Original Article

High Sensitivity C-Reactive Protein Level Increases with Rise in Body Mass Index and not Affected by Perceived Stress in Young Saudis

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Abstract

Obesity is reported to be associated with chronic low-grade inflammatory state, indicated by increased plasma level of C-reactive protein (CRP). Moreover, high prevalence of overweight and obesity among young Saudis is a serious health concern. Therefore, we designed this study to investigate the effect of obesity and perceived stress on plasma high sensitivity (hs)-CRP level in young Saudis. A total of 472 young healthy males (age, 19 ± 2) were categorized as underweight, normal, overweight and obese based on their body mass index. Plasma levels of hs-CRP levels were measured by nephlometry. In addition, the level of stress among the participants was determined using PSS-14 questionnaire. The results showed about 11% (53/472) underweight, 21% (100/472) overweight, 24% (114/472) obese and 43% (201/472) normal subjects. Mean values of hs-CRP obtained from these groups showed a rising trend being minimum in underweight while maximum in obese. The mean values of hs-CRP among different BMI categories was significantly different P=0.001. We also observed a significant Positive correlation between plasma hs-CRP level and Body mass index (BMI), Weight, Waist circumference (WC), Hip circumference and Waist Hip Ratio (WHR). Thirty percent (142/472) of our participants were found to be stressed. However, there was no significant difference in their hs-CRP levels. Pearson correlation between perceived stress scores, anthropometric parameters and hs-CRP levels were not significant. On the basis of these findings we can conclude that higher the BMI higher will be the level of plasma hs-CRP level representing presence of a state of low grade systemic inflammation in overweight and obese subjects, which might lead to cardiovascular events.

Keywords: High sensitivity C-reactive protein; Body mass index; Perceived stress; Obesity

Introduction

Among the various active phase reactants, CRP is unique because of its reliability and sensitivity as an indicator of inflammation [1]. Synthesized by liver, plasma CRP level is mainly regulated by interleukin 6 (IL-6), [2] which is released by macrophages [3] and adipocytes [4]. CRP plays a role of first line defense against altered self-antigens and certain pathogens through pro-inflammatory signals and activation of complementary system, [5]. promoting phagocytosis by macrophages, thus helping the body to get rid of necrotic and apoptotic cells and bacteria. Moreover, CRP can be used as a predictor of incidences like myocardial infarction, stroke, peripheral vascular disease and sudden cardiac death, [6,7] because CRP, fibrinogen and IL-6 are recognized as major risk factors involved in the pathogenesis of atherosclerosis and cardiovascular diseases [8,9]. These inflammatory markers are evidenced to participate in the process of atherogenesis by impairment of endothelial function [10], formation of fatty streaks and plaque [11] or in the process of thrombus formation leading to myocardial infarction and strokes [12]. Further, CRP potentiates the inflammatory process in vascular endothelium [13] thus, facilitating atherogenesis through monocyte activation [11,14]. and promoting synthesis of adhesion molecules recruiting leukocytes.

Growing incidence of obesity is an important health concern all over the world because of its association with chronic diseases like type 2 diabetes, hypertension, strokes and cardiovascular problems. Furthermore, overweight and obese are more likely to develop low grade systemic inflammation and thus have more chances of increased plasma CRP levels compared to the normal weight individuals [15]. In addition, coronary heart disease mortality and total mortality is increasingly observed in individuals with raised plasma CRP levels [16,17]. This relationship between CRP and obesity can be justified on the basis that human subcutaneous tissue releases IL-6; which in turn play an important role in regulating plasma CRP level [18,19]. Therefore, it can be hypothesized that obesity might produce low grade inflammation reflected by high plasma CRP level and it is a potential reason for increasing incidence of atherogenesis that might lead to cardiovascular events [9,20,21].

Stress is well known either to cause or provoke conditions like type 2 diabetes, hypertension, hyperacidity and myocardial

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infarction. Various types of Stressors cause activation of sympathetic nervous system leading to the release of Adrenaline, nor adrenaline and Glucocorticoids [22]. Chronic secretion of these hormones may lead to endothelial dysfunction and triggers an acute phase inflammatory response [23]. Nevertheless a relationship between acute stress and elevated CRP levels has also been recognized [24]. However, results regarding relationship between chronic stress and CRP are controversial with few in favor and others denying the existence of a relationship between chronic stress and CRP [25]. Moreover, stress is also found to be a factor involved in the etiology of obesity. In a study of 208 male workers in Japan, obesity was found to be associated with psychological tension and anxiety that is mainly because of high demands and poor decision latitude at work [26]. Further they reported that, higher degrees of stress negatively affected subjects' diet, which contributed to higher rates of obesity. In obese people another reason for increasing risk of development and progression of CVD is a possible pro-inflammatory effect of oxidative stress.

