# Resistin and Obesity- Associated Insulin Resistance in Children

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**Abstract:** Obesity, defined as excess body fat, is frequently accompanied by insulin resistance. It was hypothesized that resistin links obesity with insulin resistance and diabetes, however, debate exists about its possible role. The aim of this study was to measure serum resistin level in obese non diabetic children as well as to evaluate insulin resistance in them. It also aimed at exploring the possible correlation between serum resistin level, anthropometric, clinical and laboratory parameters in obese children. This study is a cross sectional study that comprised 45 children and adolescents with simple exogenous obesity and 30 apparently healthy non-obese age and sex matched children as control group. For each subject the following was performed: history taking, anthropometric measurements including body weight, height, BMI, waist circumference, hip circumference, waist hip ratio, skin folds thickness measurements (biceps, triceps, subscapular and suprailiac) and calculation of body fat. Clinical examination and pubertal assessment were performed. Laboratory investigations including fasting serum glucose, fasting serum insulin and resistin using ELISA technique. Insulin resistance was estimated by using the Homeostasis Model Assessment (HOMA). Serum resistin levels did not significantly differ between cases (6.7 ng/ml ±3.44) and (6.6 ng/ml ±2.47), (p>0.05). Fasting insulin and HOMA were significantly higher in obese children than controls, (p < 0.001 for both). About 78% of obese children had insulin resistance (high HOMA), 66.7% had high fasting insulin, 13.3% high resistin, 31.1 % had acanthosis nigricans and 8.9% had hypertension. A significant positive correlation was found between serum resistin levels and each of fasting insulin and HOMA, (p<0.001 for both). No significant correlation was found between serum resistin, HOMA and each of BMI, body fat percentage & waist circumference, (p>0.05). A significant positive correlation was found between BMI and each of waist circumference and systolic blood pressure, (p< 0.001 & < 0.05respectively). The present study confirm the link between resistin level and insulin resistance in obese children, however it couldn't prove whether high or low resistin level is more related to insulin resistance. A significant positive correlation was found between serum resistin levels and each of fasting insulin and HOMA. No significant correlation was found between serum resistin, HOMA and each of BMI, body fat percentage & waist circumference. HOMA was found to be a significant marker for early detection of insulin resistance in obese and overweight children. [Journal of American Science 2010;6(6):256-266]. (ISSN: 1545-1003).

Keywords: Resistin- insulin- insulin resistance- HOMA- obesity- children- acanthosis nigricans.

## 1. Introduction

Obesity is a substantial public health crisis in the developed world and the prevalence is increasing rapidly worldwide in numerous developing nations. This growing rate represents a pandemic that needs urgent attention if its potential mortality and economic tolls are to be avoided. (1). Obesity is particularly alarming in children and adolescents, thus passing the epidemic into adulthood and creating a growing health burden for the next generation. (2) Childhood obesity is associated with substantial comorbidity and late sequelae, including type 2 disease diabetes. hypertension, liver cardiovascular complications. (3, 4)

The most common underlying cause of insulin resistance is central obesity. (5) Excess abdominal adipose tissue has been shown to release increased amounts of free fatty acids which directly affect insulin signaling, diminish glucose uptake in muscle, drive exaggerated triglyceride synthesis and induce

gluconeogenesis in the liver. (6) Although an accelerated atherogenic process is present, the clinical cardiovascular lesions appear later. (7) Insulin resistance may be implicated in the development of many pathological states, such as hypertension, type 2 diabetes mellitus, lipodystrophies, polycystic ovary syndrome and chronic infection. (8, 9)

Resistin, discovered in 2001, is a novel adipocyte-secreted factor that has been proposed to be the link between obesity and insulin resistance. (10) The association between resistin and obesity induced insulin resistance could be supported by the fact that: resistin expression is 15 folds higher in visceral fat than subcutaneous fat, visceral fat is considered as the major risk factor for insulin resistance and decreased insulin sensitivity. (11) However, the role of resistin in the pathophysiology of obesity and insulin resistance in humans is still controversial. Several studies have shown positive

correlations of circulating resistin levels with BMI and waist circumference, (12, 13) as well as insulin resistance. (14, 15). However, other studies found no such relationship. (16, 17, 18) These controversial results may reflect variations in the study design and the lack of adjustment for potential confounding factors. Therefore, further studies are needed to define the relationship of resistin to obesity associated insulin resistance. (19)

The aim of this study was to evaluate resistin levels in obese non diabetic children. It also aimed at exploring the possible correlation between serum resistin level, anthropometric, clinical and laboratory parameters in them.

