Original Article

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Internal Medicine Section

Association between Overweight, Obesity in Relation to Serum hs-CRP Levels in Adults 20-70 Years

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ABSTRACT

Introduction: The prevalence of overweight and obesity is progressively increasing in general population of India. There is a growing concern for obesity related morbidity and mortality. High sensitivity C-reactive Protein (hs-CRP), is an emerging inflammatory marker and a predictor of diabetes mellitus and ischaemic heart disease.

Aim: To study the relationship of hs-CRP with Fasting Blood Sugar (FBS), Body Mass Index (BMI), Waist Circumference (WC), Waist-Hip Ratio (WHR), and fasting lipid profiles of obese and overweight normotensive and normoglycaemic subjects.

Materials and Methods: The cross-sectional study was conducted on 228 subjects of age between 20-70 years from October 2014 to June 2016. The study included three groups of subjects based on BMI. Descriptive statistics were used for normally distributed variables. Pearson's correlation coefficient was used to find out the relationship among hs-CRP levels and different parameters in all groups. Linear regression analysis and multiple linear regression analysis were done to find out the independent factors affecting hs-CRP and to assess the final predictor of its variability.

Results: Out of 228 subjects, 87 (38.15%) had normal BMI, followed by 64 (28%) and 77 (33.78%) subjects were overweight and obese respectively. About 75% of overweight and 93.5% of obese subjects had high levels of hs-CRP respectively. About 68.2% of subjects with impaired blood sugar level had high levels of hs-CRP. Pearson's correlation coefficient ratio revealed moderate correlation of Total Cholesterol (TC), Low-Density Lipoprotein (LDL), TC/HDL (Total Cholesterol and High Density Lipoprotein) WHR with hs-CRP, with p-value <0.01. Linear regression analysis of various parameters with hs-CRP showed positive association (p<0.001) except Triglyceride (TGL) and negative association with HDL. FBS, BMI, WC, LDL, TC/HDL were found to be very significantly associated with hs-CRP on multiple regression analysis.

Conclusion: Overweight and obesity have significant correlation with hs-CRP, suggesting obesity is a state of chronic inflammation, and hence, hs-CRP levels can be used in assessing future morbidity risk. With an increasing prevalence of obesity in India in recent years, which has a major adverse impact on the socioeconomic and healthcare sectors of the country, hs-CRP can be used to assess the risk of obesity related disorders for an early intervention.

Keywords: Body mass index, Diabetes mellitus, Interleukin-6, Overweight

INTRODUCTION

Overweight and obesity in India is a major growing health concern due to its increasing prevalence in younger and adult population [1,2]. This makes those people vulnerable to various metabolism related diseases like diabetes mellitus, hypertension, ischaemic heart disease and cerebrovascular accidents and cancers [2,3]. Accumulation of fat may be due to excess calorie intake, lack of exercise, and interaction of various socioeconomic, environmental and genetic factors [2,3]. Adipose tissue produces numerous pro-inflammatory cytokines such as Interleukin-1 (IL-1), Tumour Necrosis Factor-α (TNF-α) and Interleukin-6 (IL-6) which are important factors in the synthesis of hs-CRP in liver. Elevated hs-CRP levels help in predicting future risk of diabetes mellitus, ischaemic heart diseases, and cerebrovascular accidents in healthy obese people [3,4,5].

We studied the association between overweight and obesity based on BMI in relation to serum hs-CRP levels. We individually assessed the relationship between hs-CRP and Fasting Blood Sugars (FBS), central obesity, and fasting lipid profile.

MATERIALS AND METHODS

The current cross-sectional study was conducted at outpatient Department of Medicine, in Kasturba Hospital, Manipal from October 2014 to June 2016. Ethical clearance was taken from Kasturba hospital's ethical committee before the start of the study (IEC NO. 615/2014). Total 228 subjects who came for routine health check-up were included after written and informed consent. The specific questions were asked regarding subjects selection criteria. Data were collected after physical examination and laboratory investigations.

Selection of Participants

The study included three groups of normotensives, normoglycemic adults of the age group 20-70 years based on BMI as Normal BMI (18.5-22.9 kg/m^2), overweight (23-24.9 kg/m^2) and obese (BMI>25 kg/m^2), according to Asian standards by WHO [Table/Fig-1] [6]. The study excluded those patients who had diabetes mellitus, malignancy, hypertension and Cardiovascular Disease (CVD), endocrinal and metabolic disorders, bronchial asthma, Chronic Obstructive Pulmonary Disease (COPD), autoimmune disorders, inflammatory diseases, and infectious diseases. The study also excluded those subjects who were smokers, who were on steroids, statins, anti-inflammatory drugs and who consume alcohol.

