ORIGINAL ARTICLE

RISK STRATIFICATION OF BODY MASS INDEX

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ABSTRACT

Introduction: Body Mass Index (BMI) is the simplest & commonly used method of measuring obesity in a general population. BMI has its limitations as it does not directly measure body fat, it is an indicator of heaviness rather than fatness, & cannot distinguish body fat from fat-free mass. Highly sensitive C reactive protein (hs CRP) has been found to be increased in subjects with central obesity& it may be useful in sub classifying BMI.

Objective: To investigate the relationship between BMI and hs-CRP in healthy subjects & to evaluate feasibility of using hsCRP as a tool for risk stratification of BMI

Material & methods: 79 normal healthy adult volunteers, age 18 to 25 years were enrolled for the Study. a detailed general physical & laboratory evaluation, BMI & hsCRP was done. Subjects were grouped as Group A: BMI <23.9 (n= 50) and Group B: > 24 (n=30).

Results: Mean age 19 +1.7 years. Male: 41.3% & Female: 58.8%. Mean BMI of the Study population was 22.37+4.0 and the mean hsCRP was 1.43 + 2.1. Group B subjects with higher BMI were significantly taller with higher waist hip ratio & their hsCRP was also significantly higher (A v/c B - 1.03 v/s 2.03) p <0.03. In both groups at various BMI cutoff values, hs CRP significantly increased with increasing BMI.

Conclusion: Link between obesity and inflammation is evident by raised hsCRP in obese individuals with higher BMI. hsCRP can be used to sub-classify BMI into high and low risk normal subjects

Key words: BMI, hsCRP, Body mass index, C reactive protein, Obesity, Screening, CRP-hs, Highly Sensitive C Reactive Protein.

INTRODUCTION

Obesity is an epidemic of the 21st century and is a major causative factor for many metabolic disorders in both developed and developing nations. Many Asian countries also face a grave burden of obesity-related disorders of increasing burden of non communicable disease such as diabetes, hypertension, and cardiovascular diseases, which develop at a younger age than in Western populations[1,2].

The most common method of measuring obesity in a population for monitoring the underlying increase in health risk is the Body Mass Index (BMI). BMI is a simple index of weight-for-height that is commonly used to classify underweight, overweight and obesity in adults. It is defined as the weight in kilograms divided by the square of the height in metres (kg/m2) BMI is popular because it is simple, quick, effective and applies to adult men and women, as well as children [3-9].

BMI has limitations, it does not directly measure body fat, it is more accurate at approximating degree of body fatness than weight alone. BMI does not have exact weight or measurement, to be considered 'normal.' There is a range within each classification to allow for different body types and shapes. very muscular individuals often fall into the overweight category when they are not overly fat. BMI is an indicator of heaviness rather than fatness, and cannot distinguish body fat from fat-free mass [10].

Highly sensitive C-reactive protein (hs CRP) an exquisitely sensitive systemic marker, an acute-phase protein which rise in response to inflammation & tissue damage, it activates the complement system via the C1Q complex [1,11-13]. CRP is not only produced within the liver, but also appears to be produced in both visceral fat and within coronary vessels. CRP even within the range previously considered normal is strongly predictive of the future risk of heart attack, stroke, sudden cardiac death [3-5,14-16].

hs-CRP levels has been found to correlate significantly hyperinsulinemia, insulin resistance, hypertriglyceridemia etc [17-20]. elevated hsCRP levels have been seen in children and adolescents with excess weight as compared to normal-weight individuals. The possible physiological mechanisms linking elevated hs-CRP to these disorders is partly mediated by adipose tissue, a main source of inflammatory cytokines [21,22]. With early rec-

ognition of metabolic syndromes preventive measures can be instituted.

Rationale for the study: Body mass index (BMI) is a commonly used measure of obesity, it is an indicator of heaviness rather than fatness, and cannot distinguish body fat from fat-free mass. CRP has been found to be increased in subjects with central obesity. CRP may be useful in sub classifying BMI a clinical measure for identifying individuals at low and high risk in healthy ranges [7]. The current study was designed to explore the correlation between indicators of obesity like BMI, WC, and WHR, and hs-CRP.

Objective of the study was to investigate the relationship between BMI and high-sensitivity C-reactive protein (hs-CRP) in healthy subjects and to look at the feasibility of BMI risk stratification using hsCRP

MATERIAL AND METHODS

80 normal young adult volunteers in the age range of 18 to 25 years were enrolled for the Study. Volunteers who satisfied the inclusion and exclusion criteria, were educated regarding the study, an Informed consent was obtained as per ICH GCP good clinical practice guidelines. Subjects with Infections, inflammatory diseases, tissue injury & Corticosteroids medications were excluded from the study. There was no financial liability on the study subjects.