#### 2. Material and Methods

This study is a cross sectional study that comprised 45 obese children and adolescents (20 males and 25 females) in the age range (7-15 years), attending the outpatient clinic of the Diabetic, Endocrine and Metabolic Pediatric Unit (DEMPU), Abo-Elrish Hospital, Cairo University during the period from January to May 2007. They fulfilled the inclusion criteria of having a BMI exceeding the 95th percentile of the same gender and age according to the Egyptian Growth Charts, (2002) and simple exogenous obesity. All cases had high waist  $95^{th}$ circumference exceeding the percentile according to the British percentiles. Thirty apparently healthy non-obese age and sex matched children (17 males and 13 females) were recruited, as control group, from the general pediatric outpatient clinic, Abo-Elrish Hospital, Cairo University. The protocol was approved by the ethics committee in the National Research Center and Abo-Elrish children Hospital, Cairo University and a written informed consent was obtained from each child's parents.

For each subject the following was performed:

- History taking including personal history, past history for systemic diseases, drug administration (corticosteroids), and family history (obesity, diabetes& hypertension).
- Anthropometric measurements including body weight, height, BMI calculation and evaluation according to the Egyptian Growth Charts (2002), [BMI = Weight (kg)/ Height (m²)], waist circumference, hip circumference, calculation of waist hip ratio and skin folds thickness measurements (biceps, triceps, subscapular and suprailiac). Waist circumference values were plotted on the waist circumference percentile curves for British children (which are used for Caucasian children). (

- 20) Calculation of body fat was done by plotting values of skin fold thickness on the British sex-specific percentile curves for body fat. (21)
- Clinical examination to confirm the diagnosis of simple obesity and to exclude signs & symptoms of acute or chronic inflammation and systemic diseases (bronchial asthma, autoimmune diseases, Cushing disease and hypothyroidism) as well as the presence of Acanthosis Nigricans. Pubertal assessment according to Tanner Staging was performed.

#### **Laboratory Investigations:**

Five cc of venous blood were drawn aseptically then left to clot. The separated serum was stored at -80°C until analytic measurement of serum insulin and resistin were performed, except for glucose which was determined immediately after blood was drawn.

## **Fasting serum glucose:**

Serum glucose was measured with glucose oxidase using a Hitachi autoanalyzer.

Stanbio Enzymatic glucose procedure No.1075; a single reagent glucose method based on a technique described by Trinder, (1959). (22)

## Fasting serum insulin using ELISA technique:

The BioSource INS-EASIA (manufactured by Europe S.A. - Rue de l'Industrie, 8 - B-1400 Nivelles - Belgium) is a solid phase Enzyme Amplified Sensitivity Immunoassay performed on microtiterplates. It is an Immunoenzymetric assay for the in vitro quantitative measurement of human Insulin (INS) in serum and plasma. Results of the samples are determined using the standard curves. Normal range 5-19µIU/ml. (23)

#### Serum resistin level using ELISA technique:

Resistin was measured by an enzyme linked immunoassay kit obtained from the BioVendor'laboratory Medicine,Inc,Palackeho(Czech Republic). Normal range is 6.6-12 ng/ml. (24)

Insulin resistance was estimated by using the Homeostasis Model Assessment (HOMA) which will be calculated according to the formula: HOMA=

#### Fasting serum insulin(IU/ml) X Fasting serum glucose (m mol/L)

22.5

(Insulin resistance being defined as a HOMA index > 3.16) The greater the HOMA value the greater the level of insulin resistance. (25)

## **Statistical Analysis:**

Data analysis was done using SPSS version 15. For comparing between two means, Student t-test of significance was done while one way analysis of variance was used to compare between more than two means. The Chi-square test of significance was used to compare frequency between two categorical variables. Correlation analysis using Pearson test was performed between different quantitative variables. P value less than 0.05 was considered significant.

#### 3. Results

This study included 45 obese children: 20 males (44.4%), 25 females (56.6%) with a mean age of 9.5 years and 30 non obese control children: 17 males (56.7%), 13 females (43.3%) with a mean age of 8.6 years. There was no significant statistical difference in between cases and controls as regards sex and age. All cases had BMI, percentage of body fat and waist circumference exceeding the 95<sup>th</sup> percentile.

