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Serum adiponectin is related to plasma high-density lipoprotein cholesterol but not to plasma insulin-concentration in healthy children: the FLVS II study

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Abstract

Although low levels of plasma adiponectin were associated with an increase in cardiovascular risk in adults, few data investigated that relationship in children. The aim of this study was to investigate the relationship between plasma adiponectin and cardiovascular risk factors in healthy children. This cross-sectional population-based study was conducted in Fleurbaix and Laventie, 2 cities in the north of France. The main outcome measure was the correlations between plasma adiponectin and adiposity variables (the body mass index, the sum of 4 skinfolds, waist circumference [WC], and percent body fat [bioimpedance]), blood pressure, plasma glucose, triglycerides, high-density lipoprotein (HDL) cholesterol and insulin. In 398 children of both sexes, adiponectin was not significantly related to age and pubertal stage. In boys only, adiponectin correlated with WC ($r = -0.19$; $P = .008$) and body mass index ($r = -0.15$; $P = .04$) but not with other adiposity variables. After taking into account WC, adiponectin was positively correlated with HDL-cholesterol in boys ($r = 0.14$; $P = .05$) and girls ($r = 0.25$; $P = .0004$), but was not correlated with insulin and homeostasis model assessment index for insulin resistance in both sexes. These results suggest that, in apparently healthy children, adiponectin is related to the level of HDL-cholesterol independently of fat mass. The relationship between adiponectin and insulin resistance previously reported in obese or diabetic children was not apparent in these subjects and may therefore occur only at later age with fat accumulation.

1. Introduction

Adiponectin is a collagen-like plasma protein abundantly present in the circulation and secreted by mature adipocytes [1], which may increase insulin sensitivity and has anti-inflammatory properties and anti-atherogenic effects [2]. In adults, decreased levels of plasma adiponectin were reported by case-control studies in obese subjects [3,4] and patients with type 2 diabetes mellitus [5], hypertension [6], dyslipidemia [7], or cardiovascular disease [8]. In apparently healthy adults, an inverse relationship was shown between plasma adiponectin and adiposity [9], insulin resistance [10], and blood pressure [11]. Furthermore, reduced concentration of plasma adiponectin may predict subsequent development of type 2 diabetes mellitus, increase in triglycerides, and decrease in high-density lipoprotein (HDL) cholesterol concentrations [5,12].

During puberty, plasma levels of adiponectin decline in boys, leading to reduced levels in adolescent boys compared to girls [13,14]. In children, cross-sectional studies reported an inverse relationship between the level of plasma adiponectin and body fat content [15] or the prevalence of obesity [16]. In children, plasma adiponectin has also been positively associated with the level of plasma HDL-cholesterol [17-19] and an inverse relationship between adiponectin and insulin has been reported [14,17]. These

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data therefore suggest that the relationship between adiponectin and some cardiovascular risk factors, including adiposity, insulin resistance, and HDL-cholesterol, may already be present in children.

However, most of these data were obtained in samples including a high proportion of obese or diabetic children, and little is known about the relationship between adiponectin and cardiovascular risk factors in healthy children from populations with low overweight prevalence. Furthermore, cardiovascular risk factors are related with each other, and whether adiponectin is precociously associated with some of them independently of others still has to be determined.

The aim of this study was to describe the relationships between adiponectin and markers of cardiovascular risk (including adiposity) in apparently healthy children from the general population.

2. Subjects and methods

2.1. Participants

The subjects were participants in the Fleurbaix-Laventie Ville Santé II (FLVS II) study, the purpose of which was to investigate genetic, metabolic, and environmental determinants of weight gain in 2 small cities in northern France. In 1999, FLVS II was proposed to the families who had previously participated in phase I of the study (FLVS I), which consisted in the clinical follow-up of children involved in a 5-year nutritional education program at school [20]. Among the 393 families who were still living in the area and could be contacted, 294 agreed to participate. The entire assessment protocol on adiposity measurements at inclusion in 1999 was completed by 508 children aged 8 to 18 years, of whom 398 had a determination of biologic parameters including plasma adiponectin.

The study protocol of FLVS II had been approved by the ethics committee of Lille in July 1998, and the data files have been declared to the Commission Nationale Informatique et Liberté.

