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RELATIONSHIP OF HIGH SENSITIVITY C-REACTIVE PROTEIN LEVEL TO ANTHROPOMETRIC PARAMETERS IN OBESE CHILDREN IN A TERTIARY CARE HOSPITAL IN BANGLADESH

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ABSTRACT

Background: Obesity is an exaggeration of normal adiposity. Adipose tissue contributes to the secretion of inflammatory cytokines. These cytokines include interleukin-6 (IL-6), interleukin-1 (IL-1) and tumor necrosis factor alpha (TNF-a), which stimulate hs-C-reactive protein (CRP) production by the liver. Hs-CRP is a marker of inflammation and early determination may help to predict the future metabolic and cardiovascular complication associated with obesity. **Objective:** To study therelationship of hs –CRP levels with various anthropometric parameters in children with obesity. **Methods:** This cross sectional study conducted at department of Paediatrics of BSMMU, Dhaka over a period of 12 months (September 2018 to August 2019). Total 110 obese children aged between 10 to 18 years with BMI ≥ 95th centile according to CDC growth chart were selected in this study after considering exclusion and inclusion criteria. Age and sex matched 55 non-obese children (normal weight children) with BMI ≥ 5th to < 85th centile were also included in this study. A structured questionnaire was prepared for each participant taken into account demographic and clinical parameters. Levels of hs-CRP were estimated in 110 obese and 55 non-obese children. These levels were then correlated to various anthropometric parameters (body mass index, BMI; waist circumference, WC; hip circumference, HC;waist hip ratio, WHR; waist height ratio, WHtR). **Results:** Hs-CRP Level was raised in 46.4% of children in obese group than non-obese group (10.9%). Mean hs-CRP Level was significantly higher in obese group than non- obese group (2.81 ± 2.62mg/L vs 0.922 ± 0.852mg/L).Among the obese group, about 58% was grade I obese and 42% was grade II obese (Severe obese). About 67% of grade II obese had hs-CRP level ≥ 2mg/L in comparison to grade I obese (31.3%). Mean body mass index (BMI), waist circumference (WC),waist-hip ratio (WHR),waist-height ratio (WHtR) were significantly higher in the obese group than in the non-obese group. Body mass index (BMI), waist circumference, waist-hip ratio, waist-height ratio were positively correlated with raised hs-CRP level in obese group. **Conclusion:** Levels of hs-CRP were significantly elevated in obese children as compared to non-obese children. Hs-CRP level was raised significantly in grade II obese children. Raised hs-CRP level in obese children was positively correlated with BMI, waist circumference, waist-hip ratio and waist-height ratio.

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INTRODUCTION

Obesity in children is one of the major global health problems now a days. Obesity is an exaggeration of normal adiposity [Redinger, 2007].

Previously adipose tissue was considered as a passive storage of fat depots playing central role in lipid metabolism. But now a new conception about adipose tissue came in front that, the expansion of the adipose tissue contributes to the secretion of inflammatory cytokines [Roth *et al.*, 2011]. These cytokines include interleukin-6 (IL-6), interleukin-1 (IL-1) and tumor necrosis factor alpha (TNF-a), which stimulate hs-C-reactive protein (CRP) production by the liver [Genest, 2010]. Hs-CRP potentiates the inflammatory process in vascular endothelium, thus, facilitating atherogenesis through monocyte activation and promoting synthesis of adhesion molecules recruiting leukocytes. These inflammatory markers are evidenced to participate in the process of atherogenesis by impairment of endothelial function, formation of fatty streaks and plaques or in the process of thrombus formation. The detection of hs-CRP level in the blood is regarded as the presence of subclinical inflammation. Elevated levels of hs-CRP is associated with obesity in obese children has been found to be associated with cardiovascular diseases, hypertension, diabetes mellitus, dyslipidemia and non alcoholic fatty liver diseases [Lobstein Lobstein). Hs-CRP level ≥ 2 mg/L indicates low grade inflammation. Therefore the early diagnosis of low grade inflammation in obese children by doing hs-CRP is particularly important. The objective of the study is to know the relationship of hs–CRP levels with various anthropometric parameters in children with obesity.

