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Serum Catestatin as a Novel Biomarker of Cardiometabolic Risk among Diabetic Children

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ABSTRACT

Background: Along with decreased sympatho-adrenal flow, catestatin has a number of cardiovascular effects. Reduced plasma catestatin levels could be a sign of a predisposition to develop metabolic and hypertensive diseases.
Aim and objectives: To assess the function of catestatin in cardiometabolic risk assessment among diabetic children.
Subjects and methods: This case-control study was carried out on 108 children at Pediatrics Department, Zagazig University Hospital. Children were divided into 2 groups: (Group A): Case group 54 children with diabetes, (Group B): Control group 54 apparent healthy children at same sex and age. Every infant was subjected to serum catestatin concentrations measurement using ELISA Kit.
Result: Median Catestatin in diabetic group was 8.35 ng/ml (6.16 – 17.41) while that for Control group was 11.19 ng/dl(7.42 -16.56), the difference was statistically significant ($p< 0.05$).
Conclusion: Serum Catestatin was related to diabetes and it cannot be considered as a good biomarker of cardio metabolic risk among diabetic children. Further larger scale studies are needed to confirm our results.
Keyword: heart, blood pressure, coronary artery disease, and metabolic, catestatin.

INTRODUCTION

According to the World Health Organization, diabetes is rising globally and is affecting people of all ages. Childhood diabetes is considered a persistent metabolic condition associated with potentially fatal effects. Diabetes in children is less well-known than diabetes in adults because it seems foreign to many people, even medical experts [(1)].

The third most prevalent chronic illness in children is diabetes mellitus, and up until around 15 years ago, almost all patients had type 1 diabetes [(2)].

Given that diabetes is seen as a metabolic condition, a wide range of consequences that might impact many physiological systems are linked to childhood diabetes. The cardiovascular adverse events are regarded as the most serious and frequent of these problems. Diabetes causes a number of physiologic changes, some of which may affect the electrical and contractile activity of the myocardium, which is considered to be the main reason of these occurrences [(3)].

To help in predicting the course of metabolic diseases and outcome in the diabetic pediatric population, novel molecular biomarkers are constantly required. In the past ten years, it has become clear that the release of catecholamines, stimulation of baroreceptors, activity of the sympathetic nervous system, and fat metabolism, monocyte, human neutrophil, antimicrobial properties, mast cell migration, and myocardial functions are just a few of the physiological processes that the endogenous peptide 21-aa Catestatin (Cts) regulates [(4)].

Cts has both central and peripheral cardio-suppressive impacts, particularly with regard to the cardiovascular system. Central impacts result from the increase in variability of heart rate and baroreflex sensitivity. A reduction in blood pressure (which stimulates release of histamine and causes vasodilation) and an inhibition of catecholamine production are examples of peripheral effects [(5)].

Additionally, Cts have the ability to directly affect myocardial function. Under basal and stimulated circumstances (isoproterenol and endothelin), they may have adverse inotropic and lusitropic effects via a ß2-ARGi/o-NO-cGMP dependent pathway. Through a PI3K-AKT-eNOS pathway, Cts have an antiadrenergic action. Additionally, they may shield the heart from excessive sympathetic activation. The possible cardioprotective effects of catestatin against ischemia/reperfusion injury were also investigated [(6)].

PATIENTS AND METHODS

This case- control study was carried out on 108 children who attended at the Pediatrics department, Zagazig University Hospital during the period of the study. Children were divided into 2 groups: a case group of 54 children with diabetes mellitus and a control group of 54 children who appeared to be healthy and matched the preceding case group in terms of age and sex.
Diabetic children with clinical and laboratory evidence, both sexes were included in the study. Children with chronic kidney disease, heart disease, or any blood disorder or malignancy and children with CNS or congenital problems were excluded from the study.

Methods:

All children were subjected to:

- Complete history taking, which includes: personal history, primary complaint, history of the current condition, and previous medical history.
- Complete clinical evaluation, which included a thorough physical examination and careful attention to anthropometric measurements.

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-Body weight: weight the closest 10 gram or 0.01 kg.Kilograms was used to express the measurements.

-Standing Height: on a stadiometer and centimeters were used to express the results.

