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Elevated circulating levels of the serum acute-phase protein YKL-40 (chitinase 3-like protein 1) are a marker of obesity and insulin resistance in prepubertal children

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ABSTRACT

YKL-40 (chitinase 3-like protein 1) is a newly recognized protein that is secreted by activated macrophages and neutrophils and expressed in a broad spectrum of inflammatory conditions and cancers. It has also been associated with endothelial dysfunction and diabetes in adults. Its role in childhood obesity has not been evaluated yet. Our aim was to evaluate the associations of serum YKL-40 levels with markers of obesity, inflammation, and insulin resistance in children. Forty-one obese prepubertal children and 41 age- and sex-matched lean controls were included, and serum YKL-40 levels were determined. Body mass index (BMI), blood pressure (BP), body fat percentage, fasting glucose, insulin, homeostasis model assessment for insulin resistance (HOMA-IR) index, whole-body insulin sensitivity index, lipids, white blood cell (WBC) count, C-reactive protein, and fibrinogen levels were also assessed. Obese children had higher YKL-40 levels compared with controls ($P = .003$). Insulin-resistant individuals showed higher YKL-40 compared with non–insulin-resistant individuals after adjusting for age and BMI (adjusted $P = .039$). Serum YKL-40 levels were positively correlated with age, BMI, body fat percentage, fasting glucose and insulin, HOMA-IR index, whole-body insulin sensitivity index, systolic BP, mean BP, and WBC count ($P < .05$). After adjustment for age, sex, BMI, WBC count, and systolic BP, HOMA-IR index remained significantly associated with YKL-40 levels ($P < .001$). The study suggests that YKL-40 levels are elevated in obese youth and represent a marker of insulin resistance even in

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childhood. Prospective studies are needed to determine whether children with elevated YKL-40 levels are at higher risk for future cardiovascular disease.

1. Introduction

Nowadays, childhood obesity is reaching epidemic proportions, being the most important chronic disease in this age group [1]. It is also associated with an increased risk for several metabolic complications as well as other problems. In particular, insulin resistance is the most common metabolic alteration related to obesity and constitutes an important link between obesity and other metabolic as well as cardiovascular complications [2]. Adipose tissue seems to play a key role in the pathogenesis of insulin resistance through several released molecules that can affect different steps in insulin action, thus suggesting that adipose tissue represents a complex and highly active metabolic and endocrine organ [3]. However, although adipocytes express and secrete several endocrine hormones, many secreted proteins are derived from the nonadipocyte fraction of adipose tissue that contains other cellular elements such as connective tissue matrix, nerve tissue, stromovascular cells, or immune cells. Obesity may therefore be characterized by a state of chronic low-grade inflammation because circulating levels of markers of inflammation, both proinflammatory cytokines and acute-phase proteins, have been found elevated in the obese [4,5].

In this context, YKL-40, a newly recognized inflammatory molecule, could possibly play a role in this obesity-related inflammation. The abbreviation YKL-40 is based on the 1-letter code for the first 3 N-terminal amino acids tyrosine (Y), lysine (K), and leucine (L) and its apparent molecular weight. Its gene is localized in a highly conservative area on chromosome 1q31-q32, and its crystal structure has been described previously [6]. Increased YKL-40 expression has been already associated with the presence of a number of different diseases including cancers and autoimmune and chronic inflammatory conditions. Especially, it is expressed by a plethora of different types of human tumors as well as by embryonic and fetal cells, macrophages during late state of differentiation, activated neutrophils, arthritic chondrocytes, differentiated vascular smooth muscle cells, and fibroblast-like synovial cells [7]. A diversity of YKL-40 actions has so far been described: it plays a role in extracellular tissue remodeling by modulating the rate of type I collagen fibril formation; functions as a growth factor for fibroblasts and chondrocytes; acts as a chemoattractant for endothelial cells; stimulates their migration; promotes migration and adhesion of vascular smooth muscle cells, thus suggesting a role in angiogenesis; and controls mitogenesis by initiating MAP kinase and PI-3K signaling cascades in fibroblasts. It has also been regarded as an acute-phase protein or even as an autoantigen capable of inducing T-cell responses [6,7]. Cellular receptors mediating its biological effects have not been identified; however, it is regulated by interleukin-6 (IL-6) and tumor necrosis factor–α, requires sustained activation of NF-kappaB, and can bind to collagen types I to III [7].