MATERIALS AND METHODS

This case control study was conductedin Department of Paediatrics (Paediatric Endocrinology Clinic, Paediatric Outpatient and Inpatient Department), Bangabandhu Sheikh Mujib Medical University (BSMMU) and was approved by the Institutional Review Board (IRB) of the BSMMU. The study was carried out from September 2018 to August 2019. A total of 165 children healthy study population were recruited from those who came for screening at Bangabandhu Sheikh Mujib Medical University. After taking written consent, study subjects were allocated in following two groups:

Group A (Obese group): Total 110 newly diagnosed case of obese children (≥ 95th centile) and Group B (Non obese group): Age and sex matched 55 normal weight healthy children (BMI ≥ 5th to < 85th centile) according to CDC age and sex specific BMI criteria. Obese group were further subdivided into grade I and grade II obese group. In Grade I obese group there was 64 obese children with BMI ≥ 95th centile and < 120% of 95th centile and in Grade II obese group newly diagnosed 46 obese children with BMI ≥ 120% of 95th centile according to CDC age and sex specific BMI criteria. Subjects suffering from any liver or renal diseases, infection, inflammation, taking any steroid and were in dietary restriction were excluded from the study. A detailed history was taken, then physical examination and measurement of anthropometric indices were done. The weight was measured with using electronic weighing machine (Tanita, Japan) placed on a flat surface to a nearest 100g with barefoot and light clothing. Standing height was measured withstadiometer and measurement was done to the nearest 0.1 cm.BMI was calculated as the ratio between weight (in kilograms) and the square of the height (in meters). Waist circumference (WC) was measured to the nearest 0.5 cm in midway between the lowest rib and the superior border of the iliac crest by using a non-extensible and non-elastic measuring tape during expiration and inferences were drawn in percentiles. It's reference value was taken as:≥ 90th centile - raised and < 90th centile – normal [Bennett *et al.*, 2014] and hip circumference is measured around the widest portion of the buttocks. Then the weight-hip ratio was calculated. The WHO (2011) recommends reference value of raised waist-hip ratio: for Male ≥ 0.90 and for Female ≥ 0.85 [Prevention and National Center for Health Statistics, 2016] [Hiur *et al., 2003*]. Waist-to-height ratio (WHtR) was calculated by dividing waist circumference by height in cm. A WHtR ≥ 0.5 is an indicator of abdominal obesity in both adults and children at any age [Hiur *et al., 2003*].

Plasma hs-CRP level: Blood sample were collected from the study subjects by venipuncture in clean and dry test tube without anticoagulant. Under all aseptic precautions 2 ml of venous blood was collected from the study subjects by using disposable syringe from the ante-cubital vein. The needle was detached from the nozzle and blood was transferred immediately into a dry clean test tube with a gentle push to avoid hemolysis and which was kept in standing position till clot formation. Serum was separated by centrifugation (5 min, 3000 rpm) within 30-120 min of collection. Then 1 ml clear serum was collected in Eppendorf tube and then hs-CRP was measured by nephelometric system (BN ProSpec, SIEMENS, USA). After measuring, hs-CRP was categorized according to American college of cardiology (ACC) and American Heart Association and Centers for Disease Control and Prevention (AHA/CDC) in 2013. Categorization of the hs-CRP level was [Knight, 2015]

- High risk ≥ 2 mg/L
- Low risk < 2 mg/L

Statistical analysis of data: Data were expressed as mean ± standard deviation (SD) and frequency and percentage. Data were analyzed by Chi-square test, Fisher's exact test and unpaired student t-test was used for quantitative data. Pearson correlation coefficient test and scatter diagram was applied to evaluate the correlation between the variables. p-value ≤ 0.05 was considered as statistically significant.