-Body Mass Index (BMI):Published international age and gender specific reference values for BMI in infants and children and the task force recommended the use of BMI (calculated as weight in kilograms divided by height in meters square) derived normative percentile for the diagnosis of overweight if BMI is at least 85th percentile but less than 95th percentile for age and sex. And obesity if BMI is at least the 95th percentile but less than 97th percentile for age and sex. And morbid obesity if BMI is more than 97th percentile for age and sex. BMI= weight (kg) / length (m^2).

-Vital signs including: blood pressure measurement using an inflated bladder situated halfway between the olecranon and acromion, with a breadth of at least 40% of each child's arm circumference **(7).** The measurements were taken in a quiet room . For each infant three readings were obtained in the same visit with a minimum of one-minute rest between each determination and the average was recorded.

- Echocardiography: were performed for all subjects by using a Philips Epiq CVx Echocardiogrphic device (Philips, Hamburg, Germany) with a 3,5-MHz phased array transducer) while simultaneously capturing electrocardiograms to enable for flow timing. The first imaging planes were the parasternal long- and short-axis views, then the apical four and two-chamber views. The interventricular septum (IVS), the thickness of the left ventricular posterior wall (LVPW), the left ventricular end diastolic (LVED), and the left ventricular end systolic (LVES) were among the cardiac parameters that were investigated. The left ventricular ejection fraction and fraction shortening were computed from M-mode tracings.

$$Conventional\ LV\ systolic\ function\ (EF\ \%) = \frac{(LV\ diastolic\ volume - LV\ diastolic\ volume)}{LV\ diastolic\ volume}$$

$$FS\ \% = \frac{(LV\ end\ diastolic\ diameter - LV\ systolic\ diameter)}{LV\ end\ diastolic\ diameter}$$

With the help of the continuous wave Doppler's measurement of the tricuspid regurgitation peak velocity was used to calculate the systolic pulmonary artery pressure (sPAP) **(8).**

- **Laboratory investigation:**

-Lipid profile assessment: 5 ml morning blood samples (without anticoagulant) were collected from all children after a minimum of 12 hours fasting, and with the routine procedure (determination of total cholesterol (TCh), high-density lipoprotein cholesterol (HDL), low density lipoprotein cholesterol (LDL), and TG were performed by colorimetric enzyme method on a RA-50 Chemistry Analyser spectrophotometer (Bayer), using LABTEST reagents), and using an automated instrument.

-Fasting blood glucose (FBG) measured enzymatically with an automated analyzer (Olympus Au 400)

-Hb A1C measure by HPLC (Sigma-Aldrich, Egypt).

Cardiometabolic risk among chidren was diagnosed using Metabolic risk score in children (MetS score). Body mass index was employed to verify the categorical variable MetS's presence (BMI) > 90th percentile for both gender and age, and at least two of the following results are true: (1) Blood sugar level in the morning >110 mg/dL; (2) systolic and or diastolic blood pressure >95th percentile for age, sex and height, (3) HDL-cholesterol <5th percentile for age and sex; (4) TG >95th percentile for age and sex **(9).**

- Serum Catestatin concentrations measurement using ELISA Kit: Cat.No E4996Hu:(Biosign, China) This test use the quantitative sandwich enzyme immunoassay technique. Catestatin-specific antibody has been pre-coated on a microplate. After standards and samples are pipetted into the wells, the immobilized antibody binds any catestatin that may be present. After removal of unbound chemicals, the wells are incubated with a biotin-conjugated antibody specific for catestatin. After washing, the wells are treated with Horseradish Peroxidase (HRP) that has been conjugated to an avidin. After a wash to remove any unbound avidin-enzyme reagent, a substrate solution is introduced to the wells, and color develops in direct proportion to the amount of catestatin bound during the initial stage. The color's intensity increases while the color's expansion is stopped is gauged.

Ethics approval:

The protocol for this study was approved by both the Institutional Review Board [IRB] and the local ethics committee at Zagazig University's Faculty of Medicine. All procedures of this study was governed by the Declaration of Helsinki, the International Medical Association code of ethics for human subjects research

Statistical analysis

With the help version 22 of the special sciences statistics program SPSS (SPSS Inc. Chicago, IL, U.S.A.), all data were gathered, tabulated, and statistically evaluated. Regression analysis, independent t-test Mann -Whitney test, paired t-test, chi square test (2), and fisher exact were used.