Recently, YKL-40 has been described as a marker of inflammation, endothelial dysfunction, and diabetes in adults and implicated as an independent predictor of overall and cardiovascular mortality [8-11]. Moreover, an independent association between increasing levels of YKL-40 levels and increasing levels of albuminuria (which represent an early marker of vascular complications) has previously been detected both in type 1 and type 2 diabetes mellitus patients [12,13]. These data suggest that YKL-40 may be considered as a potential indicator for risk assessment at least in adults. To our knowledge, its role in childhood obesity has not been evaluated yet. In this study, we measured serum YKL-40 levels in obese and nonobese prepubertal children to investigate their possible association with obesity, inflammation, and insulin resistance in children.

2. Patients and methods

2.1. *Participants*

Forty-one of a total of 51 consecutively screened obese prepubertal children of Greek origin, aged from 4 to 11 years, who visited the Endocrinology Outpatient Unit of the 4th Department of Pediatrics, Faculty of Medicine, Aristotle University of Thessaloniki, for obesity evaluation between the years 2008 and 2010 were included in the study. Ten participants were excluded because of receiving medication or being diagnosed with acute, chronic, or autoimmune disease (3 patients with Hashimoto thyroiditis under medication, 2 patients receiving antibiotic treatment, 4 patients with a history of allergic asthma, and 1 patient receiving antihistamines because of allergic rhinitis). Children were classified as obese or nonobese according to international age- and sex-specific body mass index (BMI) cutoff points defined by the International Obesity Task Force to define childhood obesity [14]. Forty-one age- and sex-matched nonobese, nonoverweight prepubertal children that visited the General Pediatrics Outpatient Unit of the 4th Department of Pediatrics for routine physical examination during the same period were also recruited to serve as controls. In total, more than 200 subjects were screened to obtain the 41 matched lean participants. Control subjects met the same exclusion criteria (receiving medication or being diagnosed with acute, chronic, or autoimmune disease).

The study was approved by the Ethics Committee of the Faculty of Medicine, Aristotle University of Thessaloniki; and informed written consent was acquired from all participants' parents or guardians.

2.2. *History-anthropometry*

Initially, data of personal history of chronic or autoimmune disease or receiving medication were collected, whereas data regarding other parameters possibly related to YKL-40 expression such as socioeconomic status, household type (urban or rural), family history of chronic or autoimmune conditions, and other parameters were not obtained. After this, all

individuals underwent complete physical examination. Weight and height were measured (SECA 711 scale, Hamburg, Germany; Harpenden stadiometer, Veeder-Root, Elizabethtown, NC), and BMI was calculated as weight (kilogram)/height^2 (square meter). Body mass index z scores were also calculated for each participant using a Web-based calculator (http://stokes.chop.edu/web/zscore/) that was based on the Center for Disease Control and Prevention growth charts [15]. Body fat percentage (BFP) was assessed through bioelectrical impedance analysis (Maltron Analyzer BF-906, Essex, UK). All participants were also classified as prepubertal using Marshall and Tanner criteria (defined by pubic hair stage and breast stage I for girls or pubic hair stage and gonadal stage I for boys) [16,17]. Blood pressure (BP) at rest was measured twice with a digital sphygmomanometer (DINAMAP, Johnson & Johnson Medical, Arlington, TX) and then averaged. Mean BP was calculated from the equation mean BP = (systolic BP + 2 × diastolic BP)/3.

