Serum vaspin level and metabolic syndrome markers in obese children

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Abstract

Introduction: Childhood obesity is associated with substantial co- morbidity and late sequelae, it is a major risk factor for chronic diseases and plays a central role in the insulin resistance and metabolic syndrome. The most common underlying cause of complications is central obesity. Insulin resistance and metabolic syndrome may be implicated in the development of many pathological states.

Aim: The purpose of this study was to asses different indices of obesity, metabolic syndrome and to study the level of serum vaspin as an indicator of insulin resistance in obese non diabetic children. Anthropometric, clinical and laboratory assessment performed to all children.

Patients And Methods: This case- control study included 45 obese children compared to 45 healthy lean who were recruited from the outpatient clinic of the National Nutrition Institute from September 2013 to January 2014.

Results: Most of the cases 93.3% were exceeding the 90th percentile of waist circumference. Twenty- one cases had high systolic and diastolic blood pressure over 90th percentile. Metabolic syndrome was highly prevalent among obese children 53.3%. Thirty- one cases were on pre-diabetic level of HBA1c. Insulin resistance was detected in 47.7% of cases and acanthosis nigrican was found in 68.9% of obese children. High serum vaspin level was found in 24 cases, with no statistical significant difference between cases and control or between male and female cases.

Conclusion: The prevalence of the metabolic syndrome is high among obese children, and it increases with worsening obesity. Biomarkers of an increased risk of adverse cardiovascular and diabetic outcomes are already present in these children. Body fat in obese children does not influence serum vaspin levels.

Keywords: Childhood Obesity, Insulin resistance, Metabolic Syndrome, Vaspin.

مستوى الفاسبين فى مصل الدم ودلالات متلازمة الأيض فى الأطفال المصابين بالسمنة

المقدمة: تزايد معدلات الإصابة بسمنة الأطفال يعد من أخطر المشكلات الصحية فى القرن الحالي. وتتخذ هذه المشكلة أبعاداً عالمية وهى تصيب العديد من البلدان منخفضة الدخل والبلدان متوسطة الدخل ولا سيما المناطق الحضرية منها. يتعرض الأطفال المصابين بالسمنة لمخاطر الإصابة بالأمراض المزمنة مثل أمراض القلب وأمراض السكر من النوع الثانى وأيضاً بمتلازمة الأيض.

الهدف: تقيم مؤشرات السمنة، متلازمة الأيض ودراسة مستوى الفاسبين بالدم وإمكانية استخدامه كمؤشر لعدم الاستجابة للإنسولين ومتلازمة الأيض فى الأطفال المصابين بالسمنة.

الأدوات: أجريت هذه الدراسة على ٤٥ طفل مصاب بالسمنة وقد تم تقييم هذه الحالات إكلينيكياً مع أخذ القياسات الأنثروبومترية وإجراء التحاليل المعملية وقياس مستوى الفاسبين بالدم وحساب معدل عدم الإستجابة للإنسولين وأيضا تشخيص متلازمة الأيض ثم مقارنة هذه النتائج بمثيلاتها لدى ٤٥ طفل من الأصحاء.

النتائج: تبين من هذه الدراسة ارتفاع نسبة حدوث متلازمة الأيض بين الأطفال المصابين بالسمنة ٥٣,٣% وأيضا ارتفاع معدل عدم الاستجابة للإنسولين فى هؤلاء الأطفال بنسبة ٥٧,٧%، لم يكن هناك فروقات ذات دلالة إحصائية ما بين المجموعات. وكانت معظم الحالات ٩٣,٣% تتجاوز معدل ٩٠ محيط الخصر. وايضا ٢١ حالة تجاوزت معدل ٩٠ فى ارتفاع ضغط الدم الانقباضى والانبساطي. وقد وجد ان ٢٤ حالة لديها ارتفاع مستوى الفاسبين فى مصل الدم.

الخلاصة: تدل هذه الدراسة على ارتفاع معدل الإصابة بمتلازمة الأيض بين الأطفال المصابين بالسمنة مما يثبت أهمية متابعة مؤشرات الإصابة بمرض السكر وأمراض القلب المزمنة فى الأطفال المصابين بالسمنة.

Introduction:

Childhood obesity is one of the most serious public health challenges of the 21st century. The problem is global and is steadily affecting many low- and middle- income countries, particularly in urban settings. The prevalence has increased at an alarming rate (Ingelsson et al., 2007).