RESULTS

Table (1) : Comparison between the studied groups regarding demographic data, anthropometric measurements, blood pressure, blood glucose, HbA1c and plasma lipids:

	Diabetic group (n = 54)	**Control group (n = 54)**	χ^2	**p**
Sex **Male** **Female**	 25 (46.30%) 29 (53.70%)	 21 (38.9%) 33 (61.1%)	0.606	0.436
Age (years)	10.57 ± 2.38	10.85 ± 2.61	-0.578	0.565
	Mean ± SD	Mean ± SD		
Weight (kg)	39.46 ± 14.41	42.31 ± 15.32	-0.996	0.321
Height (cm)	137.26 ± 12.47	138.06 ± 14.73	-0.303	0.762
BMI (kg/m2)	20.35 ± 4.98	21.36 ± 4.69	-1.088	0.279
Systolic (mm Hg)	112.74 ± 6.7	110.43 ± 6.8	1.782	0.078
Diastolic (mm Hg)	73.98 ± 4.89	72.31 ± 5.38	1.684	0.095
Fasting blood glucose(mg\dl)	151.89 ± 24.48	84.44 ± 10.68	18.557	<0.001**
HbA1c (%)	8.82 ± 1.75	4.33 ± 0.49	18.211	<0.001**
HDL cholesterol(mg\dl)	83.91 ± 12.53	71.5 ± 10.06	5.677	<0.001**
Triglycerides(mg\dl)	107.36 ± 21.81	112.02 ± 10.24	15.817	<0.001**
	Median (IQR)	Median (IQR)		
LDL cholesterol(mg\dl)	110(90 – 135)	50(40 – 60)	-8.921	<0.001**
Total cholesterol(mg\dl)	150(114.5 – 175)	110(103 – 119.25)	-5.412	<0.001**
Catestatin ng\ml	8.35(6.16 – 17.41)	11.19(7.42-16.56)	-2.094	0.024*

χ2: Chi- Square test **SD:** standard deviation **t:** Independent T test

Table (1) showed that there was statistically non-significant difference between the studied groups regarding age ,sex ,weight ,BMI ,systolic and diastolic blood pressure. But there is statistically significant difference between the studied groups regarding fasting blood glucose or glycosylated hemoglobin, triglycerides, LDL, HDL , total cholesterol and catestatin.

Table (2) Mets score among diabetic children:

	N=54	**%**
FBG≥110 mg/dl	54	100%
BMI≥95th percentile	5	9.3%
TG≥95th percentile	18	33.3%
LDL≥95th percentile	14	25.9%
SBP≥95th percentile	1	1.9%
DBP≥95th percentile	1	1.9%
HDL≤5th percentile	0	0%
Patients with cardiometabolic risk	10	18.5%

All patients had FBG≥110 mg/dl, one patient (1.9%) had SBP≥95th percentile, DBP≥95th percentile in one patient (1.9%), five patients had BMI≥95th percentile (9.3%), eighteen patients (33.3%) had triglycerides ≥95th percentile, fourteen patients (25.9%) had LDL ≥95th percentile while no patient had HDL≤5th percentile. considering patients with ≥3 risk as having metabolic risk, so 18.5% of diabetic patients had cardiometabolic risk

Table (3): Relation between metabolic risk and demographic data among diabetic children and Comparison between the studied groups regarding HbA1c and total cholesterol:

	DM patients without cardiometabolic risk	DM patients with cardiometabolic risk (≥3)	χ^2	p
	N=44 (%)	N=10 (%)		
Gender: **Female** **Male**	 25 (56.8%) 19 (43.2%)	 4 (40%) 6 (60%)	 Fisher	 0.485
	Mean ± SD	**Mean ± SD**	**t**	**p**
Age (year)	10.16 ± 2.15	12.4 ± 2.63	-2.859	0.006*
BMI (kg/m^2)	18.88 ± 2.96	26.81 ± 6.88	-3.57	0.005*
HbA1c	8.78 ± 1.81	9.03 ± 1.51	-0.413	0.031*
Total cholesterol	141.91 ± 32.88	182.6 ± 34.91	-3.495	<0.001**

This table showed that there was statistically non-significant relation between the presence of cardiometabolic risk and sex. There is statistically significant higher cardiometabolic risk with older age diabetic children and also with higher body mass index (P<0.001) respectively. There is statistically highly significant relation between presence of cardiometabolic risk with higher total blood cholesterol levels(P<0.05), and with higher HbA1c (P<0.001).