RESULTS

Study population in this study were children age between 10-18 years and clinically healthy. Comparison of demographic characteristics and anthropometric parameters between obese and non-obese groups (n = 165) are shown in table 1. Majority of children in both obese and non-obese group were 10 to 13 years of age (69.1%). Mean age of obese and non-obese children were (12.16 ± 1.77 years vs 12.33 ± 1.84 years). Female were more in frequency in both groups (54.5%) in comparison to male (45.5%). However, study population were similar in terms of gender. Mean BMI, waist-hip ratio,waist-height ratio were significantly higher in the obese group than in the non-obese group, as expected. Raised waist circumference (39.1%) was significantly higher in the obese group than in the non-obese group. Raised waist hip ratio was higher in female (56.7%) than male (38%) in obese group (Table 1). Hs-CRP Level was raised (≥ 2 mg/l) in 46.4% of children in obese group than non-obese group (10.9%). It was statistically significant (p = <0.001). Mean hs-CRP Level was significantly higher in obese group than non- obese group (2.81 ± 2.62 vs 0.922 ± 0.852). It was statistically significant (p = <0.001) are shown in Table 2. Among the obese group, about 58% was grade I obese and 42% was grade II obese (Severe obese) by BMI were shown in Figure 1. As shown in Table 3, no significant difference was found in terms of mean BMI among high risk and low risk groups.

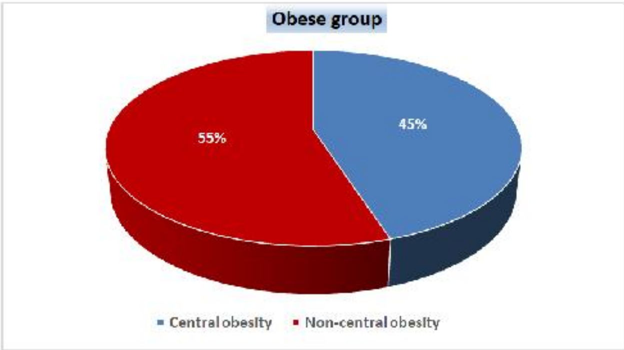

Figure 1. Percentage of central obesity and non-central obesity according to waist-height ratio (WHtR) in obese group (n=110)

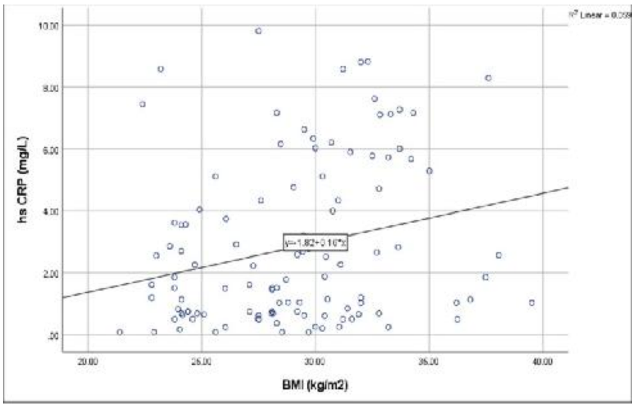

Figure 2. Correlation of BMI with hs-CRP level in obese group (n = 110)

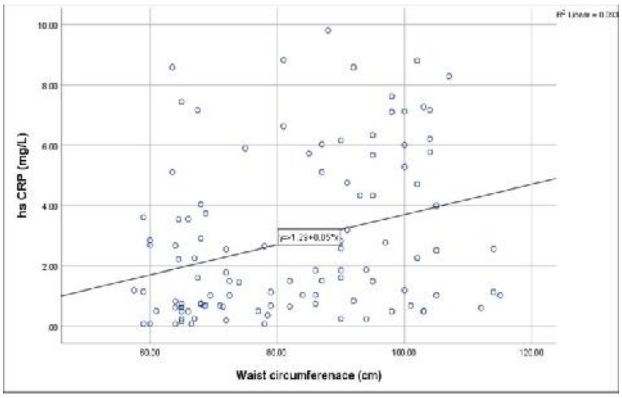

Figure 3. Correlation of waist circumference (cm) with hs-CRP level in obese group (n = 110)