2.3. Metabolic measurements

After overnight fasting, obese participants underwent an oral glucose tolerance test (OGTT) with the administration of 1.75 g of glucose per kilogram of body weight (maximum dose, 75 g) per os, and blood samples were obtained every 30 minutes for 2 hours for the glucose and insulin assay. Insulin resistance was then determined by the homeostasis model assessment for insulin resistance (HOMA-IR) index, calculated using the formula HOMA-IR = fasting glucose (FG) in millimoles per liter × fasting insulin (FI) in milli–international units per liter/22.5 [18]. Thus, obese children were further divided into 2 subgroups: insulin resistant (IR) or non–insulin resistant (NIR). In particular, insulin resistance in prepubertal children was considered when HOMA-IR was greater than the age- and sex-specific 95th percentile (defined as HOMA-IR index ≥1.88 for boys and ≥2.07 for girls), according to Allard et al [19]. The whole-body insulin sensitivity index (WB[ISI]) obtained from the OGTT was also calculated using the formula 10,000/SQRT [FG in milligrams per deciliter * FI in milli–international units per liter * (mean OGTT glucose in milligrams per deciliter * mean OGTT insulin in milli–international units per liter)] [20]. In the control group, an OGTT was not performed; and only FI and FG levels were determined. Fasting blood samples were also obtained from all participants for measurement of levels of total cholesterol (TC), triglycerides, high-density lipoprotein (HDL), and low-density lipoprotein (LDL). Levels of insulin, glucose, TC, triglycerides, HDL, and LDL were directly determined using standard methods. For the measurement of serum insulin levels, a solid phase was applied using a 2-site immunometric assay (Immulite 2000, DPC, Holliston, MA) with a coefficient of variation of 4.1% to 7.3% and a sensitivity of 2.0 μIU/mL. Plasma glucose and serum lipid levels were measured with the use of an Autoanalyzer (Architect 8000c, Abbott Laboratories, Abbott Park, IL).

2.4. Inflammation measurements

Fasting blood samples were also obtained from all participants for direct measurement of levels of total white blood cell (WBC) count, C-reactive protein (CRP), and fibrinogen levels. White blood cell count was measured using a quantitative automated hematology analyzer (Coulter Counter Model S-Plus JR; Coulter Electronics, Hialeah, FL). Simple (not high-sensitivity) CRP was determined by nephelometry (Behringwerke, Marburg, Germany). This method of determining CRP could not detect CRP levels less than 0.1 mg/dL (these values were regarded as equal to 0.1 mg/dL). The sensitivity of this method was 0.1 mg/dL. Fibrinogen was determined quantitatively in plasma with the Clauss method (STA-Fibrinogen, Diagnostica Stago, Asnières, France).

2.5. YKL-40 determination

Fasting blood samples were centrifuged immediately, and serum specimens for YKL-40 were frozen at −20°C before analysis. Serum YKL-40 was measured in duplicate by a commercial 2-site, sandwich-type enzyme-linked immunosorbent assay (ELISA) [21] using streptavidin-coated microplate wells, a biotinylated-Fab monoclonal capture antibody, and an alkaline phosphatase–labeled polyclonal detection antibody (Quidel, San Diego, CA). The sensitivity of the ELISA was 20 μg/L. The intra- and interassay coefficients of variation were less than 3.6% and less than 6.3%, respectively.

2.6. Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Sciences software version 11.0 (SPSS, Chicago, IL). Data are presented as mean values ± standard deviations for normally distributed or median (interquartile range; ie, the range of values lying between the 25th and 75th centiles) for not normally distributed variables unless otherwise stated. Categorical variables (sex) were compared between study subgroups using a χ^2 test. All continuous variables were tested for normal distribution by Shapiro-Wilk test (number of subjects in all subgroups was <50). Despite age and sex matching, differences in continuous variables between obese and nonobese children were tested with the unpaired *t* test (for normally distributed) or the nonparametric Mann-Whitney *U* test (for not normally distributed variables) because other factors possibly related to YKL-40 expression were not obtained. Comparisons between IR and NIR participants were also tested with the unpaired *t* test or the nonparametric Mann-Whitney *U* test, as appropriate; additional comparisons between IR and NIR participants were also performed after adjustment for age and BMI using a 1-way between-groups analysis of covariance. For analysis of relationships between continuous variables, univariate linear regression analysis was performed. Multivariable linear regression analysis was also used to test the independence of potential predictive factors (based on univariate analysis) in YKL-40 levels. All tests were 2-sided, and the level for statistical significance was set at $P < .05$.