Table (4) Univariate analysis of Catestatin and HbA1c in prediction of cardiometabolic risk among diabetic patients

	β	p	COR	95% C.I.	
				Lower	Upper
Catestatin (ng/ml)	.066	.122	1.068	.982	1.162
Hb A1c	.079	.122	.676	1.083	.746

Serum Catestatin non-significantly increase risk of presence of cardiometabolic risk among diabetic patients by 1.068 folds (95% CI 0.92 – 1.162). HbA1c non-significantly increase risk of presence of cardiometabolic risk among diabetic patients by 1.083 folds (95% CI 0.92 – 1.162).

DISCUSSION

Childhood diabetes is a chronic metabolic disorder associated with life-threatening complications. It is a metabolic disorder of carbohydrate, fat and protein, that affects a huge portion of the global population [(10)].

Increased blood glucose levels (hyperglycemia) are a hallmark of Type 1 diabetes mellitus (T1DM), a chronic autoimmune disease brought on by a lack of insulin, from the death of pancreatic islet -cells. One of the most prevalent endocrine and metabolic diseases affecting children is T1DM. Autoimmune T1DM, is characterized by the loss of -cells brought on by T1DM-related autoimmunity (coincident with the formation of T1DM-associated autoantibodies). Type 1b diabetes mellitus, also known as idiopathic T1DM, has a substantial hereditary component and impacts a smaller number of patients in whom no immune responses or autoantibodies are found [(11)].

Type 1 diabetic children and adolescents have a high rate of obesity, which is increasing globally at a rate of 4% each year. Teenagers with type 1 diabetes range in weight from 13.1% (aged 13–18) to 20.5% (aged 12–19), according to the Type 1 Diabetes Exchange Registry, which is a component of the National Health and Nutrition Examination Survey. According to the NHANES, 22.1% of teenagers with T1D and 16.1% of youngsters without the condition were overweight [(12, 13)].

In reality, the care of T1D, including the treatment of hypoglycemia and nutritional counseling, has improved glucose control during the past ten years, which may be a factor in unintended weight gain. Obesity, hypertension, and inadequate glycemic management all increase the possibility of developing cardiovascular disease (CVD), which is the main cause of death and morbidity in people with type 1 diabetes [(14)].

Obesity in early childhood, hypertension, and changes in glucose metabolism are all strongly linked to early mortality in adults. These findings emphasize the importance of early metabolic syndrome (MS) detection in populations of children and adolescents. MS is defined as a cluster of risk factors that includes obesity, impaired glucose tolerance, elevated triglyceride levels, low levels of high-density lipoprotein (HDL) cholesterol, and hypertension [(15)].

To help in predicting the course of metabolic diseases and prognosis in the diabetic pediatric population, novel molecular biomarkers are always required. The 21-aa endogenous peptide Catestatin (Cts) controls a number of physiological processes, such as catecholamine release, baroreceptor activation,

sympathetic nervous system activity, and heart function [4].

Catestatin inhibits catecholamine release by blocking nicotine receptors non-competitively. This mechanism of action was first described in 1997 and has since been confirmed by numerous in vitro and in vivo experiments. In light of this discovery, numerous investigations in adults have reported a relationship between catestatin levels and hypertension in both hypertensive patients as well as healthy individuals with a confirmed family history of high blood pressure. Additionally, catestatin lowers beta-adrenergic stimulation mediated by nitric oxide and increases mast cell synthesis of histamine, which results in subsequent vasodilation, both of which have an impact on blood pressure (NO), regulating oxidative stress, and other mechanisms [16].

Additionally, by lowering food intake and body weight, catestatin has beneficial impacts on the periventricular nucleus of the hamsters in hibernation that have an anti-obesity effect. It is likely that catestatin controls how fat cells operate, even if its roles in the start and progression of obesity and MS are not entirely understood by raising catecholamine levels and lowering leptin levels. Additionally, catestatin may influence nutrition absorption by functioning as a competitive leptin receptor antagonist in the small intestine, it would reduce leptin activity and, consequently, hyperglycemia [17].