There was no significant statistical difference in between cases with +ve family history of obesity, diabetes and hypertension and those with -ve family history as regards anthropometric measurements, clinical data and laboratory parameters.

A statistically significant difference was found between cases and controls as regards anthropometric, clinical and laboratory parameters except for systolic blood pressure and resistin levels (Table 1). The percentages of high fasting insulin, high HOMA and high resistin levels were significantly higher in cases compared to controls (Figure 1).

A comparison among cases according to different anthropometric, clinical and laboratory parameters is displayed in Table (2). This study revealed that resistin and insulin resistance were independent of age and pubertal stage.

The correlation between the different parameters in cases revealed a significant positive correlation between resistin level and each of fasting insulin and HOMA as well as between BMI and each of waist circumference and systolic blood pressure (Table 3)

Figure 2 & 3 show the correlation between resistin and each of fasting insulin and HOMA in cases.

Only 4 cases (8.9%), 3 females and one male showed high systolic and diastolic blood pressure for age and sex according to the age-specific percentiles of blood pressure (BP) measurements for boys and girls, while none of the controls were hypertensive. The four hypertensive cases had high HOMA and low serum resistin level, 3 of them had high fasting insulin and positive Acanthosis Nigricans. Only one patient gave positive family history of obesity and diabetes.

By grouping cases according to presence of high HOMA, Acanthosis Nigricans and altered serum resistin levels we found that:

- Twenty cases had high HOMA and low serum resistin level, among them, 8 cases had Acanthosis Nigricans.
- Six cases had high HOMA and high serum resistin level, among them, 2 cases had Acanthosis Nigricans.

Table 1. Anthropometric, clinical and laboratory data among cases and controls (\*, Significant p value; †BMI, Body Mass Index; ‡BP, Blood pressure; †HOMA, Homeostasis Model Assessment)

	Cas n=4		Cont n=3	p value	
	Mean ± S		Mean :	varue	
BMI (Kg/m <sup>2</sup> )†	31.32 5.59		16.9	2.34	0.000*
Waist circumference (cm)	89.54	12.22	55.65	5.43	0.000*
Waist hip ratio	0.93	0.50	0.8	0.06	0.000*
Body fat %	40.6	3.84	18.4	3.39	0.000*
Systolic BP (mmHg);	109.0	11.41	107.5	4.31	0.494
Diastolic BP (mmHg)‡	69.9	7.19	64.83	4.64	0.001*
Fasting glucose (mg/dl)	90.93	9.10	86.40	9.38	0.039*
Fasting Insulin(µIU/ml)	23.98	10.61	15.96	4.61	0.000*
НОМА†	5.40	2.54	3.4	0.99	0.000*
Resistin(ng/ml)	6.74	3.44	6.62	2.47	0.871
Puberty (No-%) • Pubertal	34	75.6	12	40	0.002*
• Pre-Pubertal	11	24.4	18	60	0.002*
Acanthosis nigricans (No- %)	14	31.1	0	0	0.001*
• Present • Absent	31	68.9	30	100	0.001

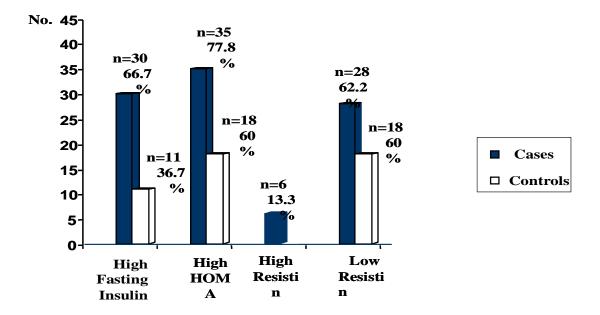


Figure 1. Frequency of abnormal laboratory parameter values among cases and controls (High HOMA > 3.16; Low resistin level < 6.6ng/ml; High fasting insulin level >  $19\mu IU/ml$ ; High resistin level > 12ng/ml)

Table 2. A comparison among cases according to different anthropometric, clinical and laboratory parameters (\*\*, p< 0.001; \*, p< 0.05;  $^{\varepsilon}$ , p< 0.05 between low & normal resistin;  $^{\circ}$ , p< 0.05 between high & normal resistin; †BMI, Body Mass Index; ‡BP, Blood pressure; ||HOMA, Homeostasis Model Assessment)

