

## Urinary PGF- 2 $\alpha$ and Carotid intima Media Thickness in Simple Obese Children: a Cross-sectional Study

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### ABSTRACT

**Background:** Obese children of all ages show signs of low-grade chronic inflammation. Circulating acute phase reactants (CPR) and urinary PGF-2 $\alpha$  are used to determine the severity of inflammation. Childhood obesity-related inflammation seems to have a key role in the advancement of atherosclerosis. Obesity is a key contributor in the evolution of metabolic disorder and collection of cardiovascular risk variables that may lead to heart illness and stroke. Doppler ultrasound estimations of the intima media thickness (IMT) are a practical, direct, and noninvasive method for evaluating and detecting preclinical artery wall diseases. It was connected to cardiovascular risk variables and was able to foresee the likelihood of future cardio-cerebrovascular disease.

**Objectives:** The aim of this research was to look into inflammatory status as measured by serum highly sensitive acute phase reactants (hs-CPR), oxidative stress as measured by urinary PGF-2 $\alpha$ , early arterial wall anomalies as measured by IMT, and associations between the above studied parameters, clinical, and anthropometric measurements.

**Methods:** The research included 40 obese children aged 4 to 12 years who were chosen from The Outpatient Clinic of Children University Hospital, Faculty of Medicine, Minia University. A control group of 25 age and sex matched seemingly healthy youngsters was also recruited. Patients and controls had a comprehensive clinical assessment and had their serum hs-CRP and urine PGF-2 $\alpha$  levels analyzed. High-resolution B-mode ultrasonography was used to assess IMT in the right and left carotid arteries.

**Results:** Serum hs-CRP and PGF-2 $\alpha$  levels in obese children were considerably greater than in controls. Obese juvenile patients had considerably greater median values of the left and right carotid arteries than controls.

**Conclusion:** Serum CRP and Urinary PGF- 2 $\alpha$  were the most important and statistically significant factors affecting IMT and can predict CVD risk in obese children.

**Keywords:** BMI, IMT, PGF-2 $\alpha$ , Simple obese children, Cross section study.

### INTRODUCTION

Obesity is described as having a body mass index (BMI) of 95th percentile or above for children of the identical age and sex. Obesity in children has been shown to be more prevalent in industrialized nations, although it is also becoming more prevalent in underdeveloped countries <sup>(1)</sup>.

In Egypt, obesity had been markedly increased among children and adolescent from 2004 to 2007. As it was 2.4% among boys and 4.5% among girls in the former, while 5.5% among boys and 5.6% among girls in the later <sup>(2)</sup>.

Multiple cardiovascular risk factors as, hypercholesterolemia, hypertriglyceridemia, low levels of HDL, hyperinsulinism, insulin resistance, and hypertension were found to be associated with obesity <sup>(3)</sup>. Obesity has been linked to a raise in systemic inflammatory indicators like serum C-reactive protein (CRP) and urinary PGF-2 $\alpha$ , which originate in adipose tissue, the liver, and numerous inflammatory tissues <sup>(4)</sup>. Obesity is accompanied with hepatic rise of CRP, which is elevated in response to IL-6 released from visceral adipose and reaching the portal circulation <sup>(4)</sup>. Furthermore, in addition to CRP produced by the liver, CRP produced by adipose tissue may have a role in obesity-related elevated CRP levels <sup>(1)</sup>.

Prostaglandin (PG)-F2 $\alpha$  is regarded as a valid oxidative stress indicator. PGF2 $\alpha$  levels are increased in obese children. In urine, the concentration of PGF2 $\alpha$  is forty times higher than that in plasma <sup>(6)</sup>.

IMT is a new, noninvasive marker for detecting circulatory abnormalities and thereby CVD in children who are obese <sup>(7)</sup>. The goal of this research was to look into inflammatory status as measured by serum highly sensitive acute phase reactants (hs-CPR), oxidative stress as measured by urinary PGF-2 $\alpha$ , early arterial wall abnormalities as measured by IMT, and associations between the above studied parameters, clinical and anthropometric measurements.

