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Research

Association of Total and High Molecular Weight Adiponectin with Components of Metabolic Syndrome in Mexican Children

Short title: Adiponectin in Mexican Children

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What is already known on this topic?
Childhood obesity is related to several impaired biochemical parameters, including the concentration of Total- and HMW-adiponectin. A low adiponectin concentration was related closely to the prevalence of MS.

What this study adds?
The strong inverse correlation between adiponectin levels and biochemical parameters related to carbohydrate metabolism, contribute to the hypothesis that low adiponectin levels are associated with an elevated risk of diabetes. It reinforces the early role of insulin resistance at future vascular events. The circulating concentration of Total adiponectin may represent an excellent biomarker to evaluate the risk of metabolic complications in young children and interventions to reduce obesity in school children are needed.

Abstract
Background: Childhood obesity linked to metabolic alterations, tend to appear simultaneously with altered adipocytokines. suggesting its role in pathogenesis development. Low circulating level of Total and High Molecular Weight adiponectin have been associated with components of the metabolic syndrome and could represent an independent risk factor with potential use as biomarker. **Aim**: To examine the prevalence of the metabolic syndrome in scholar children and to compare the degree of association of Total and High Molecular Weight adiponectin levels with biochemical parameters related to the metabolic syndrome.
Methods: The study included a population of 155 boys and girls, from 8 to 11 years old. Anthropometric and biochemical parameters were evaluated according to weight and metabolic syndrome status. A correlation analysis was fitted to establish an association between adiponectin concentration and metabolic indicators.
Results: The prevalence of metabolic syndrome was of 10.3%. Impaired biochemical parameters, including Total and High Molecular Weight adiponectin, were associated with obesity. The adiponectin level was significantly lower in MS than in Non-MS subjects (4.5 vs. 5.4 µg/mL). Total- but no High Molecular Weight adiponectin concentration was negatively correlated with blood pressure, fasting insulin, and Homeostatic Model Assessment for Insulin Resistance.
Conclusions: In young children, the Total-adiponectin level is associated with impaired biochemical parameters and could be an excellent early predictor of metabolic complications.
Keywords: Adiponectin, children, insulin resistance, metabolic syndrome, obesity

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Introduction

Childhood obesity is a complex disorder linked to metabolic and clinic abnormalities, such as insulin resistance, dyslipidemia, and hypertension. Various combinations of these impaired metabolic functions, even in children, define the metabolic syndrome (MS) (1). Its simultaneous occurrence demonstrates that the accumulation of adipose tissue is a frequent etiologic basis. This tissue secretes numerous physiologically active peptides with common properties to cytokines, commonly known as adipocytokines, such as leptin, interleukin-6, resistin, C-reactive protein, and adiponectin. While most of the adipocytokines promote dysregulated metabolism, adiponectin contributes to maintaining energy balance, insulin sensitivity, blood pressure, immunological processes, angiogenesis, fat metabolism, and homeostasis. When adiponectin levels are low as occurs in central obesity, the risk for metabolic alterations increases in adults, adolescents, and children (2,3,4).
Circulating adiponectin exists as multimers of High-, Medium-, and Low-Molecular-Weight (HMW, MMW, and LMW respectively), with predominant HMW and LMW isoforms. In adults, the low HMW adiponectin concentration reflects

metabolic abnormalities related to obesity, insulin resistance, and vascular alterations in a better way than Total-adiponectin (5). Multifactorial disorders such as metabolic syndrome may be affected by factors dependent on the study population. In Japanese children, the HMW adiponectin was inversely correlated with obesity and insulin resistance (6). Although the Mexican population is a combination of a genetic mixture, significant heritability for adiponectin and obesity traits substantiate a genetic contribution to circulating cytokine levels in Hispanic children (7,8). Furthermore, the age population is an important factor related to the pathophysiology of metabolic syndrome and adiponectin concentration (9). Therefore, this study was designed to investigate the association of Total and HMW adiponectin levels with components of the MS, and its possible role as an early risk marker in young Mexican children.

