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Research Article

Obesity and High Sensitivity C-Reactive Protein Level in Indian Population

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Abstract

The study was aimed to assess the relation between high sensitivity C-reactive protein (hs-CRP) and obesity in Indian population. Obesity is increasing to epidemic proportions in India to such an extent that the prevalence of obesity has also been found to be rising in children and adolescents leading to various coronary events and inflammatory conditions like cardiac disorders, atherosclerosis etc. in young adults. Obesity is associated with the release of many inflammatory cytokines from adipose tissue among which IL-6, one of the proinflammatory cytokines produced from adipose tissue, plays a major role in stimulating the release of CRP-a novel inflammatory marker released from the liver. In this study, we tried to study the role of hs-CRP and the trend of its increase in Indian population with various levels of obesity. The subjects in the study were participants from voluntary health check-up in Medicine-OPD at Dr. Ram Manohar Lohia Institute of Medical Sciences, Lucknow, India. The study population was matched for age, BMI, WC, and WHR. Subjects with BMI >30 waist circumference/hip circumference ratio were considered as obese for this study. Baseline characters such as blood pressure, cholesterol levels and glucose level were measured along with the changes in the hs-CRP level in the subjects and the same was compared with those with BMI > 30, serving as control. It was found that the level of hs-CRP increases with obesity and may lead to various medical complications if left unattended as obesity have been found to be linked with number of atherogenic, hypertensive and metabolic disorders known till date.

Keywords: *High Sensitivity C-Reactive Protein; Obesity; Metabolic Syndrome; Inflammatory Cytokines; Body Mass Index*

Introduction

Obesity, a well-known problem in developed as well as developing countries has been found to be associated with number of health issues such as hyperinsulinemia, insulin resistance, dyslipidemia, and vascular dysfunction. Obesity have been found to be associated with elevation in the level of various serum inflammatory markers such as interleukin 6 (IL-6), tumor necrosis factor-α (TNF-α), soluble tumor necrosis factor receptor II (sTNF-RII), and C-reactive protein (CRP) suggesting that it is an "inflammatory disease" [1]. Body mass index (BMI) an indicator of body heaviness rather than fatness where body fat cannot be distinguished from fat-free mass is usually measured in terms of waist-to-hip ratio (WHR). Waist-to-hip ratio (WHR) is a measure of regional fat distribution, whereas waist circumference (WC) is a measure of central obesity.

CRP, formerly considered a biomarker for inflammation, is now also viewed as a significant player in endothelial dysfunction and atherosclerosis. The increased production of cytokines and acute-phase response proteins, such as high-sensitivity C-reactive protein (hs-CRP), which occurs in obesity, is related to insulin resistance, endothelial dysfunction, and atherosclerosis [2]. CRP, a member of the

pentraxin family of proteins is also an acute phase reactant synthesized mainly by the liver in response to stimulation by pro-inflammatory cytokines and adipocytes. Serum CRP levels are elevated rapidly generally beyond 10 mg/dl with a concomitant elevation of erythrocyte sedimentation rates in response to acute infections, inflammatory conditions, and trauma [3].

Among the various active phase reactants, CRP is unique because of its reliability and plays a role of first line defence against altered self-antigens and certain pathogens through pro-inflammatory signals and activation of complementary system, 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 [4] because CRP, fibrinogen and IL-6 are recognized as major risk factors involved in the pathogenesis of atherosclerosis and cardiovascular diseases [5]. These inflammatory markers are evidenced to participate in the process of atherogenesis by impairment of endothelial function, formation of fatty streaks and plaque or in the process of thrombus formation leading to myocardial infarction and strokes [4]. Further, CRP potentiates the inflammatory process in vascular endothelium thus, facilitating atherogenesis through monocyte activation and promoting synthesis of adhesion molecules recruiting leukocytes [6]. 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 [6]. In addition, coronary heart disease mortality and total mortality is increasingly observed in individuals with raised plasma CRP levels [5]. This relationship between CRP and obesity can be justified on the basis that human subcutaneous tissue releases IL-6; which in turn plays an important role in regulating plasma CRP level [6]. 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 [7].