### PATIENTS AND METHODS

From April 2020 to April 2021, cross-sectional research was done at Pediatric Department, Faculty of Medicine, Minia University Children Hospital. This research comprised 40 obese children (Group I) who were chosen from the Outpatient Clinic of the University Children Hospital. Their ages varied from 4 to 12 years. According to the Egyptian Growth Charts, children with simple exogenous obesity have a BMI over the 95th percentile <sup>(8)</sup>.

**Exclusion criteria:** Obese children with chronic diseases as diabetes mellitus, endocrinal disorders as Cushing syndrome. Also, hereditary diseases, and systemic inflammation as systemic lupus erythematosus or under any medication as corticosteroids.

A control group of 25 age- and sex-matched seemingly healthy youngsters (Group II) was also recruited, with ages ranging from 7 to 11 years.

**Baseline clinical assessment:** All patients and controls underwent a general medical examination, which

included vital signs, especially blood pressure, dietetic history, regular exercise, sports participation, past history of systemic diseases, administration of drugs (corticosteroids), and family background (obesity, diabetes, and hypertension). Anthropometric measures were acquired, and the Egyptian Growth Charts were used to depict bodyweight, height, and waist circumference (WC) [8]. Weight (in kilos) divided by length squared (length<sup>2</sup>) in meters yielded the BMI, which was shown on the Egyptian Growth Charts [8].

**Laboratory analysis:** All were subjected to the following laboratory tests: Subjects were seated for the test between 8:00 and 9:00 a.m., and three ml of venous blood were collected aseptically after a 12-hour fast and permitted to clot. The separated serum was kept at -70°C until the immunoenzymometric test was used to evaluate hs-CRP and lipid profile (Moonblind Inc. in the United States provided the kits).

**Urine sampling:** Prior to the blood sample, all of the children completed an overnight urine collection. Urine samples were kept at 80°C until the urinary PGF-2α was measured using an immunoenzymometric assay (Neogen Corporation in the United States provided the kits).

**Carotid duplex study:**

B-mode and color-coded duplex sonography of the extracranial carotid and vertebral arteries were underwent to all patients and controls. IMT was assessed in a 1-cm section proximal to carotid bulb dilatation.

**Ethical considerations:**

Minia University Faculty of Medicine's Institutional Review Board and Medical Ethics Committee gave their approval to this research. This study followed the World Medical Association's

**Code of Ethics for Human Investigations (Declaration of Helsinki).**

**Statistical analysis**

Statistical program for the social sciences version 21 was utilized to examine the data (SPSS Inc., Chicago, Illinois, USA). The mean and standard deviation were utilized to characterize quantitative variables. Frequency and percentage were employed to convey qualitative data. The unpaired independent sample student t-test was performed to compare means. The chi-square test was employed to compare qualitative variables. Pearson's correlation coefficient was utilized to determine the correlation between two quantitative variables. A P-value ≥ 0.05 was deemed statistically substantial. The statistical tool Prism 3.0 was utilized to examine all of the data (Graph Pad software, San Diego, CA, USA). Microsoft Office Excel 2007 was utilized to create the graphs.

**RESULTS**

Group (I) obese children, their ages varied from 4 to 12 years with a median of 9.41 ± 1.60 years. Twenty five were males (62.5%) and fifteen were females (37.5%). Group (II) were enrolled as a control group, their ages varied from 7 to 11 years with a median of 9.04 ± 1.35 years, fifteen were males (60%) and ten were females (40%). Age, gender, and systolic blood pressure (SBP) were insignificant in obese and control children (p-value > 0.05). Weight, height, BMI, WC and diastolic blood pressure (DBP) were substantially greater in obese children than in controls (p-value < 0.05). There were 4 (10%) obese children with hypertension versus none in control group with insignificant difference (p-value > 0.05). Prehypertension was reported in 3 (7.5%) obese children versus none in control group with insignificant variance (p-value > 0.05) as shown in table (1).