Table 1
Characteristics of study subjects

	Boys	Girls	*P*
n	204	194	
Age (y)	13.7 ± 2.4	13.6 ± 2.6	.88
Tanner pubertal stage (%)			
1	18.7	16.5	
2	18.7	11.9	.03
3	18.7	20.6	
4	31.0	28.4	
5	12.8	22.7	
BMI ($kg.m^{-2}$)	18.5 ± 3.2	19.0 ± 3.3	.15
Percent body fat	13.3 ± 6.5	23.1 ± 8.1	<.0001
Sum of 4 skinfolds (mm)	37.3 ± 24.2	49.3 ± 23.0	<.0001
WC (cm)	67.6 ± 8.9	65.1 ± 7.7	.003
% Overweight[a]	8.4%	8.9%	>.99
% Obese[a]	1.5%	2.1%	.72
Plasma adiponectin ($\mu g\ mL^{-1}$)	11.9 ± 4.8	13.5 ± 5.1	.001
Plasma insulin ($mUI\ L^{-1}$)	5.5 ± 3.0	6.7 ± 3.8	.0007
Plasma glucose ($g\ L^{-1}$)	0.86 ± 008	0.84 ± 0.07	.01
HOMA index for insulin resistance	1.18 ± 0.76	1.40 ± 0.86	.006
Plasma triglycerides ($g\ L^{-1}$)	0.63 ± 0.27	0.69 ± 0.28	.02
Plasma HDL-cholesterol ($g\ L^{-1}$)	0.60 ± 0.13	0.60 ± 0.12	.64
Systolic blood pressure (mm Hg)	111 ± 12	105 ± 11	<.0001
Diastolic blood pressure (mm Hg)	62 ± 9	62 ± 9	.49

Values are expressed as mean ± SD or %.

[a] According to age- and sex-related BMI cutoff points established by Cole et al [21].

Table 2
Mean plasma adiponectin concentrations ($\mu g\ mL^{-1}$) according to Tanner pubertal stage in boys and girls

	Boys		Girls	
	Mean value (95% CI)	*P*	Mean value (95% CI)	*P*
Tanner 1	14.2 (12.4-16.2)	.0003	12.4 (10.9-14.2)	.27
Tanner 2	11.6 (10.2-13.3)		13.5 (11.5-15.7)	
Tanner 3	10.4 (9.1-11.9)		12.7 (11.2-14.3)	
Tanner 4	9.6 (8.7-10.7)		13.2 (11.9-14.6)	
Tanner 5	9.8 (8.4-11.5)		11.2 (10.0-12.6)	

Plasma adiponectin was log-transformed.
Results are given as the exponent of the mean value of log-adiponectin adjusted in mixed models taking into account a family variable as a random effect.

2.2. Measurements

Clinical examinations at inclusion in 1999 were performed at home by 6 trained physicians. Height (to the nearest 5 mm) was measured with a stadiometer. Weight (to the nearest 0.1 kg) and body composition were determined barefoot, in light clothes with a Tanita TBF 310 body fat analyzer (Tanita, Neuilly sur Seine, France). Overweight and obesity were defined using age- and sex-related body mass index (BMI) cutoff points established by Cole et al [21] from the pooling of 6 large nationally representative growth studies in children. Briefly, these cutoffs were drawn from centile curves obtained that at age 18 passed through the cutoff points of 25 and 30 $kg\ m^{-2}$ which define overweight and obesity in adults. The bicipital, tricipital, suprailiac, and subscapular skinfolds were measured twice (to the nearest 0.1 mm) with a Harpenden caliper and the average of the 2 measurements was used in analyses. Waist circumference (WC) was recorded to the nearest 5 mm at midpoint between the iliac crest level and the lowest rib on the midaxillary line. In a sample of 64 children, reproducibility of 2 measures performed 1 week apart was similar for skinfolds, WC, and bioelectrical impedance analysis % fat measurements (intraclass correlation coefficient, 0.979-0.992). Correlation coefficient between percent body fat assessed by bioimpedance and anthropometric variables (skinfolds and WC) was higher than 0.70 in children of both sexes [22]. Pubertal stage was recorded according to the Tanner classification [23].