3. Results

3.1. Baseline data

Baseline anthropometric and metabolic characteristics of the study participants are shown in Table 1. A priori, obese and nonobese subjects did not differ with regard to age and sex,

Table 1 – Baseline characteristics of the study population

	Obese (n = 41)	Nonobese (n = 41)	P	IR (n = 23)	NIR (n = 18)	P	P [a]
Age (y)	8.5 (7.0, 9.8)	8.4 (7.1, 9.7)	.853	8.9 ± 1.2	7.2 ± 2.3	.01	–
Sex (M/F)	18/23	18/23	1.000	11/12	7/11	.567	–
BMI (kg/m^2)	27.5 (25.0, 30.3)	16.8 (15.7, 17.9)	<.001	27.9 (26.1, 30.7)	25.8 (23.0, 28.7)	.115	–
BMI z score	2.43 (2.22, 2.70)	0.47 (-0.33, 0.74)	<.001	2.39 (2.20, 2.64)	2.51 (2.25, 2.84)	.222	–
BFP (%)	34.6 (29.6, 37.5)	16.1 (14.0, 18.9)	<.001	35.4 ± 4.4	32.7 ± 5.5	.093	–
FG (mmol/L)	4.72 (4.48, 5.21)	4.64 (4.38, 4.85)	.058	5.00 ± 0.52	4.61 ± 0.24	.004	.018
FI (mIU/L)	11.4 (6.8, 17.7)	5.9 (4.1, 7.3)	<.001	17.0 (15.2, 19.8)	6.6 (4.1, 8.8)	<.001	<.001
HOMA-IR index	2.9 (1.3, 3.9)	1.1 (0.8, 1.5)	<.001	3.7 (3.2, 4.9)	1.3 (0.9, 1.8)	<.001	<.001
Mean OGTT glucose (mmol/L)	6.7 ± 0.7	–	–	6.81 ± 0.88	6.60 ± 0.66	.451	.356
Mean OGTT insulin (mIU/L)	74.1 (53.8, 124.9)	–	–	125.6 ± 69.2	58.5 ± 28.1	.001	.005
WB(ISI)	3.2 (1.8, 4.9)	–	–	2.2 (1.6, 2.9)	5.1 (4.5, 7.5)	<.001	.001
Systolic BP (mm Hg)	114.1 ± 9.9	104.0 ± 8.0	<.001	113.0 (110.0, 120.0)	115.0 (106.0, 118.0)	.906	.285
Diastolic BP (mm Hg)	65.0 (57.0, 70.0)	58.0 (55.0, 61.0)	.011	64.3 ± 7.4	61.2 ± 10.8	.306	.289
Mean BP (mm Hg)	80.0 ± 7.1	74.0 ± 4.3	<.001	82.0 (79.6, 83.6)	77.0 (72.2, 87.5)	.453	.637
TC (mmol/L)	4.22 (3.57, 4.71)	4.40 (4.04, 4.53)	.977	4.46 (3.85, 5.24)	3.93 (3.32, 4.58)	.045	.273
Triglycerides (mmol/L)	0.92 (0.63, 1.28)	0.77 (0.57, 1.10)	.065	1.16 ± 0.53	0.88 ± 0.35	.071	.326
HDL (mmol/L)	1.07 (0.90, 1.13)	1.11 (0.77, 1.26)	.549	0.99 ± 0.16	1.11 ± 0.27	.108	.029
LDL (mmol/L)	2.65 (2.25, 3.14)	3.00 (2.53, 3.19)	.058	2.79 (2.48, 3.26)	2.51 (1.98, 2.73)	.015	.113
WBC count (10^9/L)	7.24 ± 1.38	5.86 ± 1.43	<.001	7.30 ± 1.59	7.16 ± 1.10	.754	.348
CRP (mg/L)	0.39 (0.22, 0.52)	0.13 (0.10, 0.23)	.001	0.41 ± 0.19	0.31 ± 0.17	.239	.314
Fibrinogen (g/L)	3.39 ± 0.52	3.28 ± 0.66	.539	3.39 ± 0.52	3.39 ± 0.54	.979	.933
YKL-40 (μg/L)	50.7 ± 15.2	41.0 ± 10.5	.003	57.2 ± 14.7	43.8 ± 12.9	.01	.039