**Table (1):** Comparative analysis of demographic and clinical variables between obese and control groups

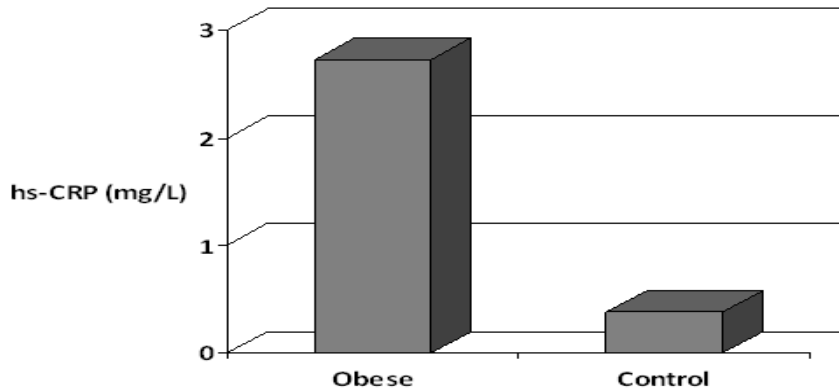
Parameters	Obese (N = 40)	Control (N = 25)	P-value	Significance
Age (years)	4-12 9.41 ± 1.60	7-11 9.04 ± 1.35	0.25	NS
Sex (M/F)	25M/15F	15M/10F	0.84	NS
Weight (kg)	28-81 50.65 ± 9.44	22-38 30.24 ± 3.93	0.0001	S
Height (cm)	100-164 134.82 ± 10.68	116-152 104.92 ± 53.14	0.002	S
WC (cm)	65-98 77.62 ± 6.24	48-64 56.48 ± 4.92	0.0001	S
Hypertension	4 (10%)	0 (0%)	0.10	NS
Prehypertension	3 (7.5%)	0 (0%)	0.16	NS

Regarding median of total cholesterol, LDL-cholesterol HDL-cholesterol and triglycerides (TG), there was no variation in the obese and control (Table 2).

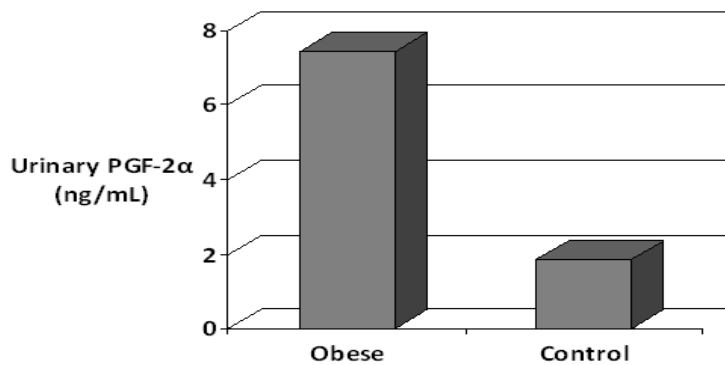
**Table (2):** Comparison of lipid profile in obese and control group children

Parameters	Obese (N = 40)	Control (N = 25)	P-value	Significance
Total cholesterol (mg/dL)	173.62 ± 9.06	170 ± 10.74	0.15	NS
HDL-cholesterol (mg/dL)	59.65±10.98	55±7.43	0.09	NS
LDL-cholesterol (mg/dL)	97.46±6.68	96.98±11.83	0.83	NS
Triglyceride (mg/dL)	82.57 ± 8.24	79.28 ± 12.36	0.20	NS

In obese children serum hs-CRP and urinary PGF-2α were substantially greater compared to controls (p- < 0.05). (Figure 1 & 2).



**Figure (1):** Mean of serum hs-CRP (mg/L) in obese and control group children



**Figure (2):** Mean of urinary PGF-2α (ng/mL) in obese and control group children

When compared to non-obese control children, obese children had considerably greater IMT in both the left and right carotid arteries (p- < 0.05) (Table 3).

**Table (3):** Comparison IMT between obese & control groups

Parameters	Obese (N = 40)	Control (N = 25)	P-value	Significance
Right IMT (mm)	0.35-0.56 0.42 ± 0.03	0.30-0.40 0.31 ± 0.02	0.0001	S
Left IMT (mm)	0.36-0.49 0.42 ± 0.02	0.31-0.41 0.32 ± 0.02	0.0001	S
Mean IMT (mm)	0.39-0.50 0.42 ± 0.01	0.31-0.41 0.32 ± 0.02	0.0001	S

Correlation of serum hs-CRP and Urinary PGF-2α with other parameters in obese children showed that there was a substantial association of PGF-2α with WC (r = 0.475; p-value = 0.002) and a substantial association of hs-CRP with WC (r = 0.383; p-value = 0.015). There was a substantial association of IMT with BMI (r = 0.89; p-value = 0.0001), WC (r = 0.85; p-value = 0.0001), PGF-2α (r = 0.89; p-value = 0.0001) and hs-CRP (r = 0.83; p-value = 0.0001) as shown in table (4).

