

Adiponectin could be a comprehensive marker of metabolic syndrome in obese children

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Abstract

Objectives: The objectives were to investigate the relationship between the serum adiponectin level and the metabolic syndrome (MS) phenotype in children, and to examine the independent association between the serum adiponectin level and the individual components of MS.

Design: A cross-sectional design was used.

Subjects: Fifty-six obese children with a body mass index \geq 95th percentile for age and sex, and 50 normal-weight children matched for age and sex with the obese children, were used as controls.

Outcome measures: The main outcome measure was the serum adiponectin level.

Results: The serum adiponectin level was significantly lower in obese children, than in the normal-weight controls (7.35 ± 3.1 μ g/dl vs. 10.64 ± 3.04 μ g/dl). Obese children with MS have a significantly lower serum adiponectin level compared to obese children without MS (5.92 ± 1.9 μ g/dl vs. 8.57 ± 2.1 μ g/dl). There was a significant negative correlation between the serum adiponectin level and waist circumference, triglyceride levels, systolic blood pressure, diastolic blood pressure, and fasting blood glucose. The serum adiponectin level correlated positively with the level of high-density lipoprotein cholesterol. After controlling for the confounding effect of age, sex and visceral fat, the adiponectin level remained a significant predictor of the MS [odds ratio (OR): 0.76, 95% CI: 0.63-0.91].

Conclusion: Adiponectin demonstrated a consistent relationship to each MS component. Adiponectin may be a comprehensive marker of the MS condition.

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Introduction

The prevalence of obesity has increased dramatically as a result of modern lifestyles, and is now one of the most important targets of public health programmes.¹ Paediatric obesity is a complex and growing global problem. In Egypt, the prevalence of obesity among school children was found to be 14.7% among boys, and 15.08% among girls.² Childhood obesity increases the risk of obesity in adulthood, and is associated with cardiovascular disease risk factors, such as hypertension, diabetes mellitus and dyslipidemia.³

In 1988, Reaven et al described “the metabolic syndrome” (MS) as a link between insulin resistance and hypertension, dyslipidaemia, type 2 diabetes, and other metabolic abnormalities associated with an increased risk of atherosclerotic cardiovascular disease in adults.⁴ However, nowadays, this problem is observed with even greater frequency among children, particularly those with excess body mass. Identification of causes or aetiological factors for the

development of MS is important, so that suitable measures can be instituted to prevent and cure the syndrome.⁵

Although the underlying pathophysiology of MS is unclear, insulin resistance is thought to be a central abnormality in the pathogenesis of the disorder.⁶ Recent studies suggest that, besides insulin resistance, the adipocyte-derived hormone adiponectin may be an important predictive marker for MS.⁷ Adiponectin is the most abundantly expressed adipokine in adipose tissue.⁸ Adiponectin is a multifunctional protein that exerts pleiotropic insulin-sensitising effects. It reduces hepatic glucose production,⁹ and increases glucose uptake and fatty acid oxidation in skeletal muscle.¹⁰ Moreover, adiponectin may possess anti-atherogenic properties by inhibiting the expression of adhesion molecules and smooth muscle cell proliferation, as well as suppressing the conversion of macrophages to foam cells.¹¹ An anti-inflammatory role of adiponectin has also been reported.¹²

Low plasma adiponectin levels are predictive of insulin resistance and type 2 diabetes in adults.¹³ Children with type 2 diabetes have significantly lower adiponectin levels than their normoglycemic counterparts.¹⁴ Thus, it is thought that low levels of circulating adiponectin may be an early marker of metabolic disease risk in children. To date, limited investigations have examined the associations between adiponectin and MS in children. Because adiponectin is related to, and may be contributory to, the development of insulin resistance and the MS, investigations examining the independent associations may offer further insights into the pathways mediating obesity and chronic disease in children.

The overall objective of this study was to investigate the relationship between the serum adiponectin level and the MS phenotype in children. The secondary objective was to examine the independent association between the serum adiponectin level and the individual components of MS.

Method

A cross-sectional study was carried out among children aged 10-12 years in 14 primary schools (government and private schools) in an urban area of the city of Ismailia, Egypt. The multi-stage stratified cluster random sampling method was applied. The prevalence of obesity and overweight was 13.6%. A simple random sample was used. A list of all obese children was compiled, from which 56 obese children were eventually included. (Printed tables of random numbers were used).

Children were eligible for inclusion in the study if their body mass index (BMI) was $\geq 95^{\text{th}}$ Egyptian percentile for age and sex for the obese group, and if they had a BMI between the 25th-75th percentiles for age and sex for the control group. Recently developed Egyptian BMI percentile charts were used.¹⁵ Exclusion criteria were the presence of any cardiac, renal, rheumatic, metabolic, or endocrine disease. The control group included 56 normal-weight children, matched for age and sex with the obese children. Six of control group refused blood sampling.

The following investigations were carried out, and measurements taken, for each participating child:

A complete medical history and physical examination.