Despite the Increasing prevalence of obesity and stress among young Saudi population there is scarcity of available literature regarding the association of obesity with low grade systemic inflammation; which is a neuroendocrine response to injurious stimuli with tumor necrosis factor alpha as an essential biological driver,47 indicated through plasma hs-CRP level. We therefore hypothesis that increased hsCRP levels in young obese might be associated with BMI and it might be used as an important sign of future risk of CVD in otherwise healthy young individuals. Therefore, this study aims to investigate the effect of obesity and stress on plasma hs-CRP level in young Saudis.

Subject and Methods

We investigated 473 young healthy Saudi medical students, 19-20 years of age. The study was carried out between January–June 2016. Subjects with history or evidence of any inflammatory disease during one month prior to the study were excluded. Before starting the project permission was taken from the university Ethical committee and participants signed a written consent.

Anthropometric measurements

Anthropometric parameters such as body weight, height, waist and hip circumference were measured using standard clinical protocol [27]. BMI was calculated dividing weight in Kg by height in Meters Square. On the basis of BMI participants were classified according to WHO guidelines [28]. in four categories. Underweight BMI (< 18.5), normal BMI (18.5-24.9), pre-obese BMI (25-29.9) and obese BMI (≥30). Considering age and gender along with BMI, body fat percentage (BF%) was also calculated using following formula [29].

$$\text{Adult BF\%} = (1.20 \times \text{BMI}) + (0.23 \times \text{Age}) - (10.8 \times \text{Gender}) - 5.4$$

Gender value, Male=1 female=0

WHR was calculated as an indicator of abdominal visceral fat, by dividing waist circumference by the hip circumference [30].

Perceived stress score

Perceived stress of the participants was measured with the help of perceived stress scale 14 (PSS-14). It consists of 14 questions each with five options from never to very often. The PSS has an internal consistency of 0.85 (Cronbach α coefficient) and test-retest reliability during a short retest interval (several days) of 0.85 [31]. To make the process reliable all the questions were presented both in English and Arabic languages. The stress score was stratified as Non-stressed (<28) and stressed (≥ 28) [32].

Plasma hs-CRP

Venous blood samples (5 ml) collected under aseptic conditions were centrifuged to get plasma. hs-CRP was then measured by latex-enhanced Immunonephlometry (Dade Behring, New York, DE, USA). Both within and between assays quality control was maintained. It can measure a minimal value of 0.01 mg/dl and values below it were described undetectable.

Statistical analysis

The values are expressed as mean ± SD. High sensitivity CRP as a continuous variable was logarithmically transformed for statistical analysis to improve its skewness. The geometric mean of hs-CRP and its geometric mean standard error were used for tabular and graphical presentations. Unpaired student t test was used for continuous normally distributed variables. One way ordinary ANOVA was used for comparing 3 or more groups.

To compare PSS-14 scores of subjects from three different groups (hs-CRP low, moderate and high) the kruskal-wallis test (one way analysis of variance by rank) was used. A Pearson correlation analysis (two tails) was performed to assess any relationship between logarithmically transformed hs-CRP with anthropometric components whereas, a non-parametric spearman correlation was performed to assess relationship between PSS-14 scores and anthropometric components. All statistical analysis were performed using graphpad prism (GraphPad 6 Software, La jolla CA USA)

Results

Characteristics of the participants

This cross-sectional study included (472) Young Saudi medical students from Makkah region with a mean age of 19 ± 1 year. The participants were investigated using different tools for the identification of obesity and level of perceived stress. In addition the risk of developing cardiovascular problems was examined by measuring their plasma hs-CRP levels [Table 1]. BMI the most commonly used indicator of obesity in most of the epidemiological studies when applied to our participants showed arrangement of 14 to 55.5 and a mean value of 25.89 ± 7.65 [Table 1]. This suggests as per WHO standards majority of our participants fall in the overweight category. However, many workers are of the opinion that BMI can't distinguish between fat mass and lean body mass and therefore, WC and WHR are better indicators of central or abdominal fat. Mean values of WC (88.03 ± 18.21), WHR (0.93 ± 0.19) and BF% (19.47 ± 9.19) were also recorded [Table 1]. In addition mean values of hs-CRP (0.28 ± 0.02) and perceived stress score (24.66 ± 5.83) of the participants were also established [Table 1]. Our participants are neither obese nor stressed. Whereas, based on the hs-CRP majority is in the average (medium) risk group for developing cardiovascular problems.