**Table (4):** Correlation of serum hs-CRP and Urinary PGF-2 $\alpha$  with other parameters in obese children

Parameters	Urinary PGF-2 $\alpha$		hs-CRP	
	R-value	P-value	R-value	P-value
Urinary PGF-2 $\alpha$	1	--	0.158	0.331
hs-CRP	0.158	0.331	1	--
BMI	0.046	0.777	0.289	0.071
WC	0.475	0.002*	0.383	0.015*
SBP	0.097	0.551	0.329	0.038*
DBP	0.084	0.607	0.384	0.014*
Total cholesterol	0.183	0.258	0.240	0.136
TGs	0.010	0.952	0.222	0.169

Multiple stepwise linear regression analysis revealed that BMI ( $\beta = 0.42$ ; p-value = 0.006) and PGF-2 $\alpha$  ( $\beta = 0.38$ , p-value = 0.004) were the most important and statistically significant factors affecting IMT while the other parameters (WC, HDL-cholesterol and hs-CRP) were less important (Table 5)

**Table (5):** Multiple stepwise linear regression analysis was used to determine the relationship between IMT (mm) and other important factors in obese children

	Beta co-efficient	t-value	p-value	Significance
(Constant)	--	6.487	0.0001	S
BMI	0.428	2.853	0.006	S
Urinary PGF-2 $\alpha$	0.385	3.020	0.004	S
hs-CRP	0.082	0.690	0.493	NS
HDL-cholesterol	0.029	0.523	0.603	NS
WC	0.015	0.108	0.915	NS

**DISCUSSION**

The purpose of this research was to look into inflammatory status in the form of serum hs-CRP, oxidative stress in the form of urinary PGF-2 $\alpha$ , early anomalies of the arterial wall (described by IMT) and associations between above studied parameters, clinical and anthropometric measurements.

Group (I) obese children, their ages varied from 4 to 12 with a median of 9.41  $\pm$  1.60 years. Twenty five were males (62.5%) and fifteen were females (37.5%). Group (II) were enrolled as a control group, their ages varied from 7 to 11 with a median of 9.04  $\pm$  1.35 years. Fifteen were males (60%) and ten were females (40%). The BMI was used to measure total adiposity, but the WC is recommended as a measure of central obesity since it is an excellent predictor of abdominal fat and is more closely linked to the progression of cardiovascular disease (10-12). In terms of BMI and WC, we discovered that obese children had considerably elevated BMI and WC values than controls in our research. (P-value < 0.05). In the present study, we found that there were 4 (10%) obese children with hypertension versus none in control group with insignificant difference (p-value > 0.05). Prehypertension was reported in 3 (7.5%) obese children versus none in control group with insignificant difference. DBP values were considerably elevated in obese children than in controls (p-value < 0.05). This agrees with the results of Nageswari *et al.* (13) who showed that greater DBP in obese children might be attributed to increased vasoconstrictor tone and/or

enhanced cardiac output owing to enhanced circulatory burden on the heart as a result of increased BMI.

There were no statistically substantial variations between the obese and control groups regarding total cholesterol, LDL-cholesterol, HDL-cholesterol, and triglycerides (TG) in our research. This corresponds to the results of Giannini *et al.* (9) who observed no statistically substantial differences in lipid profiles between obese and control groups. (19) In contrast Holst-Schumacher *et al.* (14) found that obese children had greater total blood concentrations of TG but lower total serum concentrations of HDL cholesterol compared to controls, indicating that changes in lipoprotein concentrations and components are likely connected to the increased risk of CVD associated with obesity. These discrepancies in lipid profile results between studies might be explained by differences in food habits and physical activity patterns among children from various socioeconomic backgrounds (15).