Overweight and obese children are likely to stay obese into adulthood and more likely to develop non communicable diseases like diabetes and cardiovascular diseases, hyperlipidemia, liver and renal disease, and reproductive dysfunction at a younger age. Overweight and obesity, as well as their related diseases, are largely preventable. Prevention of childhood obesity therefore needs high priority (Ball et al., 2006).

The increasing prevalence and severity of obesity in children and adolescents has provided greater emphasis on the wide variety of comorbid conditions and complications that can be experienced as a consequence of obesity. These complications can occur both in the short term and in the long term. Some complications, earlier thought to be long- term issues, which would only occur in adulthood, have now been shown to occur in children and adolescents. These findings have raised concerns about the overall health experience of those who develop obesity early in life and have even raised questions about whether the obesity epidemic might shorten the life span of the current generation of children. In this paper, I will examine current knowledge regarding the different organ systems that may be impacted by childhood obesity (Daniels, 2009).

Adipose tissue secretes a variety of bioactive peptides that play important roles in insulin action, energy metabolism, inflammation, and cell growth through endocrine, paracrine, or autocrine routes. Some of these adipokines may locally regulate fat accumulation by modulating growth proliferation of adipocytes. Excess fat accumulation may in turn cause dysregulation of adipocyte function, including oversecretion of deleterious adipokines and hyposecretion of advantageous ones (Auguet et al., 2011)

Vaspin is a novel adipokine with potential insulin sensitizing effects. It was identified as a member of serine protease inhibitor, which was highly expressed in visceral adipose tissue (VAT) of rats at the age when obesity and insulin resistance peaked. Despite several reports about vaspin expression in fat tissue and serum vaspin levels in human, correlations between circulating vaspin levels and parameters of insulin sensitivity and metabolic syndrome are unclear. Until now, no study evaluating the association of circulating vaspin levels with the abdominal fat accumulation has been undertaken (Hida et al., 2005).

Obesity is associated with a wide array of metabolic complications in adults. These include insulin resistance, dyslipidemia and type 2 diabetes mellitus. These metabolic complications have now also been found to be associated with obesity in adolescents. Obesity during childhood is associated with decreased insulin sensitivity and increased circulating insulin levels. They have also shown that these abnormalities often persist into young adulthood. Insulin resistance is an important factor in the development of type 2 diabetes (Ingelsson et al., 2007).

The period of growth and development during adolescence is associated with a normal increase in insulin resistance. If additional insulin resistance develops related to obesity during this time, then it may lead first to glucose intolerance, and then to type 2 diabetes mellitus. The prevalence of type 2 diabetes has increased in adolescence and has been reported in children as young as 8 years of age. Although the classification of type 1 and type 2 diabetes is complex in obese adolescents, a review from the American Diabetes Association reports that as high a proportion as 45% of newly diagnosed cases of diabetes in children and adolescents are now type 2 diabetes in the era of increased prevalence and severity of obesity in young individuals (Daniels, 2009).

Dyslipidemia may occur in children and adolescents as a result of obesity. The most common abnormality of lipids and lipoproteins associated with obesity is an increase in triglycerides and a decrease in high- density lipoprotein cholesterol. This has been called atherogenic dyslipidemia because of its potential to accelerate atherosclerosis. Obesity can also contribute to an increase in low- density lipoprotein cholesterol. However, it is unclear if this is a direct effect or related to increased levels of saturated fat and cholesterol often present in the diet of overweight individuals during childhood (Daniels, 2009).

The Adult Treatment Panel III of the National Cholesterol Education Program defined a clinical entity known as the Metabolic Syndrome. This constellation of risk factors, including elevated blood pressure, increased triglycerides and low high- density lipoprotein cholesterol, has been shown to cluster in individuals who are obese, particularly those with central or abdominal adiposity (NCEP, 2002).

Patients And Methods:

This case- control study included 45 obese children compared to 45 healthy lean who were recruited from the outpatient clinic of the National Nutrition Institute from September 2013 to January 2014. This includes full personal, past history for systemic diseases, drug administration (as corticosteroids), pattern of physical activity and symptoms covering various systems, and family history of chronic non- communicable diseases (obesity, diabetes, cardiovascular diseases and hypertension).

All anthropometric measurements have been obtained using standardized equipment, and following the recommendations of the International Biological program (Hiernaux and Tanner, 1969).