Hs-CRP has been found to be an important precursor of metabolic syndrome (MetS) and type 2 diabetes, and a strong predictor of early stage cardiovascular disease (CVD) even when within the clinical normal reference range. Adipose tissue plays a critical role in the induction of chronic low-grade inflammation via hsCRP production in the liver by synthesizing cytokines especially interleukin-6 (IL-6). Measures for overweight are among the strongest correlates of CRP concentrations to such an extent that a close relationship between inflammation and overweight may help to explain the greater susceptibility to CVD among these individuals [8]. Concentrations of acute-phase reactants such as IL-1 receptor antagonists (IL-1RA) and IL-6 in blood increases with age could be a potent marker of CVD in elderly as well [8]. Since IL-6 level is associated with hs-CRP, it could be well predicted that the later also increases with age, but any interaction between age and adiposity for CRP has not been clearly investigated. IL-6 is a proinflammatory cytokine that is secreted by skeletal muscles, white blood cells, hepatocytes, and adipose tissue. It has been found to be higher in obese individuals as compared to the non-obese ones and is associated with the development of insulin resistance, the metabolic syndrome, T2D in these individuals [9]. Positive correlations have been observed between IL-6, BMI and percent fat mass (PFM). IL-6 also plays an anti-inflammatory role by reducing TNF-α and interferon-γ and stimulatesIL-1RA. The proposed mechanism of this metabolic effect is reduction of glucose transporter-4 and insulin receptor substrate-1 expression in response to IL-6 exposure [9]. The present study aims to examine the correlation between BMI and inflammation markers hs-CRP and IL-6.

Materials and Methods

This was a community-based cross-sectional study based on data from Medicine OPD at Dr. Ram Manohar Lohia Institute of Medical Sciences, Lucknow, India. A total of 75 subjects aged 30 and over, belonging to both male and female genders participated in the study. Baseline characteristics of the subjects like blood pressure, fasting glucose and cholesterol levels were recorded as part of routine checkup. These parameters were used to examine the potential health issues that may arise in near future if the patients are left attended. Hs-CRP and IL-6 levels were measured using commercial kits and analyzed by chemiluminescence method on AU-480 Beckmann Coulter. This study was approved by the Institutional Ethical Committee. Written informed consent was obtained from each participant enrolled in the study.

Three groups of BMI: The patients were categorized into three groups as follows:

- Group 1: < 25 Waist circumference/Hip circumference ratio
- Group 2: = 26 to 30 Waist circumference/Hip circumference ratio
- Group 3: > 30 Waist circumference/Hip circumference ratio

***Group 1 and 2 consists of subjects serving as control in the study while Group 3 consists of subjects serving as test group of the study.

Statistical analysis

Values were expressed as Mean ± SD. Correlations were done by calculating Pearson's correlation coefficient. All statistical analysis was done at 5% level of significance using SPSS software.

Result and Discussion

Table 1 shows the baseline characteristics of the groups under study. Control group consisted of subjects with waist to hip ration lesser than 30 cm while study group consisted of individuals with this ration above 30 cms. As we can see in table 1, the waist circumference, hip circumference, waist to hip ratio shows significant increase ($p < 0.001$) in test group of the study as compared to the control group. We also found that the blood pressure of the test subjects as measured by systolic and dystolic blood pressure tend to increase representing the fact that obesity may also lead to hypertension which may further exaggerate the medical complications of these individuals. Obesity can result in serious health issues that are potentially life threatening, including hypertension, type II diabetes mellitus, increased risk for coronary disease, increased unexplained heart failure, hyperlipidemia, infertility, higher prevalence of various cancers [10]. Activation of the sympathetic nervous system (SNS), the amount of intra-abdominal and intra-vascular fat, sodium retention leading to increase in renal reabsorption, and the renin-angiotensin system, are considered to have important functions in the pathogenesis of obesity-related hypertension, a chronic medical condition in which the blood pressure is persistently at or > 140/90 mmHg but not at the normal level which is defined as 100-140 and 60 - 90 mmHg for systolic and diastolic pressure, respectively.