Data are presented as mean values ± standard deviations for normally distributed or median (interquartile range; ie, the range of values lying between the 25th and 75th centiles) for not normally distributed variables unless otherwise stated. Categorical variables were compared using a χ^2 test; differences in continuous variables between obese and nonobese children as well as between IR and NIR were tested with the unpaired *t* test or the nonparametric Mann-Whitney *U* test; comparisons between IR and NIR individuals after adjustment for age and BMI were tested using a 1-way between-groups analysis of covariance.

[a] After adjustment for age and BMI.

whereas IR and NIR subjects differed significantly regarding age (*P* = .01) but not sex. What is novel in our study is that obese children had higher serum YKL-40 levels compared with controls (50.7 vs 41.0 μg/L, *P* = .003) and IR individuals were found to show higher levels of serum YKL-40 as compared with NIR after adjusting for age and BMI (57.2 vs 43.8 μg/L, adjusted *P* = .039). These results remained significant even when BMI z scores were included in the analyses (data not shown).

3.2. *Univariate associations between YKL-40 and other anthropometry, metabolic, or inflammatory markers*

The results of univariate linear regression analysis for all children are summarized in Table 2. In the whole group, YKL-40 levels were positively correlated with age, BMI, BFP, FG, FI, HOMA-IR index, WB(ISI), systolic and mean BP, and WBC count (*P* < .05). Correlations between YKL-40 levels and HOMA-IR index as well as between YKL-40 and FG and FI levels also remained significant when analyses were done separately for obese and nonobese subjects (data not shown).

3.3. *Multiple linear regression analysis with YKL-40 as dependent variable*

As shown in Table 3, multivariable linear regression models were also performed on the basis of the univariate analysis (Table 2). In all 3 models, insulin resistance markers remained significantly associated with YKL-40 levels after adjustment for other confounding factors. Particularly, after adjustment for age, sex, BMI, WBC count, and systolic BP, HOMA-IR index remained significantly associated with YKL-40 levels (adjusted r^2 = 0.334, *P* < .001).

Table 2 – Univariate linear regression analysis between YKL-40 levels and other clinical or biochemical parameters in the whole sample

	β (unstandardized)	95% CI	P
Age	2.016	(0.332, 3.700)	.02
BMI	0.852	(0.378, 1.325)	.001
BMI z score	3.828	(1.562, 6.095)	.001
BFP	0.547	(0.242, 0.851)	.001
FG	12.804	(5.267, 20.342)	.001
FI	1.132	(0.726, 1.538)	<.001
HOMA-IR index	5.021	(3.292, 6.751)	<.001
Mean OGTT glucose	4.225	(–2.298, 10.748)	.195
Mean OGTT insulin	0.062	(–0.18, 0.142)	.123
WB(ISI)	–1.719	(–3.159, –0.279)	.021
Systolic BP	0.582	(0.295, 0.869)	<.001
Diastolic BP	0.286	(–0.141, 0.713)	.186
Mean BP	0.729	(0.261, 1.197)	.003
TC	4.059	(–1.004, 9.122)	.114
Triglycerides	8.566	(0.548, 16.583)	.037
HDL	5.047	(–8.308, 18.403)	.453
LDL	–1.298	(–6.909, 4.314)	.646
WBC count	2.487	(0.328, 4.646)	.025
CRP	12.200	(–11.159, 35.559)	.297
Fibrinogen	0.022	(–0.058, 0.103)	.574

CI indicates confidence interval.