Parameters used

Height (m) was measured with the patient standing against an upright surface touching it with heels, buttocks and back on a level smooth surface. Subject wearing normal clothing was made to stand in the centre of on an electronic weighing machine. Weight (kg) was recorded. Calculation of BMI was done using the formula as Weight (kg)/ Height (m^2). Waist Circumference (WC) was measured in the

middle of lower margin of ribs and the upper border of iliac crest at the completion of regular expiration. The hip circumference was measured accurately at the greater trochanters level where buttocks protrude the maximum. The limit for WC for men and women were 90 cms and 80 cms respectively. WHR limit for men and women were 0.9 and 0.85 respectively [6]. FBS, lipid parameters and serum hs-CRP levels were estimated in subjects, who were overnight fasting (approximately 12 hours) since last dinner by drawing blood samples. The range of normal FBS and Impaired FBS were 70-100 mg/dL and 101-125 mg/dL respectively. As per ATP III guidelines the normal range of TC is 140-200 mg/dL and TGL is 60-150 mg/dL. The normal levels of HDL Cholesterol and LDL Cholesterol are 40-60 mg/dL and 50-130 mg/dL respectively. The normal level of hs-CRP in adults is <5 mg/L [7].

Laboratory Analysis

Under aseptic precautions, blood samples were drawn, centrifuged within one hour to obtain serum/plasma for the estimation fasting lipid profiles, plasma glucose and hs-CRP levels using fully automated Roche/Hitachi Cobas E601 clinical chemistry analyzer. FBS was determined by Hexokinase method [8]. The quantitative determination of TC in serum and plasma was done by enzymatic, colorimetric method with Cholesterol Oxidase-Peroxidase (CHOD-POD) [9]. Triglycerides levels were estimated by colorimetric end point-Glycerol Phosphate Oxidase, Phenol+Aminophenazone (GPO-PAP) [10]. Estimation of HDL-Cholesterol was done by direct homogenous enzymatic colorimetric method [11]. LDL Cholesterol was calculated as: Total cholesterol- (HDL-TG/5) [12]. Quantitative estimation of hs-CRP level was done by particle enhanced turbidimetric assay using COBAS INTEGRA 400 plus clinical chemistry analyser [13].

STATISTICAL ANALYSIS

Statistical analysis was performed using SPSS version 16.0 for windows. Descriptive analysis was done (Mean and Standard Deviation) to analyse the continuous variables in normal distribution. Median and interquartile range was used to summarise skewed variables. Pearson's correlation coefficient was used to find out the relationship among hs-CRP levels and different parameters in all groups. Linear regression analysis and multiple linear regression analysis was done to find out the independent factors affecting hs-CRP and to assess the final predictor of its variability. It was considered statistically significant when a p-value of <0.001.

RESULTS

Total 228 subjects were analysed in three groups according to BMI as normal, overweight and obese. A total of 127 (55.70%) were males and 101 (44.30%) were females. Out of total patients, 87 (38.15%) patients had normal BMI, followed by 64 (28.07%) and 77 (33.78%) patients were overweight and obese, respectively.

In view of skewed distribution, the median, interquartile value was calculated for WHR with median of 0.891 and, IQ of 0.13, hs-CRP (mg/L) with median of 5.3 and IQ of 6, and TC/HDL with median of 5.19 and IQ-3.04). [Table/Fig-2] showed that hs-CRP values are higher in overweight and obese subjects. [Table/Fig-3] showed higher hs-CRP levels are seen in majority of subjects with IFG level. [Table/Fig-4] indicates in both female and male subjects high WC is associated with high hs-CRP levels. [Table/Fig-5] showed the relationship between hs-CRP and lipid parameters. As shown, hs-CRP correlated positively with most of the parameters.

On Linear regression analysis, all the anthropometric parameters, FBS and lipid parameters are significant predictors of hs-CRP level except TGL. Among lipid parameters, HDL is a negative predictor yet was significant with p<0.001. Out of all lipid parameters TGL, TC, HDL were not considered as significant predictors i.e., only LDL and TC/HDL were considered to have significant contribution. As TGL was not significant, it was eliminated, and further multiple regression analysis was done with other variables. Multiple regression analysis of variables with hs-CRP showed that there was quite significant correlation with BMI, WC, WHR, LDL, FBS, TC/HDL with p-value <0.001 [Table/Fig-6].