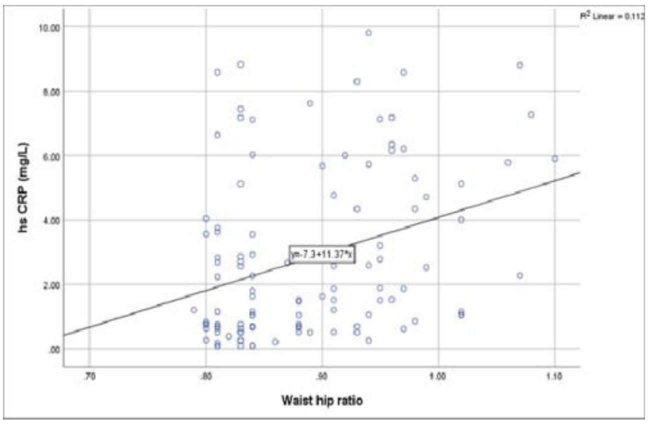

Figure 4. Correlation of waist-hip ratio with hs-CRP level in obese group (n =110)

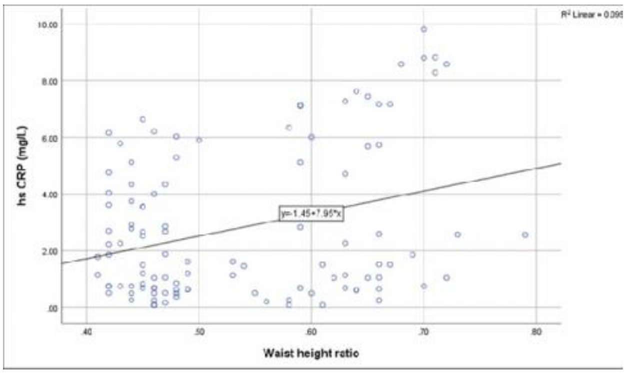

Figure 5. Correlation of waist-height ratio with hs-CRP level in obese group (n =110)

However, in grade II obesehs-CRP level ≥ 2 mg/L was significantly elevated than hs-CRP level < 2 mg/L (58.8% vs 25.4%). Meanwaist circumference, waist-hip ratio, waist-height ratio were significantly higher in high risk group. Raised waist circumference was significantly higher in the high risk group than in the low risk group. Waist-height ratio was significantly higher in high risk group in comparison to low risk group (60.8% vs 32.2%). Waist-hip ratio in both male and female was not statistically significant (Table 3).

To investigate hs-CRP level, grade II obese had significantly elevated mean hs-CRP level as compared to grade I obese (4.33 ± 2.83 vs 1.71 ± 1.79). About 67% of grade II obese had hs-CRP level ≥ 2mg/L in comparison to grade I obese (31.3%). It was statistically significant (p = <0.001) areshown in (Table 4). To explore the relationship of hs-CRP level with the anthropometric parameters of obese group, Scatter diagram were performed in the obese group with the use of Pearson's correlation coefficient (r). As shown in figure 2, 3, 4, 5, hs-CRP level significantly positive correlation of BMI (r = 0.243, p = 0.010), waist circumference (WC) (r = 0.305, p = 0.001), waist hip ratio (WHR) (r = 0.335, p = <0.001) and waist height ratio (r = 0.309, p = 0.001).

DISCUSSION

Obesity in children is a major global health problem now a days. Obesity are associated with a number of co-morbidities, including cardiovascular diseases, hypertension, diabetes mellitus, dyslipidemia, and non alcoholic fatty liver diseases [Lavie, 1932; Afshin *et al.*, 2017]. It has been shown that chronic low grade sterile inflammation associated with obesity contributes to the development of those co-morbidities. Although hs-CRP is an important mediators of inflammation, several studies showed that the raised hs-CRP among obese children, indicating that exists a certain level of inflammation

Therefore the early diagnosis of low grade inflammation by doing hs-CRP has become a research priority in the context of obesity and related co-morbidities. In this study, mean age of obese and non-obese children were (12.16 ± 1.77 vs 12.33 ± 1.84). In obese and non-obese group, 54.5% were female and 45.5% were male. In a study done in Indonesia among the obese children and on that study, mean age of children were similar to present study and no significant sex difference was observed [Regina, 2011]. Pires et al. [2014] showed similar results to our study.