Methods

Subjects

A total of 155 children between the ages of 8 and 11 were randomly selected to participate in a cross-sectional study from six representative elementary schools in five districts in a northwestern urban region of Mexico. Schools were selected from lists made available by the Educational Authorities. The protocol was presented to the school board, classrooms were selected, and parents were required to sign a written consent form to allow their children to participate. Children without medical therapy, with parental permission and fasting, were included. The initial population consisted of 294 children, of whom 85 were excluded for not meeting the inclusion criteria or declined to participate. The day of blood sampling, 44 children were eliminated for not having parental permission or not being fasting, another ten were dismissed for failing to obtain the blood sample by stress at the moment of sampling. There were no cases of children on medication or kidney disease excluded from the study. The study protocol was approved by the Research Ethics Committee of the Faculty of Medicine, Autonomous University of Sinaloa, with registration number CONBIOÉTICA-25-CEI-003-20181012; procedures were in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Volunteers were informed about the aim of the study, and the written consent were obtained from their legal guardians.

Anthropometric variables

Anthropometric variables were measured according to standardized procedures (10). Body weight (BW) was measured with children wearing lightweight clothing and no shoes, to the nearest 0.1 kg using a standardized electronic digital scale (Tanita BC-553; Illinois, USA). Height was measured to the nearest 0.1 cm using a portable stadiometer (Seca-214; Hamburg, Germany) with the head in the Frankfort horizontal plane. Waist circumference (WC) was measured with a non-elastic, flexible measuring tape at the mid-point between the iliac crest and the lower edge of the ribs at the end of a normal expiration. Body mass index (BMI; kg/height in m2) was calculated and classified according to the age- and gender-specific cut-off points proposed for the World Health Organization (WHO) (11).

Clinical and Metabolic Parameters

Systolic and diastolic blood pressures were obtained on the right arm with the child seated, after rest, using a digital sphygmomanometer and appropriated sized cuff. Venous blood samples were collected in the morning (8:00 to 9:00) by direct venipuncture after an overnight (10 to 12 h) fast. Plasma and serum were separated by centrifugation, aliquoted, and immediately frozen at −80 ºC for later analysis. Glucose oxidase method (RANDOX Laboratories Ltd., Antrim UK) was used to quantify fasting blood glucose levels. Triglyceride (TG), total cholesterol (TChol), high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) were measured using an enzymatic colorimetric method (RANDOX Laboratories Ltd., Antrim UK). Insulin, total- and HMW-adiponectin, were measured by enzyme-linked immunosorbent assay (ELISA) using commercially available kits (ALPCO Immunoassays; NH, USA). Assays were conducted according to recommendations of fabricant.

Classification of Pediatric Metabolic Syndrome

Currently, a standardized definition of MS exists for adults, but not for children and adolescents. Therefore, modified criteria from the WHO was applied to perform the diagnosis of MS in children (12). It requires either insulin resistance, hyperglycemia, or known diabetes plus the presence of 2 of 3 other risk parameters: hypertension (elevated age/gender systolic and/or diastolic blood pressure ≥ 90th percentile), dyslipidemia (hypertriglyceridemia ≥ 150 mg/dL or low-serum HDL-C < 39 or < 35 mg/dL in boys and girls respectively), and central obesity (age/gender waist circumference ≥ 90th percentile or BMI ≥ 95th percentile). The impaired fasting glucose was considered with the cut-off points ≥ 100 mg/dL or fasting insulin ≥ 75th percentile (13). Insulin resistance was expressed as homeostasis model assessment for insulin resistance (HOMA-IR) calculated as the product of the fasting plasma insulin level (μUI/mL) and the fasting plasma glucose level (mmol/L), divided by 22.5 (14).

Statistical Analysis

Data are presented as the means ± standard deviation. *T*-Test was used for comparison of continuous variables where applicable and by ANOVA with Tukey-Kramer *post hoc* comparison being used to evaluate group differences. Boys and girls were combined in the same groups due to there were no significant sex-related differences in the anthropometric and biochemical data in the obese and non-obese children. Total- and HMW-Adiponectin were correlated to anthropometric, biochemical, and clinical parameters using the Pearson correlation coefficient. The statistical differences were considered significant at $P<0.05$. All statistical analyses were performed using the statistical software NCCS v.2007 (15).