Table 3
Correlation coefficients (P value) between plasma adiponectin[a] concentration and cardiovascular risk factors in boys and girls

	Boys	Girls	P[b]
n	204	194	
BMI[a]	−0.15 (0.04)	−0.07 (0.33)	.42
Percent body fat	−0.09 (0.20)	0.03 (0.69)	.23
Sum of 4 skinfolds[a]	−0.10 (0.14)	−0.06 (0.39)	.69
WC	−0.19 (0.008)	−0.06 (0.43)	.05
Plasma insulin[a]	−0.01 (0.84)	−0.01 (0.87)	>.99
Plasma glucose	−0.08 (0.25)	−0.14 (0.06)	.55
HOMA index for insulin resistance[a]	−0.02 (0.96)	−0.03 (0.65)	.92
Plasma triglycerides[a]	−0.004 (0.96)	−0.19 (0.01)	.06
Plasma HDL-cholesterol	0.18 (0.009)	0.26 (0.0003)	.41
Systolic blood pressure	−0.06 (0.36)	−0.06 (0.40)	>.99
Diastolic blood pressure	−0.09 (0.21)	0.004 (0.95)	.97

All variables were previously adjusted for age and pubertal stage by mixed models which took into account familial correlations as a random effect. Models with WC included additional adjustment for height.

[a] Log transformed.

[b] Differences in correlation coefficients between boys and girls.

A 20-mL fasting venous blood sample was drawn at inclusion in 1999 for measurement of plasma glucose, triglycerides, HDL-cholesterol, and insulin (Bi-Insulin IRMA kit, Sanofi Pasteur, Marnes la Coquette, France). Total plasma adiponectin concentration was measured from frozen samples in 2004 (Adiponectin RIA kit, HADP-61HK, Linco Research, St Louis, Mo). The homeostasis model assessment (HOMA) fasting index for insulin resistance [24] was calculated.

2.3. Statistical analysis

The analysis was conducted separately in boys and girls. We compared the characteristics between sexes, and between subjects included or not in the analysis with Student t test and Pearson's χ^2 test.

The relationships between adiponectin and each of the other variables were studied by sex and expressed as correlation coefficients, in each sex separately. To adjust for age and pubertal stage, these coefficients were estimated through a 2-step procedure. In the first step, we performed, in each sex separately, mixed linear models with adiponectin or other biologic or anthropometric variables as the dependent variable, and adjusted for age and pubertal stage (and height if the dependent variable was waist or hip circumference), as the independent variables declared as fixed effect. As the recruitment of participants was based on family units and included siblings, a nuclear family variable was added to the models as a random-effect variable to adjust for correlations between siblings. In the second step, we correlated the residuals of these regression models to obtain partial correlation coefficients between adiponectin and the considered variable, which had been adjusted for confounding factors in step 1. For adiponectin, BMI and skinfolds, insulin and triglyceride measurements, and HOMA index of insulin resistance, a logarithmic transformation was performed because of a skewed distribution.

All analyses were performed with the SAS statistical package (version 8.2, SAS, Cary, NC).

3. Results

3.1. Population characteristics

We have excluded from the analysis 110 subjects in whom adiponectin measurements had not been performed (Table 1). Excluded subjects were, on average, younger than the study population especially for girls (12.7 ± 2.6 vs 13.6 ± 2.6 years; P = .02). After adjustment for age, excluded subjects had anthropometric characteristics similar to subjects retained in the analyses (results not shown). Characteristics of study subjects (Table 1) showed expected sex differences for adiposity and pubertal stage. Plasma fasting glucose, triglycerides, and insulin were higher in girls than in boys (all P < .03). Mean systolic blood pressure was higher in boys than in girls. Plasma adiponectin was significantly higher in girls than in boys.