Parameter	Test group (Mean ± SD)	Control group (Mean ± SD)	p-value
Age (yrs)	23.5 ± 2.28	18.7 ± 0.73	0.387
BMI (kg/m^2)	34.5 ± 2.85	20.5 ± 1.65	< 0.001
WC (cms)	70.7 ± 6.80	50.5 ± 3.32	< 0.001
HC (cms)	80.8 ± 5.77	68.7 ± 3.58	< 0.001
WHR	0.84 ± .059	0.66 ± .027	< 0.001
SBP	130.8 ± 8.72	110.8 ± 5.03	< 0.001
DBP	99.2 ± 6.83	68.9 ± 7.57	0.003
TC (mg/dl)	177.9 ± 42.79	124.8 ± 25.19	0.001
HDL-C (mg/dl)	32.6 ± 6.26	29.3 ± 7.27	0.005
LDL-C (mg/dl)	98.4 ± 36.27	89.3 ± 19.05	0.032
VLDL (mg/dl)	31.02 ± 5.36	29.35 ± 3.482	0.005
S.TG (mg/dl)	155.11 ± 26.80	146.76 ± 17.41	0.005
FBG (mg/dl)	109.8 ± 10.86	83.6 ± 6.71	< 0.001

Table 1: *Baseline characteristics of the groups under study.*

**p value < 0.05: Abbreviations: BMI: Body Mass Index; WC: Waist Circumference; HC: Hip Circumference; WHR: Waist Hip Ratio; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure.TC: Total Cholesterol; HDL-C: High Density Lipoprotein Cholesterol; LDL-C: Low Density Lipoprotein Cholesterol; VLDL: Very Low Density Lipoprotein Cholesterol; S. TG: Serum Triglyceride; FBG: Fasting Blood Glucose.*

Table 1 also shows high cholesterol level in the test subjects as compared to the control subjects. Abnormalities in lipid metabolism are very commonly observed in patients who are obese. Approximately 60-70% of patients with obesity are dyslipidemic. The lipid abnormalities in patients who are obese include elevated serum triglyceride, VLDL, LDL-C, and Total cholesterol levels. The increase in serum triglycerides is due to increased hepatic production of VLDL particles and a decrease in the clearance of triglyceride rich lipoproteins. HDL cholesterol levels are typically low and are associated with the increase in serum triglycerides. Patients who are obese are at an increased risk of developing cardiovascular disease and therefore treatment of their dyslipidemia is often indicated [11]. Small dense LDL particles have a decreased affinity for the LDL receptor resulting in a prolonged period of time in the circulation. These small particles enter the arterial wall more easily than large particles and then they bind more avidly to intra-arterial proteoglycans, which traps them in the arterial wall. Finally, small dense LDL particles are more susceptible to oxidation, which could result in an enhanced uptake by macrophages. The greater the increase in BMI, greater is the observed abnormalities in lipid levels. Approximately 60 - 70% of patients who are obese are dyslipidemic while 50 - 60% of patients who are overweight are dyslipidemic [8].

Table 2 shows that baseline hsCRP changed with significant differences among the three BMI groups while no significant change was observed for IL-6 level in these subjects. Studies have shown that obesity related metabolic syndrome is associated with increase in the levels of a number of markers of inflammation especially CRP, which further leads to increased risk for cardiovascular disease and diabetes [12]. Detection of this systemic inflammation marker may help in the identification of individuals who are at high risk for developing cardiovascular disease and diabetes [12]. Obesity leads to metamorphological changes in the body that further causes metabolic disorders in various tissues such as skeletal muscle, liver, cardiovascular, integument, pulmonary, cerebral and coronary arteries. Elevated hs-CRP in obese people shows frequent episodes of infections. Excessive secretion of IL-6 activates the hepatic pathways to release the large amount of acute-phase proteins CRP in circulation through feedback mechanism [13]. Experimental cross-sectional studies have shown that CRP along with IL-6 are contributing in the development of hyperglycemic, insulin resistance and Type 2 diabetes mellitus [14].

BMI group	WC/HC ratio (cm)	hs-CRP Mean (Range)	p-value	IL6 Mean (Range)	p-value
1	< 25	0.22 (0.07-0.44)	0.029	3.12 (2.24-7.60)	0.53
2	= 26 - 30	0.40* (0.22-0.99)	0.006	3.12 (2.27- 5.57)	0.32
3	> 30	0.86* (0.53-2.04)		3.97 (2.27- 11.13)	

Table 2: *Baseline hs-CRP and IL-6 level in the three BMI groups.*
**p value < 0.05, Abbreviations: hsCRP: High Sensitivity C-Reactive Protein; IL-6: Interleukin-6.*

