High-Sensitivity C-Reactive Protein in Metabolic Healthy Obesity (MHO)

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ABSTRACT

BACKGROUND

Metabolically Healthy Obesity/Metabolic Healthy Obesity (MHO) is a paradox in scientific medical literature and discussion is still on regarding the safety status of MHO phenotype. It is an obesity phenotype where the subjects have BMI more than or equal to 30 Kg/m^2 but are devoid of conventional metabolic complications such deranged lipid profile, altered glucose tolerance, or metabolic syndrome as they have less adverse inflammatory profile, low visceral fat, less disturbed insulin signalling, and lipid metabolism. But recently studies are coming up with robust evidence that MHO is not a benign condition. It may lead to metabolic syndrome in future and it is also associated with cardiometabolic risks.

METHODS

This cross-sectional study was done in a tertiary care hospital conducted for a period of two years from October 2017 to October 2019. After obtaining institutional ethical clearance, this cross-sectional study was conducted on 120 MHO subjects, 120 metabolic syndrome (MS) and 120 Metabolic Healthy Non-Obese (MHNO) subjects. Anthropometric data was obtained, and hs-CRP was estimated and compared with MS and MHNO group. The data was analysed using appropriate statistical significance tests.

RESULTS

In one-way Analysis of Variance (ANOVA), anthropometric determinants and metabolic variables differed significantly across the groups ($p<0.0001$). The mean hs-CRP in MHO was; 4.45 ± 1.46 and in the control group it was 1.84 ± 0.77 ($p<0.0001$). Using Pearson's correlation coefficient, significant positive correlation was found between hs-CRP with other anthropometric and metabolic parameters. In multiple regression analysis, Body Mass Index (BMI), Waist Circumference (WC), were significantly associated with elevated hs-CRP. Adjusted odd's (AOR) of abnormal hs-CRP in MHO was 1.9 times that of MHNO subjects.

CONCLUSIONS

MHO phenotype is associated with increased hs-CRP levels as compared to MHNO phenotype suggesting that obesity even if associated with a healthy metabolic profile, still harbour subclinical inflammation. So, subjects with MHO should be targeted for appropriate preventive strategies in the form of health education, lifestyle alterations to avoid future cardiovascular morbidities. MHO phenotype with evidence of subclinical vascular inflammation should not be considered a benign condition.

KEY WORDS

High Sensitivity C-Reactive Protein, Metabolic Syndrome, Metabolic Healthy Non-Obese

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DOI: 10.14260/jemds/2020/100

Financial or Other Competing Interests: Dr. Acharya Reports Grants from DMIMS University, outside the submitted work.

How to Cite This Article:
Rasheed A, Acharya S, Shukla S, et al. High-sensitivity c-reactive protein in (MHO). J. Evolution Med. Dent. Sci. 2020;9 (07):443-447, DOI: 10.14260/jemds/2020/100

Submission 27-11-2019,
Peer Review 22-01-2020,
Acceptance 29-01-2020,
Published 17-02-2020.

BACKGROUND

Metabolically healthy obese/Metabolic healthy obesity (MHO) is an obesity phenotype where the subjects have BMI more or equal to 30 Kg/m^2 but are devoid of metabolic complication such as deranged lipid profile, altered glucose tolerance, or metabolic syndrome. Metabolically healthy obese have a less adverse inflammatory profile, low visceral fat, fewer intrusion of macrophages into adipose tissue, and minor fat cell size, not as much of disturbed, insulin signalling, and lipid metabolism, which may make them more responsive to dietary interventions.[1-5] The estimated prevalence of MHO varies from 6 to 75 percent. [6] Available literature suggest that 10 to 25 % percent of obese individuals have a healthy metabolic status and is more common in females and its prevalence decreases with age.[7,8] MHO the term safeguards obesity with evidence of absent cardiometabolic risk factors. But contrary to the belief researches are now providing ample evidence that MHO individuals are at an increased risk of developing type II diabetes mellitus and adverse cardiovascular events.[6] A individual's health status can switch from metabolically healthy obesity to metabolically unhealthy and vice versa. An important question is whether development of the MHO phenotype is time-dependent, as many studies has shown that nearly half of initially metabolically healthy obese subjects, shifted to the metabolically unhealthy phenotype after 10 years, with similar proportions in overweight and obese subjects.[5]

Subclinical disease assessments are becoming increasingly important as they provide an overview of the actual course of disease and more reliable prediction of events than traditional risk factors for CVD. Studies have proved that High-sensitivity/High sensitivity/highly sensitive CRP (hs-CRP) is an established marker of cardiovascular disease. This circulating pro-inflammatory cytokine leads to inflammation of the coronary arteries leading to cardiovascular disease.[7] Very limited research work has been done till date focusing different parameters of subclinical cardiovascular risk profiles apart from dyslipidaemia and diabetes in MHO populations. As already researches are gaining substantial data regarding existing cardiovascular risk in MHO population, this study will interestingly add to the existing data simultaneously incorporating one of subclinical cardiovascular risk marker, High-sensitivity C-reactive protein (hs-CRP) levels and their association with MHO population.