All subjects underwent a detailed general physical examination including Blood Pressure, body weight, height, hip & waist circumference. All measures were done while subjects wore light clothes without shoes and BMI (Body Mass Index), waist and hip circumference & waist hip ratio calculated. The normal healthy study subjects were grouped as Group A : BMI <23.9 and Group B: > 24.

Concentrations of total cholesterol, triglyceride & HDL cholesterol were determined by enzymatic kinetic method using an auto analyzer. VLDL cholesterol level was calculated using the formula Triglyceride/5 & LDL using the formula [Total Cholesterol – (HDL + VLDL)]. A standard OGTT was performed on all subjects and Blood sample was analyzed for hsCRP. Fasting (basal), 30, 120 min venous plasma glucose and Insulin was measured. The serum plasma was stored at - 20 degree C until assayed. Highly sensitive C- reactive protein (hs CRP) was assessed from fasting sample by turbidimetric method.

Insulin Resistance was calculated wish mathematical models like, Homeostatic model assessment HOMA-IR. HOMA %B, Insulin Sensitivity Index ISI 0-120. The data was systematically collected in the case record form designed for the study.

Statistical Analysis:

The Student t test and Mann Whitney U test have been carried out to find the significant difference between various BMI parameters & Indices between subjects in Group A & B. The Statistical software namely SPSS 10.0 and Systat 8.0 were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables etc.

RESULTS

This is a prospective study of 80 healthy subjects in south Indian urban agglomerate. The mean age of the study population was 19 + 1.7years (18 to 25). The Sex distribution was Male: 41.3% (33) and Female: 58.8% (47). Mean BMI of the Study population was 22.37+4.085 and the mean hsCRP was 1.434 + 2.10.

In Group A : BMI <23.9 there were 50 subjects and in Group B: BMI > 24 there were 30 subjects. The study subjects Clinical characteristics in both the healthy Groups were similar. Group B subjects with higher BMI were significantly taller with higher waist hip ratio (Table 1). BMI in Group Ranged from 14.7 to 23.78 and Group B ranged from 24.11 to 39.48. Siblings of Diabetics had significantly higher BMI.

Table 1: Clinical Characteristics of Study Participants

	Group A: BMI < 23.9 (n=50)		Group B: BMI >24 (n=50)		P value (2-tailed)
	mean	SD	mean	SD	
Age	18.94	1.66	19.13	1.78	0.624
Male	20		13		0.631
Female	30		17		
Systolic BP (mmHg)	118.96	6.34	120.93	5.87	0.17
Diastolic BP(mmHg)	74.24	5.02	74.73	6.02	0.162
Siblings of Diabetics	40% (n=20)	49%	67% (n=20)	48%	0.021
Height (cms)	163.708	9.14	162.953	9.91	0.02
Weight (cms)	53.65	8.441	69.767	11.04	0.736
Waist (cms)	70.12	7.48	83.317	9.994	0
Hip (cms)	87.92	6.432	100.567	6.218	0
Waist Hip Ratio WHR	0.7965	6.36E-02	0.8267	7.14E-02	0.053

Comparison of Laboratory parameters in these healthy groups (Table 2) shows that Group B subjects with higher BMI had significantly higher Total cholesterol, triglycerides and LDL. The hsCRP was also significantly higher Group A: 1.03 v/s Group B : 2.03 (p <0.03).

Table 2: Lab Characteristics of Study Participants

	Group A: BMI < 23.9 (n=50)		Group B: BMI >24 (n=50)		Significance (2-tailed)
	Mean	SD	Mean	SD	
Total Cholesterol	152	27.064	165.533	23.218	0.025
Triglycerides	94.78	28.005	98.667	28.389	0.021
HDL	40.3	5.019	41.267	4.283	0.382
VLDL	18.58	4.725	19.7	5.621	0.342
LDL	93.428	28.446	104.233	22.266	0.079
hs CRP	**1.03878**	2.03304	**2.08**	2.08747	0.032
Glucose 0min	81.88	9.591	81.333	10.807	0.172
Glucose 30min	106.58	19.153	118.433	23.101	0.015
Glucose 120min	88.74	15.544	96.6	23.221	0.022
Insulin 0min	7.48	5.042	9.733	8.143	0.708
Insulin 30min	66.048	56.174	73.5	62.967	0.179
Insulin 120min	33.176	29.642	44.207	37.133	0.596
HOMA_IR	1.53756	1.10752	1.94881	1.56937	0.107
HOMA %B	181.89%	157.59	352.7	549.43%	0.042
ISI(0-120)	66.9201	22.9313	58.1182	21.5915	0.093