3.2. Relationship between plasma adiponectin, age, and pubertal stage

The logarithm of adiponectin concentration decreased with age in boys (β = −.045 μg mL^{-1}; 95% confidence interval [CI], −0.07 to −0.02; per 1-year increase; P = .0003) in boys but not in girls (β = −.004 μg mL^{-1}; 95%

Table 4
Partial correlation coefficients of plasma adiponectin and WC adjusted on each other with metabolic variables and blood pressure

	Boys (n = 204)		Girls (n = 194)	
	Adiponectin	WC	Adiponectin	WC
Plasma insulin[a]	0.02 (.74)	0.27 (.0001)	−0.005 (.95)	0.31 (<.0001)
Plasma glucose	−0.08 (.25)	0.014 (.85)	−0.14 (.05)	0.22 (.002)
HOMA index for insulin resistance[a]	0.01 (.87)	0.26 (.0003)	−0.04 (.62)	0.34 (<.002)
Plasma triglycerides[a]	0.04 (.56)	0.20 (.004)	−0.17 (.02)	0.30 (<.0001)
Plasma HDL-cholesterol	0.14 (.05)	−0.29 (<.0001)	0.25 (.0004)	−0.15 (.04)
Systolic blood pressure	−0.03 (.69)	0.16 (.02)	−0.06 (.44)	0.11 (.13)
Diastolic blood pressure	−0.07 (.35)	0.10 (.16)	0.02 (.77)	0.26 (.0003)

Values are given as partial correlation coefficients (significance level).

Adiponectin was log transformed.

All models included both adiponectin and WC; were adjusted for age, pubertal stage, and height; and took into account familial correlations as a random effect.

[a] Log transformed.

CI, −0.02 to 0.017; per 1-year increase; $P = .73$) and mean concentration of adiponectin tended to decrease with puberty in boys (Table 2).

In both sexes, the relationship between adiponectin and age did not differ according to pubertal stage and was not significant after adjusting for pubertal stage.

3.3. Relationships between plasma adiponectin, metabolic variables, and blood pressure

The relationships between plasma adiponectin and cardiovascular risk factors did not vary significantly according to pubertal status (results not shown) (Tables 3 and 4). After adjustment for age and pubertal stage, there was a negative correlation, in boys only, between plasma adiponectin and BMI ($R = -0.15$; $P = .04$) and WC ($R = -0.19$; $P = .008$) (Table 3). Plasma adiponectin was not correlated with insulin or HOMA–insulin resistance index in either sex, but there was a trend for a negative correlation with plasma glucose in girls ($R = -0.14$; $P = .06$). There was a positive correlation between plasma adiponectin and HDL-cholesterol in both sexes (boys: $r = 0.18$, $P = .009$; girls: $r = 0.26$, $P = .0003$), and, in girls, a negative correlation with triglycerides ($r = -0.19$; $P = .01$).

After additional adjustment for WC, plasma adiponectin concentrations remained correlated with HDL-cholesterol in girls ($r = 0.25$; $P = .0004$) and boys ($r = 0.14$; $P = .05$) and with triglycerides in girls only ($r = -0.17$; $P = .02$) (Table 4). In these models, WC was significantly associated with all biologic variables (except fasting glucose in boys and diastolic blood pressure in girls), independently from adiponectin.

4. Discussion

We identified an inverse relationship between plasma adiponectin concentration and several adiposity markers in a population of apparently healthy children with less than 10% of overweight. However, this relationship was weak and significant only in boys, particularly with WC, an indicator of abdominal fat accumulation. These findings are consistent with previous data reported in children [15,17,18]. Cnop et al [25] identified in adults a negative correlation between adiponectin and CT-assessed intra-abdominal fat, whether they found no relationship with subcutaneous fat. Therefore, total adipose mass is probably not a main determinant factor for plasma adiponectin concentration or activity, the decrease of which may only be related to a high amount of intra-abdominal fat. A lower amount of fat stored in the intra-abdominal compartment may explain that the strength of the relationship between adiponectin and total fat mass in children tended to be weaker in our study than in other reports with higher prevalence of overweight or obese subjects [15,18,19]. The fact that plasma adiponectin was measured from frozen samples may also have contributed to weakening some of the relationships assessed in our sample. Indeed, unexpectedly, Looker et al [26] observed a positive correlation between storage time and serum adiponectin in frozen sera. However, this correlation was significant only among subjects with diabetes, and no relationship was disclosed in healthy subjects. In our sample of healthy children, storage time, about 5 years, did not vary substantially among subjects. Therefore, we do not believe that the relationships we have observed are confounded by storage time of samples.