Table 1.Comparison of demographic andanthropometric parametersbetween obese and non-obese groups (n = 165)

Demographic and anthropometric parameters			Obese (n = 110)	Non- obese (n = 55)	*p*-value
Age (years)		Mean ± SD	12.16 ± 1.77	12.33 ± 1.84	0.582
		10- 13	76(69.1%)	38 (69.1%)	1.00
		14- 18	34 (30.9%)	17 (30.9%)	
Sex n (%)		Male	50 (45.5%)	25 (45.5%)	1.00
		Female	60 (54.5%)	30 (54.5%)	
BMI (kg/m²)		Mean ± SD	28.97 ± 3.987	18.08 ± 1.993	<0.001
Waist circumference (cm)		Mean ± n (%)	81.93 ± 15.96	62.96 ± 5.13	<0.001
		≥ 90th Centilen (%)	43 (39.1%)	0	<0.001
		< 90th Centilen (%)	67 (60.9%)	55 (100%)	
Waist-hip ratio		Mean ± SD	0.888 ± 0.077	0.824 ± 0.065	<0.001
	Malen (n%)	< 0.90	31 (62%)	24 (96%)	0.002
		≥ 0.90	19 (38%)	1 (4%)	
	Femalen (n%)	< 0.85	26 (43.3%)	28 (93.3%)	<0.001
		≥ 0.85	34 (56.7%)	2 (6.7%)	
Waist-height ratio		Mean ± SD	0.533 ± 0.099	0.439 ± 0.031	<0.001
		≥0.5n(%)	50 (45.5%)	0	<0.001
		< 0.5n(%)	60 (54.5%)	55 (100%)	

Table 2. Compare the obese and non-obese groups according to category of hs-CRP level (n = 165)

Hs-CRP Level	Obese (n = 110)	Non- obese (n = 55)	*p*–value
Low risk group (hs-CRP level < 2mg/L) n (%)	59 (53.6%)	49 (89.1%)	<0.001
High risk group (hs-CRP level ≥ 2 mg/L) n(%)	51 (46.4%)	6(10.9%)	
Mean ± SD(mg/L)	2.81 ± 2.62	0.922 ± 0.852	<0.001

Table 3. Comparison of anthropometric parameters between low risk group (hs-CRP level < 2 mg/L) to high risk group (hs-CRP level ≥ 2 mg/L) in obese children (n = 110)

Anthropometric parameters			Low risk group (hs-CRP level < 2 mg/L)	High risk group (hs-CRP level ≥ 2 mg/L)	*p*-value
BMI (Kg/ m^2)		Mean ± SD	28.37 ± 4.01	29.67 ± 3.89	0.087
		Grade In(%)	44 (74.6%)	21(41.2%)	<0.001
		Grade IIn(%)	15(25.4%)	30 (58.8%)	
Waist circumference (Cm)		Mean ± SD	78.68 ± 15.31	85.69 ± 16.01	0.021
		<90th centile n (%)	42(71.2%)	25 (49.0%)	<0.001
		≥90th centilen (%)	17(28.8%)	26 (51.0%)	
Waist-hip ratio		Mean ± SD	0.87 ± 0.063	0.91 ± 0.087	0.007
	Male n (%)	< 0.90	21 (35.6%)	10 (19.6%)	0.481
		≥ 0.90	11 (18.7%)	8 (15.7%)	
	Female n (%)	< 0.85	15 (25.4%)	11(21.6%)	
		≥ 0.85	12 (20.3%)	22 (43.1%)	
Waist-height ratio		Mean ± SD	0.52 ± 0.09	0.55 ± 0.11	0.048
		< 0.50n(%)	40 (67.8%)	20(39.2%)	0.002
		≥ 0.50n(%)	19 (32.2%)	31(60.8%)	