Comparison of OGTT parameters and the Insulin Resistance and Sensitivity parameters (Table 2) reveal that subjects in Group B with higher BMI have significantly higher 30min and 120 min Glucose, though within normal limits. Group B subjects with higher BMI had Insulin Sensitivity Index like % B Cell activity significantly higher 594% as against 181% in lower BMI and a trend towards significance was observed for ISI 0-120 with lower Insulin sensitivity index in high BMI subjects.

Subjects were stratified by BMI at various cutoff values quartiles ranging from 22 to 28. hsCRP significantly increased with increasing BMI (Table:3).

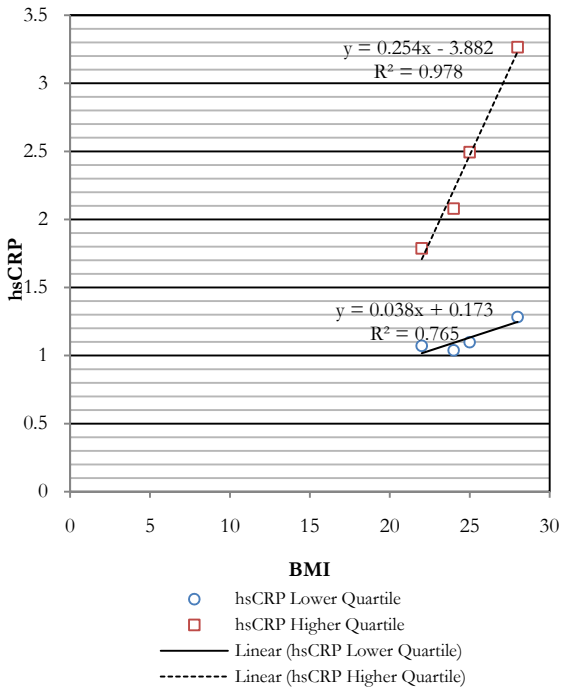
Table 3: Correlation BMI & hsCRP

BMI	hsCRP	Significance p value
24	2.08	0.033728
25	2.494737	0.010726
28	3.266667	0.025412

The subjects were grouped into lower quartiles and higher quartiles at various BMI cutoff values and hsCRP was found to significantly increase as BMI increases , subjects in lower quartiles also showed an increase in hsCRP as BMI increased but within near normal ranges of less than 1.5 hsCRP, higher quartile subjects always showed hsCRP values > 1.5(Figure 1).

DISCUSSION

The impact of obesity has been considerable in both developed and developing countries. Overweight and obesity have reached epidemic proportions in many Asian countries. And the population at large are bound to face a grave burden i.e, increase by many folds of obesity-related disorders such as diabetes, hypertension, cardiovascular diseases & cancers etc, which develop at much younger age than in Western populations. The major causative factors being lifestyle changes occurring due to rapid socioeconomic transition[1,2,11]. Early detection and prevention plays a key role in tackling this potentially huge economic and health care burden of the obesity-related disorders [24].



Risk Stratification of BMI with hsCRP: Blue: Low / High BMI subjects - demonstrate increasing hsCRP with increasing BMI

Figure 1: Subjects with BMI < 23.9 and BMI >24, hsCRP increases with increasing BMI in both the groups

Most epidemiologic studies identifying strong associations between hs-CRP and obesity indicators predominantly use anthropometric indexes [17-24]. Consequently, a strong positive association has been found between measures of obesity, such as waist circumference (WC) and body mass index (BMI), with CRP [25,26]. Moreover,

while some studies have observed a relationship between T2D and higher CRP levels [27].

In a study from India, by Ambika et al, there has been a significant increase in abdominal obesity in both sexes in the last two decades, The prevalence of overweight rose from 2% to 17.1% [27]. Prevalence of overweight/obesity among Adolescents (14-18 yrs) in Delhi is reported to be 29.0%. The risk of diabetes increases with a body mass index (BMI) of >23 kg/m2 and waist circumference of 85 cm for men and 80 cm for women in Asian Indians[3]. In our study subjects with BMI > 24 had significantly higher waist circumference (83.3cms+9.9).

