepared the first version of the manuscript. All authors contributed to writing the paper.

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