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Potential Activity of S100B Level towards Metabolic Syndrome in Obese Children.

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ABSTRACT

Paediatric obesity prevalence has increased significantly in developing countries recently followed by increased rates of associated complications such as paediatric metabolic syndrome. Adipose tissue is a good source of S100B which has been linked lately to metabolic syndrome, moreover to insulin insensitivity. This case control study has been designed to evaluate the significance of S100B as an early predictor for metabolic syndrome in obese children and to study its relation to the different parameters of the disease. Forty obese children were enrolled as cases group, out of them 17 had the full metabolic criteria and thirty healthy non-obese children of matched age and sex served as control group .Serum S100B level was estimated by ELISA. Children's anthropometrics measures', blood pressure, fasting blood glucose, and lipid profile were assessed. Significant difference has been detected between the two groups in serum S100B (p value <0.001) .A positive significant correlation has been recorded between systolic blood pressure , TG level and S100B level (P value < .001).While a significant negative correlation was documented between HDL level and S100B level. In conclusion, S100B is considered as an important influential factor in clinical studies of metabolic syndrome.
Keywords: Metabolic syndrome, S100B, Obesity, Children.

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INTRODUCTION

Paediatric obesity prevalence has increased so significantly in the developing countries recently to reach an epidemic level [1]. In Egypt 39.7% among obese school students are metabolic [2]. Paediatric obesity now is considered as a public health concern that requires an integrated approach to care [3].

The impact of obesity on physical and psychological health has long been recognized in adults, many of these obesity induced complications are now understood to occur in early childhood. Obese children and adolescents are significantly more likely than their healthy weight peers suffering from these complications, such as type 2 diabetes, coronary artery disease, and hypertension [4-6].

The coexistence of these complications with obesity has been defined as metabolic syndrome which gained more momentum in paediatric research work recently; as many subsequent studies have demonstrated the prevalence and the accompanied risk factors of metabolic syndrome in attempt to find an early diagnostic measure or interventional therapy for it [7-9].

Insulin insensitivity is a fundamental feature of this disease as well. Many novel serum biomarkers have been investigated as a tool for early prediction of metabolic syndrome in obese children [10-12]. S100B is a novel marker which has been linked lately to metabolic syndrome and insulin insensitivity; Adipose tissue is a good source of it [7-13].

This work was planned to investigate the relation of metabolic criteria in obese children to the circulating level of S100B and to evaluate the usefulness of using S100B as a predictor for diagnosis and/or disease severity indicator.

MATERIALS AND METHODS

A case control study was conducted upon 70 children aged from 7 to 14 year from those attending the Nutritional Clinic in the National institute of nutrition from October 2014 to March 2015. Children with history of psychiatric disease, neurological disorder or those who on corticosteroids therapy were excluded from the study. This study followed the regulations of the medical ethical committee of the National Research Centre Egypt .Signed informed consent was collected from parents after explaining the nature of the study prior to participation.

The children enrolled in the study were divided into 40 obese children (group A) and 30 healthy non-obese children as control (group B) of matched age and sex, with different social levels.

Children were classified according to the body mass index (BMI), defined as the weight in kilograms divided by the square of the height in meter (kg/m). Obesity is defined as BMI > 95 the percentile on the growth charts from the National Centre of Health and Statistics (NCHS).

All children were subjected to full clinical history with special focus on history of Diabetes mellitus and family history of obesity .Then thorough clinical examination and blood pressure measurement were done. Anthropometric measures were taken as follows: weight in kilograms using an electronic weight scale, height was measured using stadiometer in centimetres, waist circumference was measured at the umbilical level in centimetres and body mass index, BMI Z-score were calculated using the World Health Organization AnthroPlus®

Metabolic syndrome criteria were assessed in all children participating in the study using the definition of the National Cholesterol Education Program Panel III. At least 3 out of the 5 metabolic abnormalities were defined: (1) impaired fasting glucose (fasting plasma glucose ≥100 mg/dL); (2) hypertriglyceridemia (TG ≥150 mg/dL); (3) low HDL <50 mg/dL); (4) elevated systolic BP (BP ≥130/85 mm Hg); (5) waist circumference ≥85 cm for females and ≥ 90 in males.

After applying the metabolic criteria; group A was further divided into 2 subgroups. A1 obese children with full metabolic criteria and group A2 obese children with non-metabolic criteria.

Fasting blood samples (approximately 3 ml) were taken from all children as a part of their routine investigations .Serum was immediately separated from each blood sample and divided into portions. The first one was used immediately to measure blood glucose and lipid profile and the second portion was stored at -20 Cº till the measurement of S100B.