Oliveira et al in a study of 1319 subject, 833 women and 486 men in Portugal. reported central obesity has been shown to be significantly associated with increased levels of the inflammatory marker hs-CRP in men, while a high proportion of peripheral subcutaneous fat was inversely associated with hs-CRP in women[28].

In a study from Egypt, 150 children in the age range 6-16, BMI was 27.20 ± 12.30 kg/m2 in the obesity group and was 16.68 ± 2.00 kg/m2 in the control group. Obese group (n=100) had significantly higher hs-CRP levels than control group, hs-CRP levels were 1.40 ± 0.78 mg/dL vs. 0.56 ± 0.47. mg/dL, $p < 0.01$ [29]. a similar picture was seen in our study, subjects with BMI >24 had significantly higher hsCRP values 2.08+2.08 compared to 1.03+2.0(normal range) in subjects with BMI<23.9 [30].

Den Engelsen et al. In a study of 1721 participants , mean age 48.4 years, The median hs-CRP for the total population was 1.9 mg/L (IQR 1.1-3.6) subjects with the (metabolic syndrome) MetS the median hs-CRP was 2.2 mg/L (IQR 1.2-4.0), compared to 1.7 mg/L (IQR 1.0-3.4) in the group without the MetS ($p < 0.001$) [31]. Even though our subjects were of younger age group (19+1.7), subjects with BMI >24 had hsCRP levels which are similar to those found in subjects with metabolic syndrome [32].

Our study has demonstrated that there is association between BMI and hsCRP, as BMI increases hsCRP also increases significantly. The importance of hsCRP in Sub classifying individuals into low and high risk groups within the BMI groups was also observed.

Measuring waist circumference also helps screen for possible health risks that come with overweight and obesity. Subjects with Fat around the waist rather than at hips, are at a higher risk for heart disease and type 2 diabetes. This risk goes up with a waist size that is greater than 35 inches for women or greater than 40 inches for men. The BMI of 62.5% of the health Indian adults range from 18.5-24.99, this can empirical be applied as internationally recommended BMI cut-off points. The higher BMI, the higher is the risk for certain diseases such as heart disease, high blood pressure, type 2 diabetes, gallstones, breathing problems, and certain cancers. For Indian subjects BMI is termed Underweight Below 18.5, Normal18.5–24.9, Overweight 25.0–29.9, Obesity30.0 and Above. Our health study subjects had a mean BMI of 22.3+4.08, hsCRP 1.43+2.1.

Hs-CRP being an easily measured inflammatory biomarker and is released by the liver under the stimulation of cytokines, including interleukin-6, interleukin-1, and tumor necrosis factor-alpha. It has been shown hs-CRP has associations with endothelial dysfunction and insulin resistance syndrome [33]. Although a relationship has been found between hs-CRP and DEXA-measured trunk fat [34], our findings demonstrate that hs-CRP is associated BMI, indicating that %Fat Mass is the obesity indicator that can capture the inflammatory phenomena that are responsible for the higher likelihood of diabetes and cardiovascular events.

"High sensitivity" CRP assays is a simple and inexpensive test that has been endorsed by both the Centers for Disease Control and Prevention and by the American Heart Association as a part of the routine global risk assessment to better determine risk of heart disease and prevent clinical events. levels of CRP less than 1, 1 to 3, and greater than 3 mg/L (milligrams per liter) discriminate between individuals with low, moderate, and high risk of future heart attack and stroke [19]. Despite its lack of specificity, CRP has now emerged as one of the most powerful predictors of cardiovascular risk. Even more remarkable, CRP's predictive power resides in the range between 1 to 5 μg/mL, which was previously regarded to be normal in the era preceding the high-sensitivity CRP test, hence a high sensitive assay is required [18].

High CRP concentrations significantly correlate with insulin resistance and the metabolic syndrome in adults [19,20]. Such high risk subjects are known to future development of non communicable diseases like diabetes, Cardiovasuclar diseases and others. Such sub classification with in BMI groups has relevance in early institution of Preventive measures in high risk BMI groups like Diet, Exercise and life style modification.

The WHO Expert Consultation [34] concluded that the proportion of Asian people with a high risk of type 2 diabetes and cardiovascular disease is substantial at BMI's lower than the existing WHO cut-off point for overweight (= 25 kg/m^2). However, the cut-off point for observed risk varies from 22 kg/m2 to 25 kg/m2in different Asian populations and for high risk, it varies from 26 kg/m2 to 31 kg/m2 . In addition, sub-classify subjects into high and low risk within Normal or lower BMI levels using hs-CRP was evaluated in our study. This finding of our study has important implications for obesity screening in community surveys [36].