So we aimed in this study to compare serum catestatin level in healthy and diabetic children and evaluate the role of Catestatin in cardiometabolic risk assessment among diabetic children.

According to our findings, Body mass index (BMI) did not differ statistically significantly between the diabetic group and the control group (all three variables were non-significantly higher in the control group).

Simunovic et al. [18] reported In keeping with our findings, there was no statistically significant difference in body height between groups.

On contrast with ***Simunovic et al.*** [4] who noted that no statistical significant difference between groups regarding height(166.2 ± 16.16 vs 165.9 ± 10.59)p(0.906) but BMI z score (2.74 ± 0.46 vs 0.18 ± 0.76)p(<0.001),body weight (87.58 ± 19.05 vs 56.13 ± 11.46) p(<0.001) and BMI(30.66 ± 3.59 vs 20.19 ± 2.54)) p(<0.001) with statistically significant differences between the 2groups.

The current study showed that blood pressure measurements among studied population. Mean of Systolic blood pressure in Diabetic group was 112.74 ± 6.7 while in control group was 110.43 ± 6.8 with no difference between the two groups. Moreover, Mean of diastolic blood pressure in Diabetic group was 73.98 ± 4.89 while in control group was 72.31 ± 5.38 without any discernible statistical difference (p=0.095) between the two groups.

Our results resemble that reported by ***Ness et al.*** [19] researchers wanted to know how Patients with T2D responded to a session of intense, exhaustive exercise differently than healthy individuals in terms of heart function and volume, as well as cardiac stress biomarkers and arrhythmias. The study included people with T2D (n=7) and healthy controls (n=7). For the study, a total of 15 men volunteered. Systolic and diastolic blood pressure did not statistically substantially differ across the groups.

On contrast ***Simunovic et al.*** [4] reported that systolic and diastolic blood pressure differences across groups were statistically very significant.

In the current study we noted that laboratory glucose results among the study population showed that the mean of Fasting blood glucose in Diabetic group was 151.89 ± 24.48 while in Control group was 84.44 ± 10.68 with highly statistical substantial distinction between the two groups (p =.001).

Mean of HbA1c in diabetic group was 8.82 ± 1.75 while in control group was 4.33 ± 0.49 with highly statistical significant difference (p= <.001) between the two groups.

Our results resemble that results reported by ***Cho et al.*** [20] who reported that there was highly significance between groups regarding to HbA1c.

Similarly, our results supported by ***Simunovic et al.*** [4] who reported that there was highly statistical significance between groups regarding to fasting blood glucose and HbA1c.

Also our results resemble that reported by ***Simunovic et al.*** [18] who reported that there was statistical significance between groups regarding to fasting blood sugar.

In our current study lipid profile results among the study population revealed that mean of HDL in diabetic group was 71.5±10.06 while in control group was 83.91 ± 12.53 (P<0.001). Mean of Triglycerides in diabetic group was 107.36 ± 21.81 while in control group was 112.02±10.24 (P<0.001). Median of total cholesterol in diabetic group was 150 (114.5-175) while in control group 110 (103-119.25)(P<0.001). Median of LDL in diabetic group was 110 (90-135) while in control group was 50 (40-60) (P<0.001), the differences were statistically significant respectively.

Our results supported by ***Barakat et al.*** [21]who reported that the mean ±SD values regarding to lipid profile in diabetic group were significantly different than controls and concluded that serum lipid testing should be performed on children with type 1 diabetes since severe lipid abnormalities are linked to glycemic control. With proper dietary management and insulin medication, both can be improved.

In our current study Median of Catestatin in Diabetic group was 8.35(6.16-17.41)while in Control group was 11.19(7.42-16.56) having a statistically significant difference between the two groups (p 0.05).

Our results resemble that reported by ***Ochocińska et al.*** [22] (where they discovered that

patients with newly diagnosed T1D had a median serum CST of 35.2 ng/mL) (range 0.001–70.1), and those treated > 3 years, with a median of 20.1 ng/mL (range 0.001–305), The thorough investigation of long-term patient subgroups revealed any potential effects of disease duration. .