Table 1: Characteristics of the participants

	Mean ± SD (n=472)	Maximum	Minimum	percentile 25%	percentile 75%
Height (cm)	169.8 ± 11.25	187.5	145	166	175
Weight (kg)	74.8 ± 21.63	176	40	59	87
Waist (cm)	88.03 ± 18.21	155	54	75	99.75
BMI	25.89 ± 7.65	55.76	13.84	20.39	29.97
Body fat %	19.47 ± 9.19	20.94	5	12.86	24.36
Waist/hip ratio	0.93 ± 0.194	2.3	0.55	0.84	0.94
hs CRP (mg/dl)	0.28 ± 0.02	7.17	0.01	0.04	0.3
PSS 14 Score	24.66 ± 5.83	42	8	20	28

Values are mean ± SD, hs-CRP, high sensitivity C-reactive protein, PSS-14, perceived stress scale 14

Table 2: Comparison of plasma levels of hs-CRP among different categories

hs-CRP levels in four categories based on BMI	p-value
Underweight (n=53) vs. Normal (n=201) *	0.11 ± 0.02 vs. 0.18 ± 0.03 <0.0001
Normal (n=201) vs. Pre-Obese (n=100) *	0.18 ± 0.03 vs. 0.35 ± 0.09 <0.0001
Pre-Obese (n=100) vs. Obese (n=114) *	0.35 ± 0.09 vs. 0.46 ± 0.04 <0.0001

hs-CRP, high sensitivity C-reactive protein; BMI, body mass index. * All independent variables that showed a significant difference (p<0.05)

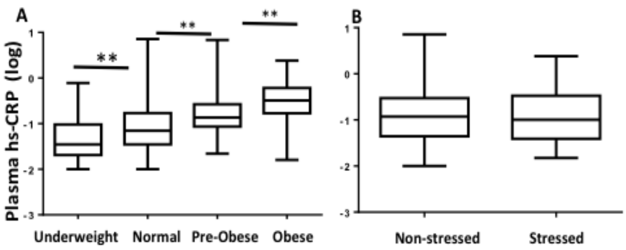

Figure 1: Distribution of plasma concentration of hsCRP among different categories

A) Box and whisker plot illustrating the distribution of plasma concentrations of high sensitivity CPR (log) in underweight (n=53), normal (201), pre-obese (n=100) and obese. One way ANOVA showed significant difference between these groups.

B) The second plot illustrates a non-significant comparison between non-stressed (326) and stressed (28) of hs-CRP (log). * shows a significant difference (*p*<0.05)

hs-CRP level increases with rise in BMI

The BMI based stratification identified our study group as 11.3% (53/472) underweight,42.95% (201/472) normal weight, 21.37% (100/472) overweight and 114 24.36% (114/472) obese subjects [Table 2]. In fact 45% (214/472) of the total participants belong to over-weight or obese group, which is quite high for their age. hs-CRP obtained from these groups [Table 2] demonstrated a rising trend being minimum in underweight and maximum among obese [Figure 1]. Moreover, comparison of hs-CRP level between different groups (Underweight vs. Normal), (Normal vs. Overweight) and (Overweight vs. Obese) was found to be statistically significant P<0.001.

Perceived stress does not affect hs-CRP level

Stress is one of the factors that tend to increase Plasma hs-CRP levels. Previously, we have established the incidence of stress in medical students [33]. In order to investigate the effect of stress on hs-CRP in healthy young subjects we divide our study group on the basis of their perceived stress score (cut point 28) in two categories, non-stressed n = 69.07% (326/472) and stressed n=30.08% (142/472). Plasma hs-CRP values obtained from non-stressed and stressed participants were compared and found not significant [Table 2 and Figure 1].

Considering the combined effect of stress and obesity on mean values of hs-CRP it was noted that, stressed participants having normal BMI had the lowest hs-CRP level. Whereas, hs-CRP level is observed to increase markedly with the presence of obesity regardless of the fact that the subject is stressed or non-stressed. This implies that, stress alone is unable to produce any significant change in the plasma hs-CRP level in our young participants while BMI has a potent effect on plasma hs-CRP level [Table 3].