	Insulin		НОМА		Resistin			Acanthosis nigricans	
	> 19µIU/ml	< 19µIU/ml	>3.16	<3.16	Low <6.6ng/ml	High >12ng/ml	Normal 6.6-12ng/ml	Present	Absent
	n=30	n=15	n=35	n=10	n=28	n=6	n=11	n=14	n=31
	Mean± SD	Mean± SD	Mean± SD	Mean± SD	Mean± SD				
BMI (Kg/m <sup>2</sup> )†	32.09±6.39	29.77±3.15	31.9±6.13	29.3±2.31	31.72±6.67	31.95±4.47	29.93±2.16	$35.21\pm7.24$	29.55±3.59**
Waist circumference(cm)	89.2±13.38	90.23±9.89	89.7±13.08	89.1±9.15	89.75±13.89	90.75±12.05	88.36±7.81	96.64±13.05	86.33±10.53**
Waist / hip ratio	0.93±0.55	0.95±0.34	0.93±0.05	0.94±0.04	0.93±0.05	0.93±0.39	0.94±0.06	0.92±0.060	0.93±0.044
Body fat %	39.59±4.1	42.78±2.08*	40.13±4.12	42.46±1.85	40.81±3.98	41.15±2.06	39.97±4.39	38.95±3.40	41.41±3.83
Systolic BP(mmHg)‡	108.17±10.8	110.67±12.8	109.5±12.45	107.0±6.75	110.36±13.39	107.5±9.87	106.36±5.05	112.5±13.69	107.41±10.07
Diastolic BP(mmHg)‡	69.33±7.28	71.0±7.12	70.1±7.52	69.0±6.15	70.35±8.26	69.16±7.35	69.09±3.75	72.50±8.26	68.70±6.45
Fasting glucose(mg/dl)	92.43±8.39	87.93±10.0	91.7±8.01	88.1±12.28	90.46±6.77	93.83±6.21	90.54±14.67	94.21±8.45	89.45±9.12
Fasting insulin(µIU/ml)			27.7±8.91*	11.1±3.71**	34.03±8.98 <sup>€</sup>	30.26±12.38 <sup>©</sup>	21.32±10.88	24.73±8.42	23.64±11.57
Resistin(ng/ml)	7.3±3.78	5.63±2.36	7.21±3.72	5.1±1.26				7.05±4.08	6.60±3.17
НОМА	6.64±2.08	2.8±0.86**			7.82±2.00 <sup>€</sup>	6.70±2.86 <sup>©</sup>	4.69±2.90	5.67±1.93	5.22±2.79

Table 3. r values of the correlation between the different parameters among cases and controls (\*, p<0.05; \*\*, p<0.001; r, Corrélation coefficient)

	HOMA		Resistin		Fasting insulin		BMI	
	[r]		[r]		[r]		[r]	
	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
	n=45	n=30	n=45	N=30	N=45	N=30	N=45	N=30
BMI	0.20	0.07	-0.02	-0.16	0.19	0.36		
Body fat%	-0.28	-0.01	0.10	-0.07	-0.26	0.52**	-0.21	0.32
Waist circumference(cm)	-0.25	0.12	-0.03	-0.12	0.06	0.18	0.84**	0.74**
Waist /hip	-0.25	-0.17	-0.01	0.21	-0.29	-0.13	-0.09	-0.49**
Systolic BP (mmHg)†	-0.01	0.27	-0.16	-0.05	-0.05	0.29	0.30*	0.30
Diastolic BP (mmHg)	-0.09	0.04	-0.13	-0.03	-0.13	0.01	0.25	0.43*
Fasting glucose(mg/dl)	0.32*	0.34	0.21	-0.13	0.14	-0.12	0.12	0.23
Fasting insulin(µIU/ml)	0.98**	0.57*	0.42**	0.09			0.19	0.36
Resistin(ng/ml)	0.45**	0.43*			0.42**	0.09	-0.02	-0.16
HOMA‡			0.45**	0.04	0.98**	a	0.20	0.10

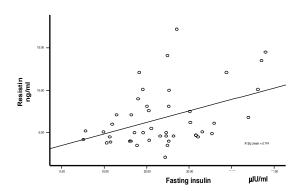


Figure 2. Correlation between serum resistin level and fasting insulin in cases  $(r=0.42;p\!<\!0.001)$ 