Table 4. Comparison of grade I obese and grade II obese according to category of hs-CRP level in obese children (n = 110)

Hs- CRP level	Grade I obese	Grade II obese (severe obese)	*p*-value
Mean ± SD (mg/L)	1.71 ± 1.79	4.33 ± 2.83	<0.001
Low risk group (hs-CRP level < 2 mg/L) n(%)	44 (68.7%)	15 (32.6%)	
High risk group (hs-CRP level ≥ 2 mg/L) n(%)	20 (31.3%)	31 (67.4%)	<0.001

In this study, mean BMI in obese group (28.97 ± 3.987 kg/m2) was significantly higher than non-obese group (18.08 ± 1.993 kg/m2). A population based Korean study showed almost similar findings. On that study, BMI of Obese children were 28.7 ± 2.9 kg/m2 and non-obese children were 19.3 ± 2.4 k/m2. [Yi, 2014]. As in the case of mean BMI, Shilpa et al. [10] and Pires et al. [8] found similar finding of mean BMI. Among the obese group, 58% were grade 1 obese and 42% were grade II obese (Severe obese). A study conducted in Spanish population and they found 41.6% had severe obese among the obese children [Cadenas-Sanchez]. About 60% of obese children had grade II obese (Severe obese) in high risk group in comparison to low risk group. It was statistically significant (p = <0.001). Paepegaey et al. [2014] showed almost similar finding (51.6% vs 48.8%) but they observed in adult population.

In the present study, mean waist circumference (WC) was significantly higher in obese (81.93 ± 15.96 cm) than non-obese children (62.96 ± 5.13 cm) and about 39% children had high waist circumference in obese group. That finding is consistent with the study done by Sardinha et al. [2016], Devi Dayal et al. [2014] and Mastori et al. [2006]. In this study, in the obese children, mean waist circumference was significantly higher in hs-CRP level ≥ 2 mg/L than hs-CRP level < 2 mg/L (85.69 ± 16.01cm vs 78.68 ± 15.31cm). About 51.0% of children had high waist circumference in the high risk group in comparison to 28.8% in low risk group. Rensburg et al. [2012] had almost similar finding to present study (47% had raised waist circumference in the high risk group). In the present study, mean waist-hip ratio (WHR) was significantly higher in obese group (0.888 ± 0.077) than non-obese group (0.824 ± 0.065).

In the obese group, 38% male and 56.7% female were had high waist-hip ratio. Mean waist-hip ratio had significantly higher in the high risk group in comparison to low risk group (0.91 ± 0.087 vs 0.87 ± 0.063). Almost similar finding observed Sadanand et al. [18] between high risk group and low risk group (0.94 ± 0.06 vs 0.87 ± 0.03). In the present study, mean waist-height ratio was significantly higher in obese group (0.533 ± 0.099) than non-obese group (0.439 ± 0.031). In the obese group, 45.5% of children had high waist-height ratio (WHtR). In a study conducted in Portuguese children and observed different results and found raised waist-height ratio (WHtR) was 21.9% of children [Rodrigues et al., 2018]. The findings of Rodrigues et al. [2018] are different due to age of children were 6-10 years as compared to present study. In the obese group, mean waist-height ratio was significantly higher in hs-CRP level ≥ 2 mg/L than hs-CRP level < 2 mg/L (0.55 ± 0.11 vs 0.439 ± 0.031). In the obese group, 52.9% children had high waist-height ratio in hs-CRP level ≥ 2 mg/L. There is no study regarding hs-CRP level in obese children in our country. Devi Dayal et al. [2014] found hs-CRP level raised in 55% in the obese group and 10% in non-obese group. This finding almost similar to the present study (46.4% vs 10.9%). Mirhoseini et al. [2018] and Rehnuma et al. [2014] observed almost similar finding to present study. In the study conducted in adults, they found 31.5% had high hs-CRP level. Bennett et al. [2014] observed different from the present study (15% had high hs-CRP level in the obese children).