Serum S100B was measured by using S100B ELISA commercial kit (EIAab®) Catalog No: E0567r according to the following principle:

The microliter plate provided in this kit has been pre-coated with an antibody specific to S100B.Samples then were added to the appropriate microliter plate wells with a biotin-conjugated polyclonal antibody preparation specific for S100B. After that Avidin conjugated to Horseradish Peroxidase (HRP) was added to each microplate well and incubated then a TMB substrate solution was added to each well. A change in color was exhibited only in the wells contain S100B, biotin-conjugated antibody and enzyme conjugated Avidin . The enzyme substrate reaction was terminated by the addition of sulphuric acid solution then the color change was measured spectrophotometry at wave length of 450nm ± 2nm. Finally, the concentration of S100B in the samples was determined by comparing the optical density of the samples to the slandered curve.

Statistical analysis was carried out using the statistical package for social sciences, version 23 for windows (SPSS Inc., USA). Continuous data were expressed as mean ± SD and were compared using Student's t-test. Spearman's rho Correlations was used for relations between S100B and other variables. comparisons were done using Mann Whitney test and Log regression was applied using the ANOVA test .Values of $p < 0.05$ were considered statistically significant.

RESULTS

The descriptive characteristics of the studied groups were presented in table 1. The mean age of group A was 10.5 ± 2.1 year and 13.8 ± 1.8 year, the two groups were matched in sex. A statistically significant difference was recorded regards, BMI Z score, waist circumference (p value = < 0.001 and < 0.001 respectively) between the cases and control group (table 1).

Table 1: The descriptive and laboratory findings of the studied groups

	Cases A (N=40) Mean ± SD	Control B (N=29) Mean ± SD	P value
Age (years)	10.49 ± 2.069	13.69 ± 1.83	
Weight (Kg)	64 ± 18.5	43.8 ± 11.5	< 0.001*
Height (cm)	139 ± 11.6	151 ± 12.7	< 0.001*
Waist circumference (cm)	100.32 ± 19.4	67.5 ± 9.9	< 0.001*
BMI	32.8 ± 5.7	18.98 ± 3.1	0.005
BMI Z score	4.019 ± 0.949	0.187 ± 1.07	< 0.001*
FBS (mg/dl)	87.3 ± 14.6	80.5 ± 10.06	0.110
Total cholesterol (mg/dl)	169 ± 45.3	134 ± 17.7	< 0.001*
HDL (mg/dl)	41.00 ± 8.24	35.27 ± 10.14	0.015
LDL (mg/dl)	108 ± 4.0	72.6 ± 17.2	< 0.001*
TG (mg/dl)	103.9 ± 45	43.5 ± 31	< 0.001*

BMI: body mass index, TG: triglycerides, SD: standard deviation, FBG: fasting blood glucose, HDL: high density lipoprotein-cholesterol and * P < 0.05 the relation is statistically significant.

Regarding the laboratory parameters a significant difference between, LDL and TG level between the two groups (p value = < 0.001 and < 0.001 respectively) has been detected (table 1).

There was a significant difference between the obese children with metabolic criteria and the control group in serum S100B (p value < 0.001) (table 2).

There was no significant difference between subgroup A1 and subgroup A2 in S100B level (table 2).

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A positive significant correlation was reported between systolic blood pressure, Triglycerides (TG) level and S100B level P value < .001 (table 3) .While a significant negative correlation was documented between HDL level and S100B level (table 4).

By using multiple regression analysis with S100B level as a dependent variable and the metabolic syndrome criteria as independent factors ; a significant relation was found between S100B level and the metabolic syndrome criteria (P = < 0.001) and the most significant factors were the systolic BP , TG level and HDL level (P =.001 , .008,.014 respectively) (table 5).

Table 2: S100B level in the studied groups.

	Cases A (N=40) Mean ± SD		Control B (N=29) Mean ± SD	P value
S100B level Pg/ml	**68.45 ± 4.65**		**17.30 ± 5.13**	**<0.001***
	Subgroup A1	**Subgroup A2**		0.091
	73 ± 2.1	**65 ± 3.17**		

* P < 0.05 the relation is statistically significant.

Table 3: Comparison between subgroups in metabolic criteria

Variable	Group A1	Group A2	P value
Weight	**66.93 ± 12.6**	**63.2 ± 21.47**	0.54
BMI Z score	**4.12 ± 1.05**	**3.95 ± 0.89**	**0.59**
Waist circumference	**105.1 ± 16.7**	**97.5 ± 20.6**	0.26
(HDL(mg/dl	**37.6 ± 7.2**	**43.4 ± 8.1**	**0.034**
(TG (mg/dl	**140.8 ± 36.5**	**85.6 ± 32.3**	**0.00***
Systolic BP	**119 ± 13**	**102 ± 12.06**	*0.001

BMI: body mass index, TG: triglycerides, SD: standard deviation, FBG: fasting blood glucose, HDL: high density lipoprotein-cholesterol and * P < 0.05 the relation is statistically significant.