Results

The study included a total of 155 children: 75 of healthy weight, 37 overweight, and 43 obese (Figure 1). The prevalence of MS was 10.3%, according to the WHO definition. At the initial analysis, children showed no significant sex-related differences in the anthropometric and biochemical data; therefore, they were combined in the same groups. Characteristics of subjects and comparisons of mean values of clinical and metabolic continuous variables were analyzed according to obesity status (Table 1). Age was similar ($P > 0.05$) between groups. In the obesity group, insulin and adiponectin had statistically higher concentrations ($P < 0.05$), while HDL-C, Total-, and HMW-adiponectin were lowest. Also, blood pressure was higher in the obesity group.

When comparisons were made according to the presence or absence of MS (Table 2), there was no difference for age ($P > 0.05$). However, weight, BMI, and WC were different between groups ($P < 0.0001$) with the highest values for the group

with MS. Insulin, HOMA-IR, LDL-C, TG, and blood pressure were statistically higher for the MS group, while Total adiponectin and HDL were lowest. Glycemia, TChol, and HMW-adiponectin have no differences.
Absolute values of adiponectin were tested in correlation analysis, and Total-adiponectin had a significant negative correlation with anthropometric parameters and biochemical variables related to carbohydrates metabolism but not with those of the lipid metabolism (Table 3). Also, an inverse correlation was observed with the number of MS components. HMW-adiponectin was inversely correlated with BW, BMI, and HDL-C and no other significant correlation resulted (Table 3).