In our study, mean hs-CRP level was significantly higher in obese group (2.81 ± 2.62 mg/L) in comparison to non-obese group (0.922 ± 0.852 mg/L). Devi Dayal et al. [2014] and Shilpa et al. [2014]) found significantly higher mean hs-CRP level in obese children to non-obese group. Mean hs-CRP level was significantly higher in grade II obese (severe obese) in comparison to grade I obese (4.33 ± 2.83 vs1.71 ± 1.79). About 67% grade II obese (severe obese) had raised hs-CRP level ≥ 2 mg/L in comparison to grade I obese (31.3%). Elevated hs-CRP levels may be associated with the development of cardiovascular diseases and diabetes by means of a variety of mechanisms: altered sensitivity to insulin, increased liberation of adhesion molecules by endothelium, increase in hepatic production of fibrinogen and platelet coagulation factor [Namburi *et al.,* 2013]. In the present study, positive correlation was observed between hs-CRP level to BMI, waist circumference and waist hip circumference. A similar study observed in Pires et al. [2014] and they found hs-CRP directly correlated with BMI (r = 0.507; p = < 0.001), waist circumference (r = 0.496; p = < 0.001). Waist hip circumference and BMI had significantly correlated with hs-CRP level [Shilpa *et al.,* 2014]. Devi Dayal et al. [14], EI-shorbagy et al. [2010] &Hatem et al. [23] found BMI had significantly correlated with hs-CRP (r = 0.253; p = < 0.011). Devi Dayal et al. [2014] found slightly different from this study and observed no correlation between waist-hip ratio with hs-CRP level.

Theunderlying mechanism behind this raised hs-CRP level with anthropometric parameters might be as follows; the adipose tissue is a source of cytokines such as tumor necrosis factor- alpha and interleukin-6, and this cytokines potentiate the production of CRP in the liver [Devi Dayal *et al., 2014p;* Hiura, 2013]. In the present study, the waist-height ratio showed the positive correlation with the hs-CRP level. There was no study about such correlation. The present study has several limitations. Most important limitation are relatively small size and cross sectional nature of the study. Further studies are required in subjects of other ethnicity to explore validity and general applicability of this findings. We suggest routine screening of hs-CRP level in obese children especially who have grade II obese (severe obese), raised waist circumference, waist-hip ratio and waist-height ratio.

CONCLUSION

In the present study, we found prevalence of hs-CRP level in obese children was 46.4%, which was significantly higher than non-obese children. Hs-CRP level was raised in obese children in presence of high BMI, raised waist circumference, waist-hip ratio and waist-height ratio. Hs-CRP level was also raised significantly in grade II obese children and showed significant positive correlation with BMI, waist circumference, waist-hip ratio, waist-height ratio in obese children.

Conflict of interest: None declared

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AAP	American Academy of Pediatrics
AC	Acanthosisnigricans
ACC	American college of cardiology
AHA	American heart association
BMI	Body mass index
BP	Blood pressure
BSMMU	Bangabandhu Sheikh Mujib Medical University
CDC	Center for disease control and prevention
CRP	C – reactive protein
DEXA	Dual energy X-ray absorptiometry
DM	Diabetes mellitus
FDA	Food and Drug Administration
GLIP	Glucagon like peptide
Hs-CRP	High sensitivity C- reactive protein
IL-1	Interleukin-1
IL-6	Interleukin-6
IL-10	Interleukin- 10
IRB	Institutional Review Board
NAFL	Non-alcoholic fatty liver disease
T2DM	Type 2 diabetes mellitus
TNF-α	Tumour necrosis factor –α
US	United States
WC	Waist circumference
WHO	World Health Organization
WHR	Waist-hip ratio
WHTR	Waist- height ratio

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