In our research, we discovered that obese children's hs-CRP levels were substantially greater than controls. Previous investigations showed increased levels of hs-CRP in obese children and adolescents, showing that there is already a certain amount of inflammation in the early stages compared to the non-obese population (16). As a consequence of our findings, Akinci *et al.* (17) found a correlation between obesity and inflammation, which is translated by significant high concentrations of hs-CRP in obese children in comparison with control group. Confirming our findings, Giannini *et al.* (9) explained the role of hs-CRP

as a sensitive index in early detection and identification of CVD and chronic inflammatory changes. As high levels of hs-CRP was found to be associated with inflammatory changes in the vascular endothelium with subsequent development of atherosclerosis. As a result of activation of monocytes, production of adhesive molecules and attraction of leucocytes to endothelial cells.

Our result showed that urinary PGF-2 $\alpha$  was substantially greater in obese children compared to controls. That is inconsistent with **Ostrow *et al.***<sup>(18)</sup> who indicated that the high level of urinary PGF-2 $\alpha$  in obese children than in non-obese is highly associated with development of atherosclerosis. Atherosclerosis of the arterial wall was found to be mediated by oxidative stress, as a result of vasoconstriction, platelet aggregation and vascular smooth muscle proliferation in response to PGF-2 $\alpha$  release.<sup>(9)</sup>

IMT is a well-known subclinical atherosclerosis marker that may also predict potential cardio-cerebrovascular illness<sup>(7)</sup>. The IMT was assessed in obese and non-obese patients in our research. We discovered considerably greater IMT in both the left and right carotid arteries in obese pediatric patients compared to non-obese control children, as well as substantially greater values in both the left and right carotid arteries (P-value < 0.05). Our results coincide with the results obtained by **Fang *et al.***<sup>(19)</sup> who revealed that IMT was considerably higher in obese children compared to non-obese children of same age and gender, suggesting that early atherosclerotic alterations occur in obese children. Furthermore, the result of the present research was in accordance with **Stabouli *et al.***<sup>(20)</sup> who found that C.V complications could be early detected and identified in obese children and adolescents by evaluation of IMT which was found to be substantially enhanced in obese than in non-obese children. However, in contrast with our results, **Tounian *et al.***<sup>(21)</sup> found that IMT could be affected by multiple factors as, the age of populations examined, the duration and degree of obesity, the duration and severity of hypertension coexist, if cardiovascular risk factors exist, physical exercise or a sedentary lifestyle, and a target organ lesions presence with genetic predisposition. All these factors explained why IMT did not significantly differ among obese and non-obese children.

In our research, we discovered a substantial link between hs-CRP and waist circumference (WC) in obese children. Confirming our results, **Oliveira *et al.***<sup>(22)</sup> found similar results and concluded from their study that the most reliable anthropometric indication of CVD risk is waist circumference, and measuring hs-CRP in obese populations may be effective for predicting and recognizing early stages of CVD. Furthermore, in obese children, we discovered a favorable relationship between hs-CRP and both systolic and diastolic blood pressure. This finding is similar to **El-shorbagy & Ghoname**,<sup>(23)</sup> who reported that hs-CRP may be used

as a measure of cardiovascular risk in obese children and adolescents, according to the same findings<sup>[24]</sup>.

In our study, a direct correlation was found between urinary PGF-2 $\alpha$  and WC in obese children. This finding is similar to that of **Araki *et al.***<sup>(24)</sup> who discovered that plasma PGF-2 $\alpha$  levels were positively linked with WC and indicated that these findings suggest that increased visceral fat accumulation causes oxidative stress in children. An examination of many stepwise linear regressions found that BMI ( $\beta = 0.42$ ;  $p = 0.006$ ) and PGF-2 $\alpha$  ( $\beta = 0.38$ ,  $p = 0.004$ ) were the greatest important and statistically significant factors affecting IMT while the other parameters (WC, HDL-cholesterol, and hs-CRP) were less important. These results are somewhat in line with **Giannini *et al.***<sup>(9)</sup> who documented an independent effect of urinary PGF-2 $\alpha$  on the increasing IMT within obese subjects.

## CONCLUSIONS

Serum CRP and urinary PGF- 2 $\alpha$  were more increased in obese children and holds promise for cardiovascular risk prediction.

**Limitation of the study:** Because many patients refused to participate in this trial, the sample size was reduced.

## Declarations:

**Consent for Publication:** I certify that all authors agreed to submit the work.

**Availability of data and material:** Available

**Competing interests:** None

**Funding:** No fund

**Conflicts of Interest:** no conflicts of interest.

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