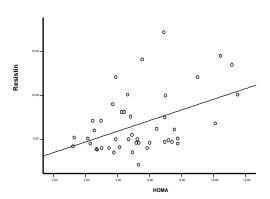


Figure 3: Correlation between serum resistin level and HOMA in cases. (r = .45 P<0.001)

## Discussion

Although obesity, defined as excess body fat, is frequently accompanied by insulin resistance, the molecular basis for the link between obesity and insulin resistance has not yet been clarified. (9) Identifying IR in children may be of substantial clinical importance and has been proposed as a strategy for identifying high-risk children for targeted diabetes prevention interventions. (26)

The 95<sup>th</sup> percentile of BMI was chosen as a cut off level for obesity as this is the agreed upon level incriminated with insulin resistance and cardiovascular risk. (27) Although waist circumference, being an index for central or visceral obesity, is more related to insulin resistance and its health consequences, (28, 29) we could not use it as an inclusion criterion for enrollment of cases because we don't have norms for our country.

Many studies stressed the importance of family history of diabetes, hypertension and obesity in assessment of health risks in obese children. (30) However, in the present study, despite of having +ve family history of obesity (53.3%), type-2 diabetes (35.6%) and of hypertension (28.9%) among obese children there was no significant statistical difference in between cases with +ve family history and those with -ve family history as regards anthropometric data measurements, clinical and laboratory parameters. Similarly, Goran et al., (2003) showed no influence of positive family history of type 2 diabetes mellitus on fasting glucose, insulin level and insulin resistance in a group of pre-pubertal obese children.

It was hypothesized that resistin links obesity with insulin resistance and diabetes, but this has not been studied in children and adolescents to date. (18) In the present study the resistin levels did not significantly differ between obese children and controls. This agrees with the findings of some investigators (9, 18, 32). On the contrary, other investigators had found significantly higher resistin levels in obese compared to non obese controls. (13, 33-35)

We found no statistical difference in serum resistin level between girls and boys in both cases and controls and this agrees with the finding of Schaffler et al., (2004).(36) Other studies, on the other hand, reported significantly higher serum resistin levels in girls than in boys. (13, 18, 32) However Li et al., (2009) reported that the gender related difference in serum resistin levels was quite significant only when comparing pubertal groups suggesting a link with development.(13) However these relations with gender and age in children have not always been found. (37-39)

In the present study as well as in some other studies waist circumference and BMI did not show

any significant correlation with resistin level. (16, 17, 26) On the contrary, some other studies have found that obesity markers were positively correlated with resistin levels (12, 13). However, Li et al., (2009) emphasized that none of these associations was found when exclusively analyzing the prepubertal group, thus pointing to a role played by puberty on the serum level of resistin (13). On the other hand, Gambino et al., (2005) found a significant correlation between serum resistin level and waist circumference in healthy non obese control group.(17)

In the present study a link between resistin level and insulin resistance in obese children was confirmed by finding a significant positive correlation between serum resistin levels and each of fasting insulin and HOMA which agrees with the findings of Silha et al., (2003) and Koebnick et al., (2006). (14,15) On the other hand Li et al., (2009) reported that only few indices of insulin resistance were linked with plasma resistin in either gender (13). On the contrary, other studies found no significant correlation between serums resistin levels and insulin resistance (18, 33, 40, 41). However, Gambino et al., (2005) found a correlation between serum resistin and fasting insulin only in normal subjects. (17)

In this study, 24.5% of cases had normal resistin level, 13.3% had high level and 62.2% had low level. A significant difference between cases with either high or low resistin level on one hand and cases with normal resistin on the other hand was found regarding fasting insulin level and HOMA. These observations suggest that altered resistin level whether high or low can be related to insulin resistance associated obesity.