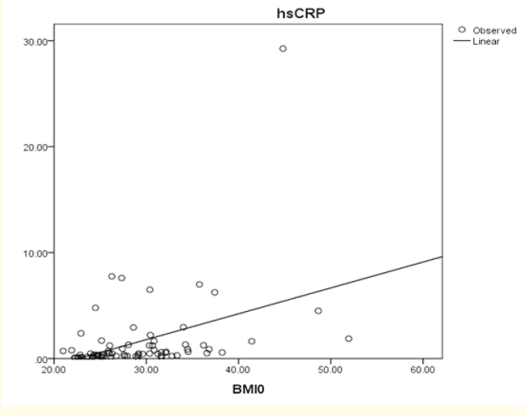

Figure 1: *Correlation between BMI & baseline hs-CRP (r = 0.505; p < 0.001).*

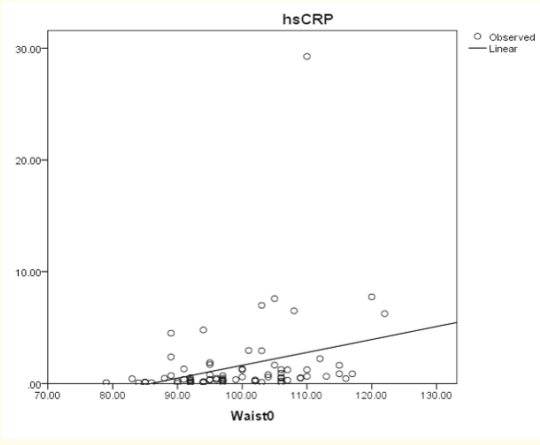

Figure 2: *Correlation between Waist Circumference and hs-CRP. (r = 0.40; p < 0.001).*

CRP a liver derived pentraxin, that is associated with increased cardiovascular risk even in the absence of acute inflammation. In past few years, it has emerged as one of the most promising biomarker for future cardiovascular events and peripheral vascular diseases in the obese individuals. CRP might also promote the formation of intimal neovessels in vulnerable atherosclerotic plaques resulting into the increased likelihood of plaque rupture [15]. Many research studies have tested the use of CRP level as a potent marker for the initiation and monitoring of treatment in obese individuals.32 Obesity activates the pathways for the production of abnormal adipokine and cytokines which can be considered as biological markers of inflammation [15].

Obesity-induced inflammation has been considered as a protective mechanism, which stops the body from losing activity or fitness by storing the fat in tissues and organs by anabolic process. Inflammation is also a catabolic process which breaks down the organs and tissue to control the body weight within the normal limits [16]. The accumulation of macrophage and lymphocyte in adipose tissue might contribute to the pathogenesis of obesity associated disorders but in recent research studies it has been found that adipose tissue acts as a secretory organ, which synthesizes various hormones, peptides and cytokines, which are involved in food intake regulation, inflammation, coagulation and blood pressure control, glucose and lipid metabolism [16]. All the individuals included in this study were also interviewed for the risk factors i.e. hypertension, hyperlipidemia, diabetes mellitus, drug intake, alcohol and smoking and found that these conditions did not illustrate any relation with obesity and levels of hs CRP. In obese individuals the non-pharmacological methods such as weight loss, food habits and regular exercise may help in controlling the CRP to attain a normal level, which may help to reduce the risk of development of various diseases.

Conclusion

We conclude that, hs-CRP was significantly correlated with obesity indices and metabolic markers in obese subjects. Positive relationships were seen for hs-CRP levels and obesity indices which include weight, BMI, WC, HC and WHR. These findings suggest that, even small differences in obesity indices may affect inflammation and metabolic indices among obese subjects. It may imply that weight reductions in these groups of subjects may have the potential to help these populations in terms of cardiovascular and metabolic benefits. Thus, these metabolic characters along with hs-CRP can be used as markers to monitor the health issues in obese subjects. Sustained inflammation is considered a strong risk factor for developing many diseases including CVDs, metabolic syndrome, diabetes, and cancer. As a risk factor, obesity predisposes to a pro-inflammatory state via increased inflammatory mediators IL-6 and TNF-α. IL-6 is linked more to the obese state that influences the liver to synthesize and secrete CRP, which is a feature of systemic inflammation.

These inflammatory states are followed by vascular and endothelial dysfunction and characterized by decreased nitric oxide and elevated reactive oxygen species leading to oxidative stress. Oxidative stress and inflammation if left untreated, further initiates multiple chronic medical complications like atherosclerosis, hypertension, alteration of metabolic markers, and thus major adverse cardiovascular events.

Competing Interest

The authors declare that there is no competing interest.

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