Table 4: Correlation between S100B and other variables

Variables	r	p
BMI Z score	**0.26**	**0.1**
Waist circumference (cm)	**0.262**	**0.12**
FBS(mg/dl)	**0.159**	**0.32**
TG(mg/dl)	**0.576***	**<0.001**
HDL(mg/dl)	**-0.398***	**0.016**
Systolic BP	**0.596***	**<0.001**

r: Pearson correlation and * P < 0.05 the relation is statistically significant.

Table 5: Multiple Regression analysis

Predictors	t	Sig.
Systolic BP	**3.703**	**.001**
FBS(mg/dl)	**-.784**	**.441**
TG(mg/dl)	**2.875**	**.008**
HDL(mg/dl)	**-2.665**	**.014**
Waist cir.(cm)	**.408**	**.687**

Dependent Variable: S100B
Predictors: (Constant), Waist, HDL, TG, FBS, systolic BP

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DISCUSSION

Obesity of childhood and adolescence has universally grown along with that of the adults. The dramatic increase of paediatric obesity rates is followed by increased rates of associated metabolic complications, such as paediatric type 2 diabetes mellitus and paediatric metabolic syndrome [14-15].

Given the importance of increased prevalence of obesity and insulin resistance in children, this work has estimated the level of S100B which had been linked to both conditions recently. Thus the aim of this study was to evaluate the role of S100B as an early predictor of metabolic syndrome in obese children and to investigate its relation with the clinical and laboratory parameters of these conditions.

S100B is a calcium binding protein found in adipose tissue [16] which appears to be the important source of it. S100B is closely linked to the regulation of cellular energy metabolism involved in the lipolysis [17] the release of S100B from adipocytes is reduced by insulin and up regulated by stress [18].Therefore, an increased adipose tissue mass or changes of insulin metabolism such as insulin resistance would most probably play a key role in elevation of S100B levels.

The results of this study revealed that the mean level of S100B is found to be significantly higher in obese children compared to the control group ($P<0.01$).This result is in compatible with the study of Steiner et al. [19] who demonstrated that a physiological S100B levels in humans appear to closely reflect adipose tissue mass. S100B serum levels in BMI Obese subjects (BMI ≥ 30) was significantly elevated in comparison to normal weight (BMI < 25) subjects. In another study by the same author [20] S100B level was proved to be elevated in parallel with insulin.

In the current study all the obese children had metabolic criteria but only 17 (42.5%) had the typically full criteria and the rest of the group only fulfil one or two criteria (A2).

S100B serum level is elevated in all obese children (group A), but there is no significant difference between its level in subgroups A1 and A2 .This could be explained by the fact that the elevation of S100B started early with the development of any metabolic symptoms ;even with only one metabolic criteria without the full clinical syndrome .

Up to 30% of obese people do not display the "typical" metabolic obesity-associated complications. For this group of patients, the term "Metabolically Healthy Obese (MHO)" has been established during the past decades and has been the focus of research activities. The development and severity of insulin resistance as well as (subclinical) inflammations seems to play a key role in distinguishing metabolically healthy from metabolically non- healthy individuals. Therefore, S100B level is elevated in these cases as it is down regulated by insulin.

This support our hypothesis that S100B marker can be used as an early predictor for metabolic syndrome as it was documented to be elevated in obese children at risk to develop metabolic syndrome even without the full typical criteria.

The various routine measures of lipoprotein metabolism have been used usually to identify patients with insulin resistance and dyslipidemia, and therefore, at increased risk of metabolic and cardiovascular risk. In the current study significant difference between the obese children and the control group in TG level and LDL levels $P = < 0.001$ and $P = < 0.001$ respectively. This finding is in agreement with many previous studies which used these laboratory parameters to evaluate or screen for metabolic syndrome; using TG and LDH level a ratio of triglyceride (TG)/HDL-cholesterol (HDL-C) (10) and also using non-high-density lipoprotein cholesterol as a simple way to identify apparently healthy individuals who are insulin resistance (IR) and at increased cardio metabolic risk [21-22].

Positive significant correlation was observed between TG level and S100B level and a negative correlation was found between HDL level and S100B level. Although these parameters are reliable as a routine workup in identification of metabolic syndrome they can't be used as a sensitive screening test as the risk of cardiovascular complication is already developed at this stage.

In the current study, these laboratory parameters along with the systolic blood pressure have a significant relation with S100B level. This is in conformity with the study of Ho et al., about metabolic risk factors in chronic kidney disease as the mean arterial pressure was the most powerful predictor **[23].**

Taken together, it could be concluded that S100B was the most powerful predictor for metabolic syndrome risk in obese children which should therefore considered as an important influential factor in clinical studies of metabolic syndrome.

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