Assessment of BMI was done using categories reported by the World Health Organization (WHO) Child Growth Charts Standards for age and sex (2007). Obesity considered when BMI exceeds 95th percentile (Schwarz and Freemark, 2010).

Waist Circumference was measured using inelastic insertion tape to the nearest 0.1cm, with the subject in a standing position; the tape was applied horizontally midway between the lowest rib margin and the iliac crest. Assessment of waist circumference was done using categories reported by Fernandez et al. (2004). Thorough medical general examination (head& neck, chest, heart, abdomen, upper& lower limbs) including measurement of blood pressure and comparing it to age specific blood pressure percentiles reported by (Nhanes, 2004).

Blood samples were withdrawn from patients and controls after overnight fasting (>12 hours). Fasting venous blood samples were collected in heparinized centrifuge tubes. Plasma was separated by centrifugation (3000 rpm, 15 min). Separated plasma aliquots were removed and stored frozen at- 32 C until further analyses were carried out, following testes were performed: Fasting serum glucose, fasting serum insulin, serum vaspin level, Cholesterol, Triglysrides, Hdl- cholesterol, LDL- cholesterol

Insulin resistance was estimated by using the Homeostasis Model

Assessment (HOMA), which calculated according to the known formula, Insulin resistance being defined as a (HOMA index> 3.16) The greater the HOMA value the greater the level of insulin resistance (Keskin et al., 2005).

Metabolic syndrome diagnosis was done using definition developed by United State National Cholesterol Education program (NCEP, 2002) and (NCEP, 2004). Modified cutoff values for children and adolescents were used according to Lambert et al. (2004). It includes abnormalities in any three (at least) of the following components: Presence of overweight (BMI≥ 85 percentiles) or at risk for central obesity (waist circumference≥ 75 percentiles), Elevated systolic or diastolic BPs (≥ 90 percentiles) Low HDL- cholesterol levels (< 40 mg/dl), High fasting serum triglyceride levels (> 110 mg/dl), High fasting serum glucose levels (> 100 mg/dl) (NCEP, 1993)

Statistical Analysis:

Data analysis were performed using Statistical Package for Social Sciences (SPSS v.12, 2004). Numerical data were summarized using means and standard deviations or medians and ranges. Categorical data were summarized as percentages. Comparisons between groups for normally distributed numeric variables were done using the Student's t- test while for non normally distributed numeric variables were done by Mann- Whitney test. Chisquare test or Fisher's exact test were used to compare between the groups with respect to categorical data. To measure the strength of association between numeric variables, Spearman's correlation coefficients were computed. All p-values are two- sided. P- values <0.05 were considered significant.

Results:

Comparing studied sample as regard their anthropometric measurements, as shown in table (1), mean weight was 48.9 Kg in cases and 25.8 Kg in control, mean BMI was 28.3 in cases and 16.2 in control while mean waist circumference was 84 cm in cases and 58.1 cm in control.

There was significant difference in weight, BMI, Waist circumference, Hip circumference and waist hip ratio where p< 0.001*, while there was no significant difference as regard height measurement between cases and controls

Table (1) Comparison of anthropometric data in obese children and control

	Cases N= 45		Controls N= 45		P value
	mean	± Sd	mean	± Sd	
Weight (Kg)	48.9	16.7	25.8	7.6	<0.001*
Height (Cm)	129.0	17.2	124.4	14.5	0.174
BMI (Kg /m2) †	28.3	3.6	16.2	1.2	<0.001*
Waist Circumference (Cm)	84.0	9.4	58.1	5.5	<0.001*
Hip Circumference (Cm)	91.9	10.6	59.8	5.8	<0.001*
Waist Hip Ratio	0.92	0.04	0.97	0.01	<0.001*

* P value is significant if <0.05, †BMI= Body Mass Index

Comparing cases and controls in waist circumference percentile and blood pressure percentile shown in table (2), there was 42 cases (93.3%) were above the 90th percentile for waist circumference according to the waist circumference percentiles. Only 21 cases (46.7%) showed high systolic and diastolic blood pressure (> 90th Percentile) for age and sex according to the age- specific percentiles of blood pressure BP measurements for boys and girls, while none of the control were hypertensive according to the same percentiles.