The pediatric metabolic syndrome is defined as the presence of at least three of the following: abdominal obesity, (waist circumference percentile), low HDL-C level (40 mg/dl), hypertriglyceridemia (>90th percentile), hypertension (> 90th percentile), and/ or impaired glucose tolerance (42). In this study, 4 out of 45 cases (8.9%) were hypertensive, showing high systolic and diastolic blood pressure for age and sex. Hypertensive children had high waist circumference and body fat percentage (>95th percentile); also they had high HOMA and three of them had acanthosis nigricans. The presence of these risk factors makes those children more vulnerable to the development of the metabolic syndrome later on. Moreover, the association of childhood obesity with features of metabolic syndrome has been demonstrated in this study by the positive correlation found between BMI and systolic blood pressure in obese children which agrees with the findings of other investigators (29,

43, 44). In accordance to the results of Weiss et al., 2004 and Vardi et al., 2007, this study found a positive correlation between BMI and waist circumference in obese children. (29, 43)

Our results are consistent with previous studies that demonstrated that obesity is one of the most important risk factors for insulin resistance. In the present study, HOMA was used for assessment of insulin resistance. Fasting insulin and HOMA levels were significantly higher in obese children compared to non-obese controls reflecting the relation between obesity & insulin resistance. These results agree with the results of other investigators (9, 44, 45). In consistent with that, Salbe et al., (2002) found that insulin concentrations increased with increasing adiposity. (46) Similarly Rudzka-Kocjan et al., (2006) and Zou et al., (2007) found a significant correlation between BMI and insulin resistance. (9, 45)

It is interesting to notice that up to 60% of normal controls had high HOMA compared to 77.8% of obese children. This could be explained in the healthy controls by the fact that puberty is associated with temporary increases in insulin resistance with a peak reduction in insulin sensitivity by 25–30% during Tanner stage 3 with complete recovery by pubertal completion (47, 48). Regarding the effect of gender, we found no significant difference in HOMA value between males and females in both cases and controls and this agrees with Zou et al., (2007) who found no correlation between HOMA and gender. (9) On the other hand it disagrees with the findings of other investigators, (26,49, 50) who found that girls had significantly higher mean HOMA than boys after adjustment for race, age, and weight. This may reflect the effect of puberty on insulin resistance, as girls experience puberty at an earlier age than boys. The absence of sex difference in the present study could be attributed to the small sample size.

This study revealed that resistin and insulin resistance were independent of age and pubertal stage and this was in accordance to the finding of Reinehr et al., (2006) (32). Interestingly, Gerber et al., (2005) reported that in both obese and lean children resistin correlated with age and Tanner stage. (18) On the other hand, Zou et al, (2007) found a significant correlation between insulin resistance parameters, age and sexual development (9). Recently, Li et al., (2009), stated that in both boys and girls resistin tended to decrease with age. (13)

Almost 67% of obese children in this study had high fasting insulin level which is more or less in the same range as that recorded by Freedman et al., (1999) who found that 58% of the obese individuals studied in the age group of 5–17 years showed elevated insulin levels.(51) A much higher value of

83.02% was reported recently by Rudzka- kocjan et al., (2006) (45). This difference could be attributed to the effect of puberty as Klein et al., (2004) found that fasting insulin values were greater in pubertal than prepubertal girls. (48) In the present study hyperinsulinemic children showed higher HOMA and body fat percentage than obese children with normal fasting insulin thus confirming the association between obesity, hyperinsulinemia and insulin resistance. Similarly Lee et al., (2006) reported a high correlation between HOMA-IR and insulin levels. (26)

Acanthosis nigricans is pathognomonic for insulin resistance. (52) In the present study, it was observed that 14 out of 45 cases (31%) had acanthosis nigricans which is more or less similar to that found by Vardi et al., (2007), (35%) in a study on obese pre pubertal and adolescent children (43). It was observed that children with acanthosis nigricans showed significantly higher BMI and waist circumference than cases without acanthosis nigricans, again confirming the relation between adiposity& insulin resistance.

The present study confirm the link between resistin level and insulin resistance in obese children, however it couldn't prove whether high or low resistin level is more related to insulin resistance. A significant positive correlation was found between serum resistin levels and each of fasting insulin and HOMA .No significant correlation was found between serum resistin, HOMA and each of BMI, body fat percentage & waist circumference. HOMA was found to be a significant marker for early detection of insulin resistance in obese and overweight children.

Future studies with a larger sample size are recommended to explain the link between resistin and obesity associated insulin resistance. Regular monitoring for blood pressure, fasting glucose, fasting insulin and HOMA as well as presence of acanthosis negricans are highly recommended for early detection of insulin resistance in obese and overweight children. Also norms of waist circumference and waist hip ratio age and sex specific percentiles should be determined for every country or every ethnic and racial group. More concern should be given to the role of schools in treatment of obesity including psychological therapy, healthy food education, healthy dietary habits, exercise programs and medical follow up.

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