- **Anthropometric measurements:** Height was measured to the nearest centimetre using a rigid stadiometer, and weight was measured to the nearest 0.1 kg using a calibrated balance scale. BMI was calculated as weight in kilogrammes divided by the height in meters squared. Waist circumference was measured at the level of the umbilicus, at the end of normal expiration.¹⁶ We included children whose waist circumference was $\geq 90^{\text{th}}$ percentile for age and sex.
- **Blood pressure measurements:** Blood pressure was measured by the auscultatory method, using a sphygmomanometer with a suitable cuff size. Three readings were taken while the subjects were seated, and the last two measurements were averaged for analysis.

- **Blood investigations:** A blood sample was collected from each child in the morning after an overnight fast to measure fasting blood glucose, high-density lipoprotein (HDL) cholesterol, triglycerides (TGs) and adiponectin. Serum glucose, HDL cholesterol and TGs were measured by standard enzymatic methods (Boehringer Mannheim reagents), using a fully automated analyser (Behring® RXL autoanalyser, Germany). Serum adiponectin was determined with an enzyme immunoassay (human adiponectin ELISA Kit®, B-Bridge International, California, USA).

The definition of MS applied in this study was defined according to the latest International Diabetes Federation consensus definition of MS in children and adolescents.¹⁷ According to this definition, MS is considered to be present in the age group 10 to < 16 years if there is abdominal obesity (waist circumference $\geq 90^{\text{th}}$ percentile for age and sex), and the presence of two or more other features among these four parameters: elevated TGs (≥ 150 mg/dl), low HDL cholesterol (< 40 mg/dl), elevated blood pressure (systolic blood pressure ≥ 130 mm Hg, or diastolic blood pressure ≥ 85 mm Hg), and impaired fasting glycaemia (glucose ≥ 100 mg/dl).

Statistical analysis

The data were analysed using the statistical package, SPSS®. Descriptive statistics were used to present the characteristics of the study population. Continuous data were compared using Student's t test. Pearson's correlation coefficient was used to establish the association between plasma adiponectin concentrations and the clinical parameters of MS. A logistic regression analysis was used to assess the independent association between the serum adiponectin level, and the individual components of MS. Statistical significance was considered to be p-value < 0.05 .

Results

The characteristics of the study population are tabulated in Table I. There was no significant difference between the two groups regarding the age and sex. The mean BMI percentile was significantly higher in the obese group (97.4 ± 1.8), than in the control group (51.8 ± 18.6). The mean serum adiponectin level was significantly lower in the obese group, compared to the control group. The prevalence of MS among the obese children was 44.6%.

Table I: Characteristics of the study population

	Obese children	Control	p-value
Number of subjects	56	50	0.213
Age (years)	11.1 \pm 0.9	10.9 \pm 1.1	0.513
Sex			
Female	31	28	
Male	25	22	0.372
Weight (kg)	61.7 \pm 7.8	34.7 \pm 8.9	0.005 ^a
Body mass index	28.4 \pm 2.2	18.2 \pm 3.9	0.009 ^a
Body mass index percentile	97.4 \pm 0.8	51.8 \pm 18.6	0.009 ^a
Waist circumference (cm)	83.5 \pm 5.3	62.3 \pm 9.4	0.01 ^a
Adiponectin level (μ g/ml)	7.35 \pm 3.1	10.64 \pm 3.04	0.03 ^a

Values are mean \pm standard deviation
a = significant difference

Table II: Distribution of individual parameters of the metabolic syndrome and adiponectin among obese children

	Obese with MS ^a (25) Number (%)	Obese without MS (31) Number (%)	p-value
Waist circumference \geq 90 th percentile	25 (100)	20 (64.5)	0.001 ^b
Body mass index	28.30	27.97	0.02
Triglycerides \geq 150 mg/dl	16 (64)	3 (9.7)	0.000 ^b
High-density lipoprotein cholesterol < 40 mg/dl	20 (80)	18 (58.1)	0.013 ^b
Hypertension	6 (24)	2 (6.5)	0.001 ^b
Fasting glucose \geq 100 mg/dl	5 (20)	1 (3.2)	0.001 ^b
Adiponectin level (μ g/ml)	5.92 \pm 1.9	8.57 \pm 2.1	0.04 ^b

a = metabolic syndrome, b = significant difference

Table II shows the comparison between obese children with and without MS, according to the distribution of the individual criteria of diagnosis. There was a statistically significant difference between the obese children with and without MS, regarding the presence of all individual components of the syndrome. The serum adiponectin level was significantly lower in obese children with MS (5.92 \pm 1.9) μ g/ml, compared to those without MS (8.57 \pm 2.1) μ g/ml.

To control for the confounding effect of age and sex on the relationship between adiponectin level and MS, a logistic regression model was used (Table III). The dependent variable was the presence of MS, and the independent variables were age, sex and the serum adiponectin level. The serum adiponectin level remained a significant predictor of MS. There was a significant negative correlation between the serum adiponectin level and waist circumference, TG levels, systolic blood pressure, diastolic blood pressure and fasting blood glucose.