Table (2) comparison of waist, blood pressure percentile and presence of acanthosis nigricans in between cases and controls

Item	Cases		Control		P Value
	No.	%	No.	%	
WC † (>90th Percentile)	42	93.3	0	0	<0.001*
BP‡(>90th Percentile)	21	46.7	0	0	<0.001*
Acanthosis Nigricans	31	68.9	0	0	<0.001*

Table (3) showed the laboratory parameters of the studied sample where mean fasting glucose was 94.4 in cases and 82.5 in control, mean fasting insulin was 13.9 in cases and 4.5 in control, mean HOMA was 3.24 in cases and 0.92 in control.

There was statistical significant difference between cases and control in only Fasting Glucose level, Fasting Insulin level, HOMA, HDL and HbA1c between cases and controls (p value< 0.001*).

Table (3) Comparison of the laboratory parameters of cases and controls

	Cases N= 45		Controls N= 45		P value
	mean	± Sd	mean	± Sd	
Fasting glucose (mg/dl)	94.4	9.3	82.5	7.2	<0.001*
Fasting Insulin (µIU/ml)	13.9	7.5	4.5	2.5	<0.001*
Homa†	3.24	1.85	0.92	0.51	<0.001*
Cholesterol (mg/dl)	141.1	24.1	145.6	20.3	0.345
Triglycerides (mg/dl)	89.1	35.2	80.9	17.2	0.160
HDL‡ Cholesterol (mg/dl)	37.9	8.7	45.5	5.7	<0.001*
LDL§ Cholesterol (mg/dl)	84.9	25.5	83.8	19.3	0.807
HBA1c || (%)	5.9	0.5	5.5	0.6	0.004*
Vaspin (ng/ml)	0.73	1.68	0.54	1.36	0.977

Comparing cases and control according to serum Vaspin level as shown in Table (4); there was 21 cases (46.7%) had normal vaspin level and 24 cases (53.3%) had high vaspin level. While 22 control (51.2%) had normal vaspin level and 21 control (48.8%) had high vaspin level. no statistical significant difference was found between groups.

Table (4) Serum Vaspin level in cases and control

		Cases N= 45		Control N= 45	
		No.	%	No.	%
Vaspin (ng\ ml)	Normal	21	46.7	22	51.2
	High	24	53.3	21	48.8

Table (5) shows the correlation between serum Vaspin level in cases and laboratory parameters, no statistical significant difference was found between groups. There was negative correlation with no significant p value between serum vaspin level and LDL- cholesterol where (r= - 0.014, p= 0.927).

Table (5) correlation between serum vaspin level and laboratory parameters in cases

	Serum Vaspin Level In Cases N= 45	
	r	P
Homa†	0.032	0.836
Triglycerides	0.069	0.650
HDL- Cholesterol§	0.170	0.263
LDL- Cholesterol‡	- 0.014	0.927
Cholesterol	0.049	0.750
HBA1c||	0.157	0.303

Cases were grouped according to metabolic syndrome criteria as shown in Table (6) and Figure (1). There was 42 patient (93.3%) were above the 90th percentile for waist circumference according to their age, 21 patient (64.7%) had systolic and diastolic blood pressure above 90th percentile of their age, 11 patient (24.4%) has serum fasting blood glucose more than 100 mg/dl, 2 patient (4.45) had serum triglycerides level more than 150 mg/dl and 16 patient (35.6%) were below 35 mg/dl as for HDL serum level.

Table (6) Metabolic syndrome criteria in cases

Metabolic Syndrome Component		
	No.	%
Waist Percentile > 90th Percentile	42	93.3
Blood Pressure Percentile > 90th Percentile	21	64.7
Glucose >/= 100	11	24.4
Tg † >/= 150	2	4.4
HDL‡ Cholesterol< /= 35	16	35.6