Plasma hs-CRP level is associated with anthropometric components

Thus far we observed hs-CRP increases with rise in BMI. Therefore we examined if an association exists between hs-CRP and anthropometric variables [Table 4]. Plasma hs-CRP levels showed positive and significant (P<0.001) correlation with BMI, Weight, WC, Hip circumference and WHR. The strongest correlation (r 0.98) was observed between hs-CRP and BMI while the weakest (r 0.27) between hs-CRP and waist hip ratio [Table 3]. The correlation between hs-CRP and Height and Waist and height ratio was non-significant. Pearson correlation demonstrated a negative and non-significant correlation between hs-CRP and Stress [Table 4].

Perceived stress do not correlate with anthropometric components and hs-CRP

Around thirty (30) percent (142/472) of our participants were

Table 3: BMI has a stronger effects then stress on hs-CRP

Groups	BMI	Stress score	hs-CRP mg/dl
Normal weight + non stress (n=145)	21.78 ± 0.17	21.27 ± 0.29	0.2 ± 0.05
Normal weight + Stress (n=55)	21.67 ± 0.25	31.58 ± 0.44	0.16 ± 0.04
Overweight + Non Stress (n=66)	27.34 ± 0.19	21.43 ± 0.52	0.43 ± 0.15
Obese + Stress (n=32)	34.93 ± 1.22	31.81 ± 0.67	0.53 ± 0.09

hs-CRP, high sensitivity C-reactive protein; BMI, body mass index

Table 4: Pearson correlation assessing the association between hs-CRP and anthropometric components

Hs-CRP vs.	r	95% Confidence interval	P (two tailed)
Weight (kg) *	0.9338	0.9211 to 0.9445	< 0.0001
Waist (cm) *	0.7127	0.6649 to 0.7546	< 0.0001
Height (cm)	-0.01006	-0.1007 to 0.08078	NS
Hip circumference (cm) *	0.5074	0.4367 to 0.5718	< 0.0001
Waist hip ratio *	0.2726	0.1865 to 0.3546	< 0.0001
Waist height ratio	0.08249	-0.008334 to 0.1720	NS
BMI *	0.9823	0.9788 to 0.9852	< 0.0001
PSS-14	-0.02728	-0.1178 to 0.06364	NS

hs-CRP, high sensitivity C-reactive protein; BMI, body mass index; PSS-14, perceived stress scale 14. NS indicates not significant. * All independent variables that showed a significant association (p<0.05)

Table 5: Pearson correlation assessing the association between PSS-14 scores and anthropometric components

PSS-14 scores vs.	r	95% Confidence interval	P (two tailed)
Weight (kg)	0.001553	-0.08874 to 0.09182	NS
Waist (cm)	0.01003	-0.08032 to 0.1002	NS
Height (cm)	-0.005387	-0.09562 to 0.08493	NS
Hip circumference (cm)	0.009184	-0.08116 to 0.09938	NS
Waist hip ratio	-0.007397	-0.09761 to 0.08294	NS
Waist height ratio	0.01157	-0.07879 to 0.1017	NS
BMI	0.002576	-0.08772 to 0.09283	NS
Hs-CRP	-0.02728	-0.1178 to 0.06364	NS

hs-CRP, high sensitivity C-reactive protein; BMI, body mass index; PSS-14 perceived stress scale 14. NS indicates not significant. *Adjusted for all independent variables that showed a significant association ($p<0.05$)

found to been stressed with a perceived stress score of ≥ 28. Therefore, Pearson correlation was also performed to investigate any association between perceived stress score and different anthropometric variables as well as hs-CRP. PSS score showed non-significant correlation with all anthropometric components [Table 5]. Correlation between PSS score and hs-CRP was also found non-significant [Table 5].

Discussion

Obesity is one of the important risk factor for chronic diseases like cardiovascular, stroke, hypertension and type II diabetes mellitus. It is a major health issue in Saudi Arabia. The current study showed that 24 percent of young Saudi males are obese and increasing obesity is associated with raised plasma CRP level. Interestingly, other obesity indicating parameters like weight, waist circumference, hip circumference and waist hip ratio are also found to be significantly associated with plasma CRP level. However, in the current study we were unable to find any significant effect of stress on plasma hs CRP level and no association is observed between PSS-14 scores and anthropometric parameters and hs-CRP.