Table III: Independent association of different variables with the metabolic syndrome

Variable	Odds ratio	95% CI ^a
Age	0.55	0.39-1.31
Sex	0.49	0.25-1.22
Body mass index	0.79	0.65-0.94 ^b
Adiponectin	0.76	0.63-0.91 ^b

a = confidence interval, b = significant difference

The serum adiponectin level correlated positively with the level of HDL cholesterol (Table IV).

Table IV: Correlation coefficients of the relationships between adiponectin level and individual parameters of the metabolic syndrome

	r (correlation coefficient)	p-value
Waist circumference	-0.33	0.000 ^a
Triglyceride levels	-0.35	0.000 ^a
High-density lipoprotein cholesterol	0.21	0.009 ^a
Systolic blood pressure	-0.23	0.004 ^a
Diastolic blood pressure	-0.22	0.006 ^a
Fasting plasma glucose	-0.24	0.001 ^a

a = significant difference

Using stepwise multiple linear regression analysis, adiponectin as the dependent factor, and age, sex, waist circumference and BMI as independent factors, waist circumference and BMI were significant determinants of adiponectin; p-value < 0.0001 and 0.001, respectively.

Discussion

The MS is a cluster of interrelated risk factors that increases an individual's susceptibility to cardiovascular morbidity and mortality.¹⁸ In this study, the prevalence of MS in obese children was

found to be 44.6%. Different prevalence rates of MS among obese children have been reported in different studies. Zeitoun et al¹⁹ carried out a study in Egypt, and reported a prevalence rate of 53.6% among obese children. In England, the prevalence was reported to be 33%.²⁰ In Mexico, MS was present in 35% of obese children.²¹ In France, 42.5% of obese children were reported to have MS.²² The difference between the prevalence rates of MS between studies can be explained by the difference in the definitions used for the MS components. The present study addresses the issue in obese Egyptian children. Currently, there are no unified criteria available for the diagnosis of MS in children.²³ Furthermore, differences between different countries may imply differences in ethnic susceptibility.²⁴

Regarding the adiponectin level, the results of our study showed that obese children have a significantly lower adiponectin level, compared to normal weight controls. Furthermore, obese children with MS have a significantly lower adiponectin level compared to obese children without MS. After controlling for the confounding effect of age, sex and central obesity, the adiponectin level remained a significant predictor of MS. Waist circumference was used as an indicator of central obesity, as it has been found to be a good indicator of this.²⁵

Our results are in agreement with those of Shaibi et al,²⁶ who demonstrated that adiponectin levels are approximately 25% higher in healthy obese children, compared to those with MS. Furthermore, Valle et al²⁷ demonstrated that obese children with MS have a significantly lower adiponectin level, compared to non-obese children. Similarly, Weiss et al²⁸ demonstrated that obese children with MS have a significantly lower adiponectin level, and that adiponectin levels decreased with increasing obesity. Adiponectin levels were approximately 25% higher in healthy overweight youth, compared with those with MS (12.5 \pm 3.5 vs. 9.4 \pm 2.8 μ g/ml; p-value < 0.05).

Our results demonstrated that the adiponectin level correlated with all the individual parameters of MS. There was a significant negative correlation between adiponectin level and waist circumference, TG levels, systolic blood pressure, diastolic blood pressure, and fasting blood glucose. The adiponectin level correlated positively with the level of HDL cholesterol. These results are in agreement

the findings of Shaibi et al,²⁶ who demonstrated that adiponectin was significantly and inversely related to systolic blood pressure, waist circumference, triglycerides and two-hour glucose levels, and positively related to HDL cholesterol, independent of age, sex, body composition and insulin sensitivity. Winer et al²⁹ showed that a low level of adiponectin is associated with components of MS, such as low HDL cholesterol, and a high TG:high-density lipoprotein ratio. Saltevo et al³⁰ reported similar results for adults. He demonstrated that the adiponectin level linearly correlates with the components of MS.

The molecular basis of MS has not been fully elucidated yet. One important explanation relates to the role of adipose tissue. Adipose tissue is not merely a simple reservoir of energy stored as TGs. It also serves as an active secretory organ, releasing many peptides, complement factors, and cytokines into the circulation.³¹ In the presence of obesity, the balance between these numerous molecules is altered, such that enlarged adipocytes and macrophages embedded within them produce fewer anti-inflammatory peptides, such as adiponectin. The dysregulated production of adipocytokines has been found to be implicated in the development of metabolic and vascular diseases related to obesity.³² Adiponectin, as an adipose-derived protein, has multiple functions, including anti-atherogenic, insulin sensitising, lipid-oxidation enhancing, and vasodilatory activities.³³ Therefore, it is possible that decreased plasma concentrations of adiponectin play a significant role in the development of MS.

The lack of pubertal status or Tanner staging assignment is an important limitation to our study. The study did not allow for establishing a cause-and-effect relationship, and requires confirmation by prospective studies.

Conclusion

In conclusion, the adiponectin level is well associated with MS. In particular, adiponectin demonstrated a consistent relation to each MS component. The present results raise the possibility that adiponectin is a substantial key molecule in the development of MS, and may be a comprehensive marker of the MS condition. Further prospective studies are warranted to confirm these findings. If confirmed, measures to increase circulating adiponectin might be crucial for the prevention or management of MS.

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