Characteristics	Mean±SD
Age (years)	48.65±15.22
BMI (kg/m^2)	24.86±5.30
FBS (mg/dL)	101.61±11.70
WC (cm)	86.87±12.03
TC (mg/dL)	160.51±51.23
TGL (mg/dL)	131.85±63.15
HDL (mg/dL)	33.40±16.11
LDL (mg/dL)	1.3±46.43

[Table/Fig-1]: Baseline features of studied population.
BMI-Body Mass Index, FBS-Fasting Blood Sugar, WC-Waist Circumference, TC-Total Cholesterol, TGL-Triglyceride, HDL-High Density Lipoprotein, LDL-Low Density Lipoprotein.

	N	Normal hs-CRP	High hs-CRP	Mean±SD hs-CRP	Minimum hs-CRP	Maximum hs-CRP
Normal BMI	87	86 (98.9%)	1 (1.1%)	2.37±1.31	0.20	8.30
Overweight	64	16 (25%)	48 (75%)	6.63±2.55	2.30	12.00
Obese	77	5 (6.5%)	72 (93.5)	10.22±3.22	2.50	18.00
Total	228	107 (47%)	121 (53%)	6.18±4.13	0.20	18.00

[Table/Fig-2]: Indicates hs-CRP values across three groups.
hs-CRP values are higher in overweight and obese subjects.
hs- CRP- High Sensitivity C-Reactive Protein

FBS	Normal hs-CRP	High hs-CRP	Total
Normal (<100 mg/dL)	72 (61%)	46 (39%)	118
IFG (100-125 mg/dL)	35 (31.8%)	75 (68.2%)	110
Total	107 (47%)	121 (53%)	228

[Table/Fig-3]: Categorisation of FBS and hs-CRP.
Higher hs-CRP levels are seen in majority of subjects with IFG level.
IFG-Impaired Fasting Glucose, FBS-Fasting Blood Sugar.

	Gender	Normal hs-CRP	High hs-CRP	Total
Normal WC	M	46 (36.2%)	45 (35.4%)	91
	F	37 (36.6%)	6 (5.9%)	43
High WC	M	1 (0.8%)	35 (27.6%)	36
	F	23 (22.8%)	35 (34.7%)	58
Total	M	47 (37%)	80 (63%)	127
	F	60 (59.4%)	41 (40.6%)	101

[Table/Fig-4]: Distribution of WC with normal and abnormal hs-CRP levels.
In both female and male subjects high WC is associated with high hs-CRP levels.
WC- Waist Circumference, hs-CRP-High Sensitivity -C-Reactive Protein.

hs-CRP v/s	Pearson's Correlations coefficient (r)	p-value
TC	0.350**	<0.01
TGL	0.116	0.081
LDL	0.425**	<0.01
TC/HDL	0.455**	<0.01
WHR	0.432**	<0.01

[Table/Fig-5]: Pearson's correlation of Lipid profile and Waist Hip Ratio with hs-CRP.
**p-value <0.01 is significant.
hs-CRP correlated positively with most of the lipid parameters and WHR except TGL.
TC- Total Cholesterol, TGL-Triglyceride, LDL-Low Density Lipoprotein, TC/HDL-Total Cholesterol/High Density Lipoprotein, WHR-Waist Hip Ratio.

DISCUSSION

The present study, found a substantial positive relationship between BMI and hs-CRP and the mean hs-CRP levels were higher in overweight and obese people when compared with people with

Linear regression analysis				Multiple linear regression analysis		
Independent variable	B	β	p-value	B	β	p-value
BMI	0.541	0.69**	<0.001	0.297	0.383 **	<0.001
WC	0.239	0.7**	<0.001	0.076	0.223 **	<0.001
WHR	18.375	0.43**	<0.001	7.65	0.180 **	<0.001
TC	0.028	0.35**	<0.001	0.007	0.084	0.197
TGL	0.008	0.116	0.081	-	-	-
HDL	-0.062	-2.42**	<0.001	-0.007	-0.029	0.694
TC/HDL	0.580	0.455**	<0.001	0.431	0.339**	<0.001
LDL	0.38	0.425**	<0.001	0.38	0.425**	<0.001
FBS	0.108	0.38**	<0.001	0.050	0.143**	<0.001

[Table/Fig-6]: Linear regression and multiple linear regression analysis with hs-CRP as a dependent variable.
**p-value<0.001is highly significant.
BMI-Body Mass Index, WC-Waist Circumference, WHR-Waist- Hip-Ratio, TC-Total Cholesterol , TGL-Triglyceride WHR-Waist Hip Ratio, HDL-High Density Lipoprotein, TC/HDL-Total Cholesterol/ High Density Lipoprotein, LDL-Low Density Lipoprotein, FBS-Fasting Blood Sugar.

normal BMI. These results are in accordance with Montenegro study, Aronson D et al., Kao TW et al., and Lin CC et al., studies [5,14-16].