Discussion

The increase in childhood obesity worldwide is one of the most severe public health problems. The evidence of its association with parameters of MS, start to be stronger (7,16,17). Adipocytokines and genetic background are key players for the MS pathogenesis. In the present study, we assessed the impact of childhood obesity and MS in young Mexican children and its association with total- and HMW adiponectin. The prevalence of MS found in this study (10.3%) is higher for the general child population compared with that found in others (3 until 8.4%) using the WHO definition (18,19,20). However, it is difficult to contrast the prevalence of MS because modified definitions exist. When prevalence of MS in children and adolescents is based on the National Cholesterol Education Program's Adult Treatment Panel III (NCEP) definition, it is ranked from 4.2% until 18.6%, with 15.8% in similarly aged population (7-9 years old) to our study (21,22,23,24). This high prevalence alerts about the importance of early diagnose of MS in childhood, to prevent the progression from obesity to insulin resistance, cardiovascular diseases, and type 2 diabetes.
The analysis of anthropometric variables according to weight status confirms that each component of the MS worsens with BW increasing, independent of sex (25). Similar to other works (24,26,27), in our study, several parameters did not show significant differences between overweight and obese children, except for significantly higher WC in the obese group, which confirms its importance as a risk indicator. The impaired levels of insulin, HOMA-IR, triglycerides, HDL-C, and Total- and HMW-adiponectin in the obese group respect to the normal group confirm the remarkable impact of obesity on metabolic disorders. Compared to normal and overweight children, obese children have a higher prevalence of many components of the MS. This pattern is similar to other studies in obese children and adolescents, which low serum adiponectin levels increased risk factors of MS such as hyperglycemia, hyperinsulinemia, high blood pressure, and fat disorder (2,23,28).
The analysis, according to the presence or absence of MS, suggests that its prevalence increases directly with BMI. Similar to Turkish and Portuguese children with MS and obese Italian children, in our study, no differences were observed in TChol level, suggesting that this indicator is less critical in this age group (22,29,30). However, in Korean children, associations of non□high□density lipoprotein cholesterol with metabolic syndrome have been found (31).
Regarding biochemical parameters, the Total-adiponectin had the highest inverse correlation with HOMA-IR, followed by fasting glucose, insulin concentration, and the number of MS components. Similar findings have been described, where Total adiponectin had a strong inverse relation with HOMA-IR and obesity, and its low concentration was an essential determinant of insulin sensitivity and HDL in children and may predict type 2 diabetes (7,27,30,32,33). No significant correlation was found for biochemical parameters related to fat metabolism (e.g., triglycerides, HDL-C, LDL-C. TChol), probably due to the young age of the population and the pathophysiology of MS (22,34). Longitudinal studies showed that blood pressure and triglycerides decreased when HOMA decreases, independently of changes in body weight, supporting the hypothesis that insulin resistance is the central abnormality contributing to these cardiovascular risk factors and development of atherosclerosis and MS (22,27). The studies found that insulin resistance, or its accomplice, hyperinsulinemia could precede to dyslipidemia, enhancing the output of very-low-density lipoprotein and raising triglycerides; this lipid overload in muscle is diverted to the liver, promoting fatty liver and atherogenic dyslipidemia (35). These mechanisms affecting lipid metabolism could be at an early stage in our young population where instead we observed impaired glucose homeostasis is the principal affliction (36). These results obtained in the present study, support the early observations about the need to include the insulin resistance, as proposed in the WHO criteria, for the diagnosis of MS in children (21,29,37,38).
A protective role of adiponectin is evident early in life and compromised in youth-onset obesity, and low concentrations could be considered a risk factor (7,30,32). Even, low levels of adiponectin, modify the association between childhood obesity and adult atherosclerosis (39). In the present study, Total- and HMW-adiponectin were decreased in obese children and correlated with anthropometric variables (weight and BMI). However, whereas Total-adiponectin correlated with several biochemical parameters, HMW-adiponectin only correlated with HDL-C. Previous studies have found that sub-fractions of adiponectin have different biological effects, but their degree of association may vary according to the characteristics of the population (40,41). The latter effect may be due to the different stages of development included in the samples. The adiponectin levels decline with age in association with changes in sex hormones and growth factors, even among growing youth, total fat mass is the primary determinant of adiponectin concentrations, and the age effect is mostly a result of increased fat mass with increased age (42,43). Consistent with the above, changes in Total- and HMW-adiponectin levels in childhood obesity is different to that in elder obese patients (44); therefore, it could be until puberty when the relationship between adiponectin and the biochemical parameters of dyslipidemia is established (45).
Besides, the association of HMW adiponectin with metabolic syndrome indicators seems to be influenced by adiposity (46). In obese prepubertal children, HMW adiponectin shows a closer relationship with the improvement of carbohydrate metabolism parameters than with body fat content. Other studies confirm that the relationships of plasma adiponectin with a favorable lipid profile depend on adiposity and that central obesity plays a significant role in the relationships of adiponectin with triglycerides. These findings may mean that the adiponectin may not necessarily play a favorable role in lipid metabolism, and it might have multiple effects on this metabolic process based on the underlying condition. Different studies have demonstrated that adiponectin concentrations have ethnic variance and were lower in Asian as compared to African-American children, were positively related to insulin sensitivity and HMW was not superior in predicting metabolic variables (47,48,49). Our data indicate that, in the context of the metabolic syndrome in Mexican children, HMW might not be of predominant relevance. Hence, the relationships between adiponectin levels and anthropometric and biochemical indicators in children appear to be independent of sex and influenced by ethnicity and lifestyles associated with modernization. It could be relevant to consider the genetic backgrounds of cohorts in future studies and the body composition for explaining the

relevance of adiponectin in the metabolic syndrome.

Study Limitations

Limitations of our study are mostly due to the limited sample size and its cross-sectional nature; however, our findings are consistent with the idea that ethnic differences influence the distribution of adiponectin isoforms and their relationship with metabolic parameters.

Conclusion

Childhood obesity is related to several impaired biochemical parameters, including the concentration of Total- and HMW-adiponectin. A low adiponectin concentration was related closely to the prevalence of MS. The strong inverse correlation between adiponectin levels and biochemical parameters related to carbohydrate metabolism, contribute to the hypothesis that low adiponectin levels are associated with an elevated risk of diabetes. The lacking correlation of Total- and HMW-adiponectin with fat metabolism indicators could be explained by the young age of the study population. Furthermore, it reinforces the early participation of insulin resistance at future vascular events. Therefore, the circulating concentration of Total adiponectin may represent an excellent biomarker to evaluate the risk of metabolic complications in young children and interventions to reduce obesity in school children are needed. Additionally, a consensual pediatric definition of MS is needed in order to better comparisons between studies and populations, and adequate screening and evaluation of children at risk or with MS.