In our study regarding the metabolic syndrome among diabetic children, number of patients with FBG≥110mg\dl was 54 (100%),number of patients with BMI≥95th percentile was 5(9.3%), number of patients with TG≥95th percentile was 18(33.3%), number of patients with LDL≥95th percentile 14(25.9%), number of patients with SBP≥95th percentile 1(1.9%), number of patients with DBP≥95th percentile 1(1.9%), number of patients with HDL≤5th percentile 0(0%), number of patients with cardiometabolic risk 10 (18.5%). So 18.5% of diabetic children had cardiometabolic risk.

In our study the relationship between gender and the prevalence of cardiometabolic risk was statistically insignificant P(0.485).

Our results supported by ***Skinner et al.*** [(23)] that showed that there was statistically non-significant relation between the presence of cardiometabolic risk and gender.

According to According to the findings of the current study, there is a statistically significant relationship between presence of cardiometabolic risk with older age diabetic children and also with higher body mass index (P<0.001) respectively. Our results supported by ***Skinner et al.*** [(23)] who reported that there is There is a statistically significant correlation between age and body mass index and the prevalence of cardiometabolic risk. The study included 8579 children and young adults with body mass indices at the 85th percentile or higher, as determined by growth charts given by the Centers for Disease Control and Prevention. 46.9% of people had excess body weight, of which 36.4% were class I obese, 11.9% were class II obese, and 4.8% were class III obese. In both male and female subjects, the mean values for some but not all cardiometabolic indicators increased with greater severity of obesity.

The results of this investigation revealed a statistically significant link between the prevalence of cardiometabolic risk and total serum cholesterol P(<0.001).

In youth, atherosclerosis study, the Youth Atherosclerosis Pathobiological Determinants Study ***Strong et al.*** [(24)], Aortas and more than half of the right coronary arteries both had intimal lesions in 15 to 19-year-olds, according to an autopsy examination of participants who died from external causes. Obesity exacerbated the severity of atherosclerosis in young adult men [(25)]**.** The Bogalusa Heart Study includes, the connection between atherosclerosis risk factors and CVD risk variables was also examined in participants 2 to 39 years old [(26)]**.** Body mass index (BMI), systolic and diastolic blood pressure, total cholesterol, triglycerides, low density lipoprotein cholesterol (LDL-C), and high density lipoprotein cholesterol (HDL-C) measurements taken before death were all associated with arterial fatty streaks and fibrous plaques at autopsy.

In our study there is a correlation between the occurrence of cardiometabolic risk and HbA1c (P 0.031).

Studies have also supported the significance of glucose regulation. When compared to individuals without T1DM, adults with a HbA1c > 7.5% has been assessed to have a higher risk of acquiring coronary artery calcification by a CT scan with an HbA1c < 7.5% [(27)]**.** Studies in children are limited, but ***Shamir et al.*** [(28)] discovered that better lipid profiles and tighter glycemic control were related in a group of teenagers with T1DM. The 195 teenagers who participated in the DCCT showed decreased incidence of retinopathy and nephropathy but greater rates of hypoglycemia among those with stricter glycemic control.

It's intriguing that we found that Hb A1c did not predict cardiometabolic risk in a statistically meaningful way.

Consistent with our results ***Seo et al.*** [(29)] discovered that compared to other markers, HbA1c had a lower predictive value for predicting MetS and CMRF clustering. This can be due to the fact that compared to adults, children and adolescents' HbA1c levels were more restricted.

Last but not least, serum catestin was unable to predict cardiometabolic risk in young people with type I diabetes. However, it has been shown that in people with type II diabetes, it is a reliable indicator of cardiometabolic risk. To be clear, however, both types of diabetes have distinct pathomechanisms, and T1D should be compared to other autoimmune diseases instead. Our research on CST levels in T1D is consistent with findings in other autoimmune diseases such inflammatory bowel disease [(30)]**.**

The study has certain limitations because to the limited sample size, and more research is required to confirm catestatin's involvement in the etiology and progression of T1D.

CONCLUSION

Our study showed that serum Catestatin related to diabetes but cannot be considered as a good biomarker of cardio metabolic risk among diabetic children. Further larger scale studies are needed to confirm our results.

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