The current study showed a positive correlation between BMI and central adiposity with hs-CRP. Waist Circumference showed a significant positive correlation and WHR showed a moderate significant correlation with hs-CRP. Similar positive relationship was established between central obesity (WC) and hs-CRP levels by Kao TW et al., and Lapice E et al., which demonstrated that abdominal adiposity is connected with higher C-reactive protein which was independent of BMI [15,17]. Festa A et al., showed that WHR was considerably correlated with hs-CRP in both the genders [18]. Studies consistently revealed WHR was not a better predictor among risk factors for CVD particularly in men [19,20]. Waist Hip Ratio gives evidence of local adipose tissue distribution; however, WC is an indicator of central obesity [16]. Indians have increased total body fat and increased accumulation of truncal and abdominal fat [21]. This is why many Indian people even though have normal body weight comes under the category of metabolically obese population. This typical “Asian Indian Phenotype”, with increased WC and WHR leads to hyperglycemia and premature coronary heart disease [1]. Various studies in India revealed that 10% to 30% of adolescents are overweight. Decreased physical activity, consuming more junk foodstuffs, watching television programmes and sedentary lifestyles are common in younger people. These factors are responsible for growing predominance of obesity and overweight [1].

The current study also demonstrated that, while assessing central obesity, WC is a simple tool and better predictor than WHR and correlated better with hs-CRP than WHR particularly in men than in women which was in support of previous studies [17,22,23]. Similar results were demonstrated by Lin CC et al., in Taiwan [16]. Central obesity is found to have the strongest relationship with elevated hs-CRP levels by Florez H et al., [24]. Hence, signifying that abdomen adipose tissue is the chief source of cytokines like TNF- alpha, IL-6, which are the main determining factor of hepatic synthesis of hs-CRP. These inflammatory mediators lead to endothelial dysfunction and atherosclerosis, which play major part in the pathogenesis of ischaemic heart disease and other obesity linked morbidity [16,18].

Hyperglycemia particularly both impaired and elevated FBS has been implicated in the inflammatory process and pathogenesis of metabolic disorders, it can possibly stimulate the synthesis of hs-CRP even in non-diabetics observed in our study which is in accordance with previous studies [3,4,25,26]. Various other studies conducted by Kawamoto R et al., [27] and a community-based study by Doi Y et al., [28] also consistently yielded the same results.

The current study found mild negative correlation with HDL. HDL cholesterol has reliably revealed to have an inverse relationship with systemic inflammatory markers in various prospective studies. Latest proofs support an extensive collection of antiatherogenic properties by HDL-cholesterol, together with anti-inflammatory effects [29].

In the current study, there is a moderate positive correlation of hs-CRP with all lipid parameters which was significant except for TGL with Pearson correlation and further by regression analysis. In Montenegro study among all lipid parameters, hs-CRP has moderate negative correlation with HDL whereas TGL, LDL and TC were poorly correlated and were not statistically significant [5]. Similar results were found in a study done by Vidyasagar S et al., where, TGL and HDL were not significant predictors of hs-CRP [30]. In earlier published articles, affirmative correlations were established among levels of hs-CRP and blood glucose, triglycerides and BMI, and negative associations were established with HDL cholesterol levels [31-33].

The increase of the body adipose tissue gives rise to the increased synthesis of pro-inflammatory molecules and leads to low-grade inflammation. Thus, hs-CRP can be an early unique inflammatory indicator in the healthy obese people. Interventional measures like change in nutritional habits, life styles modification and increase in physical activity to lose of weight can be advised at the earliest and prevent future morbidities [14].

LIMITATION

Most important drawback of this study was smaller sample size, and this was a cross-sectional study. We used only one hs-CRP measurement that possibly not perfectly reveals long-term inflammatory status in the body. The biological variability of hs-CRP ranges from 10.6% to 63%. The IL-6 is an important factor in the synthesis of hs-CRP is secreted in an endocrine fashion in proportion to the enlargement of total body fat mass, principally the abdominal fat. The serum level measurements of IL-6 were not done in the current study. Even though the results backing the postulate that IL-6 manufactured by the adipocytes enhances hs-CRP concentration, direct estimation of IL-6 concentration is required in future studies to test this theory.

CONCLUSION

Obesity is a state of chronic inflammation, which has a significant correlation with hs-CRP. Waist circumference is a better predictor of central obesity in men, which correlates well with hs-CRP levels. In India, there is an increasing prevalence of obesity in both younger and adult population due to various factors, which has a severe adverse impact on socio-economic and healthcare sectors. hs-CRP is a new marker of a future cardiovascular disease which can be used to assess the risk and to initiate early intervention.

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