We have already reported the incidence of obesity is around 24.36% (114/472) among 18-19 years of male Saudis which is consistent with Zaid et al. [34] who earlier reported 28.7% of Saudi population 15 years of age and above as obese with higher prevalence among females (33.5% vs. 24.1%). Moreover, overweight and obesity is found to be associated with presence of low grade systemic inflammation indicated by higher plasma level of acute phase reactant CRP [15]. Our results also agree with this reported association between obesity and CRP and we observed a gradual and significant rise in the plasma level of hs-CRP with the increasing BMI from underweight to obese participants [Table 1 and Figure 1]. In addition significant association was observed between hs-CRP and BMI. Infact all the indicators of obesity (weight, WC, hip circumference and WHR) are associated with hs-CRP as well. Aronson et al. [35] reported obesity as the major determinant of hs-CRP in patients with or without metabolic syndrome. Further, he also established BMI as the major contributor for hs-CRP variance after multivariate regression analysis [35]. This association of obesity and BMI with increasing plasma hs-CRP level observed in our study can be explained on the basis of potential role of adipose tissue in the body in relation to the expression and release of substances like, tissue necrosis factor α and IL-6 [36,37]. Moreover, it is estimated that about 25% of IL-6 in vivo is produced by the adipose tissues [18] and synthesis of hs-CRP by liver is largely regulated by IL-6 [2].

Increasing level of hs-CRP with increasing BMI can also be explained on the basis of an indirect effect of Tumor necrosis factor-α, another cytokine released by adipose tissues. Although it is not reported to have a direct influence on the plasma hs-CRP level but is thought to potentiate the effect of IL-6 in CRP production [38]. Positive association of BMI with plasma hs-CRP and the role of adipose tissue as a CRP modulator are further strengthened by findings of Andre T [39]. A study on obese postmenopausal women observed fall in plasma CRP level with a fall of fat mass, induced through caloric restriction. This reduction in CRP level with fall of fat mass is attributed to the reduction in IL-6 production. The reduced fat mass and CRP synthesis by liver is mainly regulated by IL-6 level so fall in fat mass leads to fall in CRP through reduction in IL-6 secretion [39]. In another study John et al. [36] observed significant association between concentrations of IL-6, TNF-α and CRP and measures of total (BMI) and particularly central (W/H ratio) obesity. The increasing trend of hs-CRP level from underweight to obese as well as significant association between different obesity markers and hs-CRP levels observed in this study might suggest an increase in secretion of cytokines in general and IL-6 in particular by increased fat mass.

In-addition participants included in this study were healthy subjects of 18-19 years with no history of disease, trauma or infection during the month prior to the study therefore; this reduces the chances of any confounding subclinical disease and possible reasons for raised hs-CRP except over-weight and obesity. However, stress is one of the factors that might change the plasma CRP level of our otherwise healthy subjects. We have already established that 46% (13300/289) of Saudi medical students perceived variable degree of stress [33] and several studies reported presence of an association between acute stress and high CRP levels [24]. But, regarding chronic stress and CRP levels the results are conflicting [40,41]. In the current study we were unable to find significantly different levels of plasma hs-CRP between stressed and non-stressed. Moreover, there is no association between PSS-14 scores and anthropometric parameters and hs-CRP, which might suggest that, stress does not modulate hs-CRP level in our participants. Further, analysis of the study results to observe combined effect of obesity and stress on plasma hs-CRP level also revealed failure of stress alone as a factor to produce significant effect on plasma hs-CRP level while obesity is found to influence hs-CRP levels markedly both in presence or absence of stress. It might be possible that, our participants being young and healthy with strong physical and mental status, handles the stress smoothly and resist a rise in plasma hs-CRP level or may be the level of stress in our participants is below the threshold to induce a state of inflammation.

Overweight, Obesity and large waist to hip ratio are the indicators of considerable health risk in general and specifically cardiovascular morbidity [42-45]. Moreover, chronic low-grade inflammation has a role in pathogenesis of atherosclerosis and increased plasma hs-CRP level increases the risk of coronary artery disease [9,46]. According to the results nearly 45% (214/472) of our participants belong to overweight and obese category with increased plasma level of hs-CRP associated with an increased risk for cardiovascular disease. However, on the basis of hs-CRP, according to the American heart association standards our participants belong to average or medium risk category (0.1-0.3 mg/dl), which is alarming considering their age [47]. Keeping in view the findings of this study serious measures are required to produce changes in the diet, physical activity level and overall lifestyle of our population for the attainment and maintenance of the BMI within the normal range and as such reducing the incidence of cardiovascular and other chronic diseases.

Conflict of Interest

The authors declare no conflict of interest.

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