Authorship Contribution

Magaña Gomez, J., conceived of the presented idea, contributed to the interpretation of the results and took the lead in writing the manuscript.

Moreno-Mascareño, D., planned and carried out the experiments, and contributed to the writing of the manuscript.

Angulo Rojo, C., contributed to the design and implementation of the research, and to the writing of the manuscript.

Duarte de la Peña, G., contributed to the interpretation of the results

All authors discussed the results and provided critical feedback to the final manuscript.

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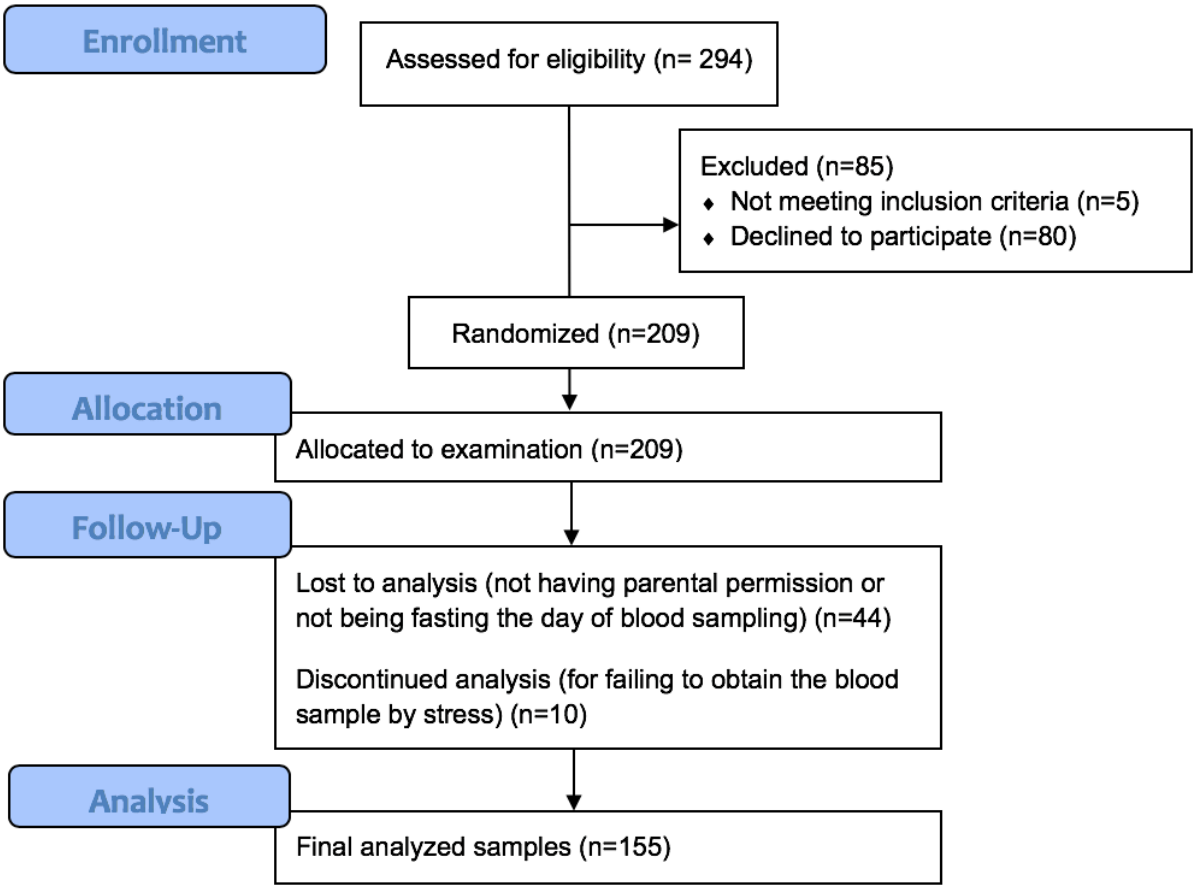