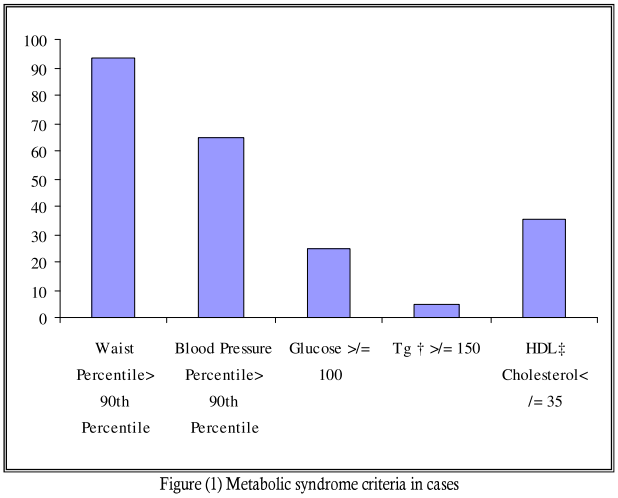

Figure (1) Metabolic syndrome criteria in cases

Table (7) and figure (2) show the frequency of metabolic syndrome criteria in as age- modified ATPIII criteria with abnormal values for at least 3 of the 5 criteria. 24 patients (53.3%) had at least 3 criteria, 14 cases (31.1%) had 2 criteria, 7 cases (15.6%) had only 1 criterion.

Table (7) Frequency of metabolic syndrome criteria in cases

Metabolic Syndrome Criteria	No.	%
None	0	0
One Criterion	7	15.6
Two Criteria	14	31.1
Three Or More Criteria	24	53.3
Total	45	100

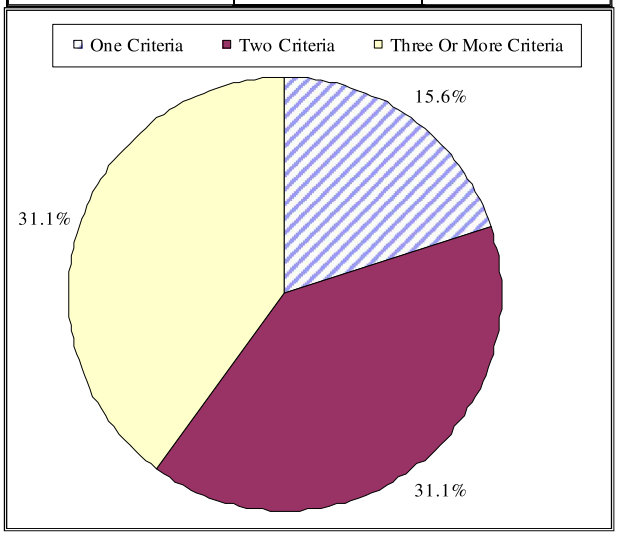

Figure (2) Frequency of metabolic syndrome criteria in cases

Table (8) shows the correlation between metabolic syndrome in cases and HOMA and serum Vaspin level. There was positive significant correlation between metabolic syndrome and HOMA (where r= 0.311 and p= 0.040*).

Table (8) correlation between metabolic syndrome in cases and laboratory parameters

	Metabolic Syndrome In Cases N= 24	
	r	P
Homa†	0.311	0.040*
Vaspin	0.086	0.575

Table (9) shows the correlation of HOMA in cases with laboratory parameters; there was positive significant correlation between HOMA and triglycerides level in cases where (r= 0.481, p= 0.001). while there was negative correlation with no significant p value between HOMA and HDL-cholesterol where (r= - 0.220, p= 0.151).

Table (9) correlation between HOMA in cases and laboratory parameters

	HOMA In Cases N= 45	
	r	P
Triglycerides	0.481	0.001*
HDL- Cholesterol§	- 0.220	0.151
LDL- Cholesterol‡	0.089	0.567
Cholesterol	0.145	0.347
Vaspin	0.032	0.836

Discussion:

The findings in present study revealed a high prevalence of high systolic and diastolic blood pressure in obese children (46.7%), Our results were in the same range of results of Rajeev et al. (1998), Singh et al. (2006) and Galhotra et al. (2009) who found considerable percentage of hypertensive obese children. However, caution should be taken when comparing the data in between different studies because different definitions for metabolic syndrome in obese children with different blood pressure percentiles were used. HOMA was used for assessment of insulin resistance. Although the hyperinsulinemic euglycemic clamp is the standard technique it is invasive, and time consuming unlike HOMA, which has been widely used in clinical research because of its simple and fast method. Moreover, because it requires only a single blood sample in the fasting state, it is practically attractive to patients and clinicians (Keskin et al., 2005).