The inverse relationship between adiponectin and insulin, identified in apparently healthy adults [4], has also been reported in children [14,17]. However, our results, in line with other studies [15,27,28], do not confirm these findings. These discrepancies may partly be explained by different adjustment methods for adiposity, age, and pubertal stage, or distinct methods for plasma adiponectin measurement. The relationship between adiponectin and insulin may also be apparent only in overweight subjects and particularly in those with a high amount of visceral fat. Experimental data on several models of knockout mice suggest a protective effect of adiponectin on insulin resistance induced by a high-fat diet [29]. Administration of recombinant adiponectin in mice resulted in a transient decrease in plasma glucose without change in insulin concentration [30]. Recombinant adiponectin may, however, not reflect the full range of metabolic effects of that hormone. The main target of adiponectin in muscular tissue is adenosine monophosphate (AMP)–activated protein kinase [31], which is involved in insulin sensitivity. Plasma adiponectin is negatively correlated to skeletal muscle lipid content [32] and increases fatty acid oxidation in muscle through activation of the AMP-dependent kinase pathway [33]. It is therefore possible that the decrease in insulin sensitivity associated with low adiponectin concentration occurs late in the course of obesity development because of both a decrease in adiponectin production by enlarged intra-abdominal adipocytes and an accumulation of triglycerides in muscle cells due to decreased fatty acid oxidation.

In the blood stream, the full-length form of adiponectin forms high molecular weight oligomers, each of which may have distinct signaling properties [30,34]. The different forms of circulating adiponectin may change between childhood and adulthood depending on other factors. This may explain part of the discrepancies between results of studies measuring total circulating adiponectin, as in ours. Recent publications have confirmed different actions of the different forms of circulating adiponectin on insulin sensitivity. Yamauchi et al [35] showed that full-length but not globular adiponectin activates the 5′ -AMP–activated protein kinase involved in gluconeogenesis in the liver and identified a protective effect of globular adiponectin in vivo against insulin resistance in ob/ob mice [36]. The ratio between high-molecular- and relative low-molecular-weight isoforms (Sa index) rather than absolute amount of adiponectin may then be critical in determining insulin sensitivity [34].

The weak relationship between total plasma adiponectin and adiposity or insulin contrasts with the stronger

relationship with HDL-cholesterol, suggesting that the association of adiponectin on lipids is independent of the amount of fat mass and insulin levels. As in a previous report in apparently healthy children and adolescents [19], we observed a relationship of plasma adiponectin concentration with blood lipids, mainly with HDL-cholesterol but also with triglycerides, even after taking into account central adiposity. In adult men, a negative correlation was identified between plasma adiponectin and very low density lipoprotein–apoB, a pool of triglyceride-rich lipoproteins, whether a positive correlation was identified with HDL-cholesterol and very low density lipoprotein–apoB catabolism [37]. However, the mechanisms explaining the relationship between adiponectin and serum HDL-cholesterol concentration are still poorly understood. In contrast to the relationship with fat mass and insulin sensitivity, mainly seen in the obese or diabetic state, the association between adiponectin and lipids can be seen across the whole range of fat mass distribution in the population and is already present in childhood.

If adipocytes are by far the main source of circulating adiponectin, the lack of, or weak, relationship between total or regional fat mass measurements and adiponectin concentration in our sample may also suggest that other features may be prominent to explain the variability of adiponectin concentration and effects in children. Bottner et al [13] identified in lean boys a decline in adiponectin levels parallel to pubertal development inversely related to testosterone and dehydroepiandrostenedione serum concentrations. Adiponectin concentration is higher in hypogonadal than in eugonadal adult men and is decreased by testosterone replacement therapy in the former [38]. These data suggest that sexual hormones are important determinants for adiponectin concentration, and recent data demonstrated that expression of adiponectin circulating forms is as well regulated by sexual hormones in rodents and humans [39]. In adolescents, the differential relationship of adiponectin with fat mass and distribution or with insulin sensitivity may therefore be related to variability in the adiponectin concentration of the different circulating forms because of increasing sexual hormones.

In conclusion, our results indicate that associations of adiponectin with blood lipid and especially HDL-cholesterol concentrations are already present in children and do not depend on adiposity or insulin sensitivity. The decrease in insulin sensitivity associated with low adiponectin concentration may therefore occur only later in the course of fat mass accumulation, in contrast with the early association between adiponectin and lipids that is seen across the whole range of fat mass distribution in the population.

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