Figure 1. Flow chart of the recruitment stage of the study

Table 1. Comparison of anthropometric, biochemical, and clinical characteristics of the study participants according to the obesity status

Variable	Normal (n = 75) mean±SD (min-max)	Overweight (n = 36) mean±SD (min-max)	Obese (n = 42) mean±SD (min-max)	*P* value
Age, years	9.6±0.9 (8-11)	9.8±0.9 (8-11)	9.6±0.9 (8-11)	>0.05
Anthropometric variables				
Weight, Kg	33.3±5.3[a] (19.9-47.1)	41.5±4.6[b] (31.0-52.4)	52.2±11.4[c] (35.3-84.3)	<0.00001
Weight *z* score	-0.66±0.5[a]	0.09±0.4[b]	1.08±1.05[c]	<0.0001
BMI, Kg/m^2	17.1±1.3[a] (14.2-19.7)	20.5±1.0[b] (18.0-22.9)	25.7±4.6[c] (19.9-49.8)	<0.00001
BMI *z* score	-0.71±0.3[a]	0.04±0.2[b]	1.2±1.04[c]	<0.0001
WC, cm	62.1±5.8[a] (50-76)	69.3±5.1[b] (56.0-80.0)	81.1±10.3[c] (57-104)	<0.00001
Fasting plasma levels				
Glycaemia, mg/dL	81.3±10.9 (52.7-112.2)	83.1±11.5 (55.1-113.3)	83.7±11.8 (60.1-107.7)	>0.05
Insulin, µU/mL	4.8±3.5[a] (0.3-18.2)	8.7±13.3[ab] (1.3-82.7)	11.4±9.6[b] (0.2-53.5)	<0.00001
HOMA-IR	1.0±0.8[a] (0.04-4.2)	1.8±2.9[ab] (0.2-18.0)	2.4±2.0[b] (0.03-11.4)	<0.00001
Total cholesterol, mg/dL	126.0±38.8 (58.1-297.1)	123.7±42.1 (59.2-221.7)	118.8±37.9 (64.5-240.3)	>0.05
HDL, mg/dL	55.3±12.7[a] (15.9-84.6)	57.3±10.9[a] (37.5-82.6)	49.2±12.4[b] (23.4-72.3)	<0.05
LDL, mg/dL	124.7±50.5 (42.1-268.9)	126.5±47.9 (48.5-282.5)	146.6±57.9 (58.7-286.0)	>0.05
Triglycerides, mg/dL	72.0±38.3[a] (29.1-302.3)	82.1±36.0[a] (36.1-211.7)	111.6±70.7[b] (30.4-364.8)	<0.001
Total adiponectin, µg/mL	5.8±1.7[a] (2.4-10.9)	5.2±1.6[ab] (2.7-10.4)	4.6±1.6[b] (1.7-8.5)	<0.05
HMW-Ad, µg/mL	3.9±2.0[a] (0.3-9.0)	3.3±1.7[ab] (1.1-6.5)	2.9±2.0[b] (0.1-8.0)	<0.05
Clinical variables				
SBP, mmHg	96.7±9.2[a] (80-115)	101.5±8.6[b] (90-125)	103.5±10.7[b] (80-130)	<0.001
DBP, mmHg	60.9±5.7[a] (50-80)	63.1±6.2[a] (50-80)	66.6±6.3[b] (60-80)	<0.0001

BMI, body mass index; WC, waist circumference; HOMA-IR, homoeostasis model assessment for insulin resistance; HDL, high density lipoprotein; LDL, low density lipoprotein, HMW-Ad, high molecular weight adiponectin; SBP, systolic blood pressure; DBP, diastolic blood pressure. [a,b,c], Literal different implies statistical differences between groups. SD, standard deviation.