Table 3 – Multivariable linear regression analysis with YKL-40 levels as dependent variable in the whole sample

Models	Dependent and independent variables	β (unstandardized)	95% CI	P
1	YKL-40 (adjusted r^2 = 0.334, P < .001)			
	Age	0.779	(−1.168, 2.727)	.426
	Sex	−0.801	(−7.183, 5.580)	.802
	BMI	−0.189	(−0.847, 0.470)	.568
	HOMA-IR index	4.074	(1.690, 6.457)	.001
	WBC count	1.303	(−1.033, 3.639)	.269
	Systolic BP	0.280	(−0.127, 0.687)	.173
2	YKL-40 (adjusted r^2 = 0.299, P < .001)			
	Age	1.222	(−0.625, 3.069)	.190
	Sex	−2.123	(−8.528, 4.281)	.509
	BFP	0.079	(−0.323, 0.480)	.696
	FI	0.754	(0.156, 1.352)	.014
	WBC count	1.479	(−0.810, 3.767)	.201
	Mean BP	0.192	(−0.321, 0.705)	.457
3	YKL-40 (adjusted r^2 = 0.322, P < .001)			
	Age	1.467	(−0.431, 3.364)	.127
	Sex	−2.465	(−8.903, 3.974)	.446
	BMI	<0.001	(−0.624, 0.623)	.999
	FG	12.273	(4.661, 19.884)	.002
	WBC count	2.549	(0.232, 4.865)	.032
	Systolic BP	0.300	(−0.113, 0.712)	.151

4. Discussion

In this study, we measured serum YKL-40 levels as an inflammation marker in obese and nonobese children. This study is the first to demonstrate that an obese prepubertal pediatric population showed elevated levels of YKL-40 as compared with lean controls. Moreover, there was a significant difference in YKL-40 levels between IR and NIR subjects. It is noteworthy that higher levels of HOMA-IR observed in IR subjects (as compared with NIR) were not due to their later age (which was closer to puberty and thus physiologically could explain the increased HOMA-IR) because this difference remained significant even after adjustment for age and BMI. These findings strengthen the fact that obesity and insulin resistance are characterized by a low-grade inflammatory state accompanied by elevated levels of circulating inflammatory molecules and suggest that YKL-40 may play a role in modulating these conditions in childhood.

YKL-40 is a well-recognized marker of inflammation, insulin resistance, and type 2 diabetes mellitus in adults [8], whereas data regarding its relationship with markers of obesity have been inconsistent. In the present study, higher YKL-40 levels were associated with greater adiposity, in agreement with a previous study [22] but in contrast to others [23-25]. These discrepancies may be due to variations in participant characteristics or sample sizes. Moreover, in a very recently published study, a positive correlation between leptin (which can be considered a complementary to BMI measure of adiposity) and YKL-40 levels has been detected in obese subjects either diabetic or not [26]. YKL-40 levels were also associated with markers of insulin resistance, even after adjustment for obesity or inflammation markers, as described by others as well [25]. It is noteworthy that these findings did not change even when BMI z scores, which represent a more accurate measure of adiposity than BMI alone, were included in the analyses. In addition, we revealed that components of the insulin resistance syndrome [27], already altered in obese children, such as high levels of BP, were related with YKL-40 levels, which is in accordance with other reports [13]. On the other hand, no significant correlations between YKL-40 and lipid profile were observed. This finding is in harmony with that of Hempen et al [23] but differs with results reported by Rathcke et al [24] that described an independent association between YKL-40 and levels of triglycerides as well as nonesterified fatty acids. All these data provide additional insights into the role of YKL-40 in the development of insulin resistance and support the hypothesis that inflammation may be one of the linkage keys between obesity and metabolic syndrome.