Impaired fasting glucose considered (Pre- diabetes). Early diagnosis and treatment of individuals with impaired fasting glucose have been shown to prevent progression to type 2 diabetes (Tsay et al., 2010). Finding of our study showed that nearly one third of obese children in this study had high fasting insulin level and 47.7% had HOMA> 3.16; Comparing obese children with non- obese controls showed statistically significant difference in all previous parameters reflecting the strong association between childhood obesity& insulin resistance, indicating higher risk of type 2 diabetes and metabolic syndrome in their childhood along with mid- adult life. These results agree exactly with Weiss et al. (2004), Joyce et al. (2006), and Thomas et al. (2008) who stated significant higher fasting insulin and HOMA in obese children than control.

Our findings are also in agreement with the one observed in the Bogalusa Heart Study in which elevated insulin levels were observed in 58% of the obese individuals studied in the same age group (Freedman et al., 1999). More recently, researchers from the Bogalusa Heart Study confirmed contribution of childhood obesity and insulin resistance to the adulthood risk of developing metabolic syndrome in adulthood, even after adjustment for childhood insulin levels (Srinivasan et al., 2002). The increasing prevalence of impaired fasting glucose and insulin resistance in obese children and adolescents has paralleled the obesity epidemic and shows no signs of reversal. Results suggest alarming increases in the incidence of type 2 diabetes and up to 30% of childhood new-onset diabetes are classified as type 2 diabetes. Therefore, the American Diabetes Association (ADA) recommends lifestyle modification with or without pharmacological interventions in both children and adults with pre-diabetes (ADA, 2008).

In the present study HOMA showed strong significant positive correlation with metabolic syndrome criteria indicating the relation between insulin resistance and metabolic syndrome and stressing on the well- known fact of using HOMA as good indicator for insulin resistance and consequently metabolic syndrome in obese children. Insulin resistance was also significantly

correlated to an abnormal lipid profile in cases but not in control group.

This result is in agreement with Steinberger and Daniels (2003) and Da Silva et al. (2005) who stated that the likelihood of metabolic syndrome significantly increased with high fasting insulin and HOMA values and being overweight during childhood and adolescence is significantly associated with insulin resistance, dyslipidemia, and elevated blood pressure in young adulthood.

In this present study prevalence of metabolic syndrome in obese children (53.3%) was more than many other studies in which the authors used the same definition of metabolic syndrome we used in this study, Cook et al. (2003), De Ferranti et al. (2004) and Aboul Ella et al. (2011) reported prevalence of metabolic syndrome ranged from (1.7%- 14.3)%. On the other hand, Zimmet et al. (2007), Kelishadi et al. (2008) and Ford et al. (2008) reported a range from (2.2%- 9.5%) of metabolic syndrome among their sample of obese children and adolescents; authors of previously mentioned studies used the new IDF criteria (IDF, 2010) to define metabolic syndrome in children.

The present study aimed to assess the levels of serum Vaspin in a sample of obese children as its role was subjected to a major debate in previous studies. In the present study, we found that serum Vaspin level in obese children was not significantly different from that of controls. Moreover, no relation could be established between metabolic syndrome components and serum Vaspin level. No statistically significant difference was found between cases and controls. We further investigated the vaspin- MetS association by controlling for BMI (a general index of obesity), waist circumference (a marker of abdominal obesity), and HOMA (representative of peripheral insulin resistance). Vaspin didn't detect metabolic syndrome in our sample of obese children, indicating that Vaspin- metabolic syndrome relationship in our sample study was not mediated to a large part via insulin resistance.

In agreement with our results, Von Loeffelholz et al. (2010) have shown that there is no association between serum vaspin and HOMA in non- diabetic humans. Seeger et al. (2008) have also reported that circulating vaspin is not independently associated with markers of glucose metabolism, and Briana et al. (2011) have shown that vaspin concentrations do not correlate with insulin levels in maternal, fetal and neonatal samples. Our results also agrees with Auguet et al. (2011) who found that serum vaspin levels are not increased in obese women and that vaspin levels do not correlate with BMI, markers of glucose or lipid metabolism and found no correlation between Vaspin and Metabolic syndrome markers. On the other hand of our findings, Choi et al. (2011) reported a significant association between vaspin and Metabolic syndrome; however, within MetS components, only raised triglycerides correlated with vaspin. Similarly, in a group of obese children and adolescents, vaspin significantly correlated with BMI, insulin, HOMA- IR, and triglycerides (Suleymanoglu et al., 2009). Moreover, El- Mesallamy et al. (2011) reported a positive association between vaspin and BMI, waist- to- hip-ratio, along with glycemic indices including HOMA- IR and fasting glucose level.

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