Table 2. Comparison of anthropometric, biochemical, and clinical characteristics of the study participants according to the presence or absence of Metabolic Syndrome

	Without MS (n = 139, 89.7%) mean±SD (min-max)	**With MS (n = 16, 10.3%) mean±SD (min-max)**	***P* value**
Age, years	9.6±0.9 (8-11)	9.8±0.7 (8-11)	>0.05
Anthropometric variables			
Weight, Kg	38.2±8.2 (19.9-68.8)	60.3±10.9 (39.9-84.3)	<0.0001
Weight *z* score	-0.21±0.76	1.8±1.0	<0.0001
BMI, Kg/m^2	19.3±3.1 (14.2-29.4)	28.2±6.3 (23.9-49.9)	<0.0001
BMI *z* score	-0.21±0.69	1.8±1.4	<0.0001
WC, cm	66.9±8.8 (50.0-94.0)	87.1±8.9 (72.0-104.0)	<0.0001
Fasting plasma levels			
Glycaemia, mg/dL	82.1±11.2 (52.7-113.3)	84.9±12.0 (64.4-107.6)	>0.05
Insulin, μU/mL	6.7±8.7 (0.2-82.6)	15.4±6.9 (8.3-32.8)	<0.001
HOMA-IR	1.4±1.9 (0.03-18.0)	3.2±1.4 (1.7-7.4)	<0.0001
Total cholesterol, mg/dL	123.5±37.8 (58.1-297.0)	122.9±51.8 (76.8-240.3)	>0.05
HDL, mg/dL	55.5±11.9 (15.9-84.6)	42.2±12.5 (23.4-64.2)	<0.0001
LDL, mg/dL	127.5±48.4 (42.1-282.6)	163.7±75.3 (67.6-286.0)	<0.01
Triglycerides, mg/dL	76.4±38.2 (29.1-302.3)	163.8±80.7 (73.5-364.9)	<0.0001
Total adiponectin, μg/mL	5.4±1.7 (2.2-10.9)	4.5±1.5 (1.7-6.8)	<0.05
HMW-Ad, μg/mL	3.4±1.9 (0.08-9.0)	3.5±2.1 (1.3-8.0)	>0.05
Clinical variables			
SBP, mmHg	98.8±9.7 (80-125)	107.5±8.4 (100-130)	<0.001
DBP, mmHg	62.4±6.2 (50-80)	67.8±6.3 (60-80)	<0.01

MS, metabolic syndrome; BMI, body mass index; WC, waist circumference; HOMA-IR, homoeostasis model assessment for insulin resistance; HDL, high density lipoprotein; LDL, low density lipoprotein, HMW-Ad, high molecular weight adiponectin; SBP, systolic blood pressure; DBP, diastolic blood pressure. SD, standard deviation.

Table 3. Pearson's correlation analysis between Total adiponectin or HMW-Adiponectin and anthropometric, clinical, and biochemical parameters in children

Variable	Total adiponectin	*P* value	HMW adiponectin	*P* value
Weight, Kg	-0.377	<0.0001	-0.189	<0.05
BMI, Kg/m^2	-0.340	<0.0001	-0.198	<0.05
WC, cm	-0.310	<0.001	-0.101	>0.05
Glycaemia, mg/dL	-0.280	<0.001	-0.043	>0.05
Insulin, μU/mL	-0.171	<0.001	-0.085	>0.05
HOMA-IR	-0.175	<0.001	-0.077	>0.05
Total cholesterol, mg/dL	0.028	>0.05	0.116	>0.05
HDL-C, mg/dL	0.113	>0.05	0.171	<0.05
LDL-C, mg/dL	0.015	>0.05	-0.002	>0.05
Triglycerides, mg/dL	-0.076	>0.05	0.120	>0.05
SBP, mmHg	-0.116	>0.05	-0.066	>0.05
DBP, mmHg	-0.136	>0.05	0.027	>0.05
No. of MS components	-0.279	<0.001	-0.109	>0.05

HMW, high molecular weight; BMI, body mass index; WC, waist circumference; HOMA-IR, homoeostasis model assessment for insulin resistance; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol, HMW-Ad, high molecular weight adiponectin; SBP, systolic blood pressure; DBP, diastolic blood pressure; MS, metabolic syndrome.