YKL-40 levels as well as markers of inflammation such as CRP and WBC count were elevated in obese prepubertal children. YKL-40 levels were also significantly correlated with WBC count but not with CRP levels. These findings are consistent with previous studies that reported significant correlations between YKL-40 levels and IL-6 [23,28] or CRP [28]. However, other studies showed that changes in YKL-40 levels do not always reflect changes in CRP or high-sensitivity CRP [23-25,29-31]. Possibly, this is due to the fact that CRP is primarily a systemic inflammation marker secreted by hepatocytes in response to proinflammatory mediators such as IL-6, whereas YKL-40 is secreted by locally activated macrophages and neutrophils, serving as a specific serologic marker of granulocyte function and macrophage activation at the site of tissue inflammation [8]. YKL-40 levels also show a more rapid peak and decline after initiation of antibiotic treatment in patients with community-acquired pneumonia, in contrast to CRP levels that decrease slowly [30]. Therefore, it is possible that YKL-40 may promote obesity-related low-grade inflammation through a pathway not fully overlapping with CRP.

The physiologic relevance of YKL-40 with respect to obesity and its related pathologies remains to be determined. In obesity, increased YKL-40 levels are believed to be secreted by active macrophages that infiltrate the inflamed adipose tissue

[32,33]. Given the basic functions of YKL-40 in mechanisms of extracellular remodeling (cell migration, chemotaxis, differentiation, proliferation, adhesion, angiogenesis, etc) [6,7], it is reasonable to speculate that YKL-40 may serve as a contributor to the response to hypoxia in areas of the fat depots, as the tissue mass increases during the progressive development of obesity [5]. On the other hand, YKL-40 may be important in obesity in that the link between YKL-40 and insulin resistance may occur through the enzyme phosphatidylinositol-3-kinase that mediates insulin-stimulated glucose uptake [34]. A pivotal signal in the cellular response to YKL-40 binding to its putative receptor is phosphatidylinositol-3-kinase–mediated phosphorylation of protein kinase B, which finally leads to decreased production of matrix metalloproteinases and chemokines [35]. Moreover, YKL-40 has recently been suggested to contribute to trap macrophages into adipose tissue by inhibition of type I collagenolysis by matrix metalloproteinase–1 [33]. Thus, increased YKL-40 secretion and delivery by its potential receptor might explain its effects on insulin metabolism.

As far as we know, this study is the first to determine serum YKL-40 levels in an obese pediatric population; and our findings are reported for the first time in the medical literature. In addition, study participants were carefully selected so that age- and sex-matched pairs are identified; however, unpaired analyses were used because other currently unknown factors possibly related to YKL-40 expression were not obtained in the present study. Our findings concerning the association of YKL-40 with obesity and insulin resistance are also strong enough and important because they have been implicated in prepubertal children; thus, they are independent of any influence that hormonal profile of puberty might have on this relationship. On the other hand, there are some limitations that have to be acknowledged: the relatively small sample size; the cross-sectional design; and the fact that we did not determine other biochemical markers of inflammation, endothelial dysfunction, or adhesion molecules that are changed in obesity and could possibly alter our results if included in the analyses. Moreover, overweight has been defined by BMI, which just represents an indirect hint of obesity; and body fat was determined by bioelectrical impedance analysis. Finally, no clamp study has been performed; and IR was assessed using the HOMA-IR method that is derived from glucose and insulin levels in the fasting state.

In conclusion, this study shows for the first time that serum YKL-40 levels are increased in obese prepubertal youngsters and suggests that YKL-40 represents a marker of insulin resistance even in childhood. These conditions are associated with increased cardiovascular risk, whereas previous studies have also described a potential role of YKL-40 in developing cardiovascular disease in adulthood. Whether higher levels of YKL-40 in pediatric populations actually predict later cardiovascular complications remains to be elucidated in the future by larger, well-defined, prospective studies.

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Conflict of Interest

The authors have no conflicts of interest to disclose.

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