In our study higher hs-CRP (>1mg/L) levels correlated significantly with BMI, waist circumference, WH ratio. 30min Glucose and120 insulin also correlated with hs-CRP. An important observation of this study is the presence of good correlation between hs-CRP and surrogate markers of insulin resistance especially ISI0-120 which take into account the 0 to 120 min Insulin and glucose values in efficiently interpreting the IR indices, unlike the other indices based on fasting values.

Data from the IRIS-II study also showed that hsCRP may also be a good marker of macrovascular risk in type 2 diabetic patients. In the state of pathologically increased demand on the beta cells, intact proinsulin appears in the plasma along with insulin and C-peptide due to the inability of enzymes to cleave excess proinsulin [37]. elevated levels of plasma high-sensitivity C-reactive protein (HSCRP) are associated with insulin resistance/hyperinsulinemia and cardiovascular autonomic dysfunction in type 2 diabetic patients without insulin treatment [38]. Diabetes mellitus (DM) counts as a CHD risk equivalent. In our study subjects % Beta was significantly higher in subjects with BMI>24.

C-reactive protein (CRP) has been shown to be associated with type 2 diabetes, but whether CRP has a causal role is not yet clear. A meta-analysis of Rotterdam Study to evaluate the association of baseline serum CRP and incident diabetes during follow-up was investigated. The risk of diabetes was significantly higher in the haplotype with the highest serum CRP level compared with the most common haplotype (OR 1.45, 95% CI 1.08–1.96). These findings support the hypothesis that serum CRP may also play role in the development of diabetes [39]. Obesity prevention and controlling for CRP levels may be necessary to eliminate its contributions to develop diabetes and cardiovascular disease (CVD)

Wajiha Farooq et al in their study on subject in the age group 39.1±11.3years. Subject with BMI <29 had hsCRP of 1.49± 0.91mg/dl, compared to BMI >30 with hsCRP 2.06±0.71(p value <0.01) [29].

Deniz Gokalp et al evaluated 117 healthy subjects aged with 20–68 yr, normal weight (BMI 18.5–25.0 kg/m2, *n*:35), overweight (BMI: 25–30 kg/m2, *n*:27) and obese (BMI ≥30.0, *n*: 55). Mean serum hs-CRP levels of obese group determined with BMI were higher than overweight and normal weight groups (7.3±5.46, 2.5±3.13, 0.66±1.1, respectively, *P*=0.0001). hs-CRP levels were positively correlated with BMI. They concluded that hs-CRP level were high in obese patients and there was close relationship between BMI and HS-CRP serum levels, similar to our findings [40].

Yang SP et al, in a study of 70 obese children and adolescents (age 8 - 17 years) and 30 non-obese healthy controls (12.6 years), found that there was significant increase of serum hs-CRP level in obese children and adolescents, the median was 2.44 (0.01 - 14.6) mg/L; the level of control group was 0.1 (0.01 - 2.1) mg/L. Multiple linear regression analysis showed that body mass index (BMI) was the only indicator which had correlation with hs-CRP. They opined that There may be a chronic low-grade inflammation and insulin resistance in obese subjects and the level of hs-CRP might be independently correlated with BMI in children [31].

A similar correlation was found in our study subjects, their hsCRP levels were found to significantly increase as BMI increases even in the Low and high BMI groups at various cutoff values. Subjects in lower BMI quartiles also showed an increase in hsCRP as BMI increased but within near normal ranges of less than 1.5 hsCRP, higher quartile subjects always showed hsCRP values > 1.5.

In this study significant increase in hsCRP was seen with increasing BMI and Waist Circumference which are clinical markers of Insulin Resistance. It was also observed that as Insulin Resistance increases hsCRP also increases. This finding of this study point to a significant role BMI in combination with a simple blood test of hsCRP can play in the early detection of future metabolic syndromes.

CONCLUSION

Link between obesity and inflammation is evident by raised hsCRP in obese individuals with higher BMI. Inflammation also plays role in atherosclerosis and other metabolic syndromes, thus it is important to screen and spread awareness regarding obesity and its outcomes in our community. BMI is a useful tool in evaluating obesity, hsCRP can be used to sub-classify BMI into high and low risk normal subjects. Our study substantiates the role of incorporating hsCRP in addition to BMI for risk stratification of normal & healthy individuals.

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