We wanted to estimate hs-CRP levels in MHO subjects, compare hs-CRP levels of MHO population with metabolic syndrome and metabolic healthy non obese (MHNO) subjects and correlate the clinical data (age, gender, blood pressure) and traditional metabolic syndrome variables (BMI, WC, FBS, HDL, TG) with hs-CRP in MHO population. High sensitivity C-reactive protein (hs-CRP) is a well-established marker of vascular/endothelial inflammation, and studies have confirmed that increased hs-CRP increases risk of cardiovascular disease (CVD).

METHODS

This cross-sectional study with comparison group entitled "High sensitivity CRP in MHO subjects" was carried out over a period of two years (October 2017 to October 2019) in a tertiary care hospital. Institutional ethical committee (DMIMSU), clearance was taken before starting the study.

All cases were randomly selected from the university students, staff, workers, and various health check-up camps organised by the hospital. Relevant demographic data (information comprised of gender, age, occupation and postal address) was collected after taking due consent. History of Diabetes mellitus, systemic hypertension was taken. Detailed drug history was obtained. Subjects with infections, sepsis, coronary artery disease, chronic liver and kidney disease, rheumatologic disorders, alcoholics, women on contraceptive pills, and subjects not giving consent were excluded. Metabolic unhealthy with normal weight phenotypes were also excluded. Detailed physical examination and anthropometric measurement in form of BMI, WC was calculated. Biochemistry analysis including FBS, TG, HDL-C was estimated.

Obesity in this study was defined as per the Body Mass Index (BMI) categories for Asian Indians that has been revised based on consensus guidelines. The revised guidelines categorise obesity as a BMI ≥25 Kg/m^2.[9] MS was defined as per the Modified National cholesterol education programme adult treatment panel III (NCEP ATP III) criteria as proposed by the AHA/NHLB [9,10]

1. Abdominal obesity (waist circumference ≥90 cm for Asian men or ≥80 cm for Asian women),
2. Triglycerides ≥150 mg/dL
3. HDL cholesterol ≤40 mg/dL for men or 50 mg/dL for women
4. Systolic/diastolic blood pressure ≥130/85 mmHg or receiving drug treatment
5. Fasting plasma glucose ≥100 mg/dL.

MHO was defined as subjects with; BMI ≥25 Kg/m^2 (as per BMI category for Asians) with less than 3 MS criteria as per revised NCEP ATP III guidelines.[9,11] In this study MHNO controls were defined as: BMI ≤25 Kg/m^2 with less than 3 MS variables.[11] After taking due consent from the participants, Serum hs-CRP, Anthropometric data including weight, height, BMI, WC was measured by standard methods.[12] Blood Pressures (BP) was measured as per standard protocol.[13] Subjects with BP ≥130/85 mm of Hg or with ongoing treatment for hypertension was included as a parameter for defining MS. Fasting plasma glucose was estimated by the Glucose Oxidase (GOD)/Peroxidase (POD) method, serum HDL by direct enzymatic method, TG were estimated using a LIQUID STABLE GPO-PAP method by machine Robonic Semi-Automatic Chemical Analyser. Quantitative hs-CRP was estimated by a solid phase ultra-sensitive enzyme immunoassay based on two-site sandwich enzyme immunoassay technique. A serum hs-CRP levels <1, 1-3 and >3 mg/L are taken as low, intermediate, and high-risk groups for CVD risk as per guidelines. This study considered hs-CRP value ≥3 mg/L as abnormal reflecting sub clinical vascular inflammation.[14]

Sample Size

As per a large Asian observational cross-sectional study the proportion of patients with subclinical carotid atherosclerosis of metabolically healthy (MHO) and metabolically unhealthy (MUO) patients were 31.2% and 43.5% respectively.[15] formula for calculating the sample size is as follows-

$$n = (Z_{\alpha/2}+Z_{\beta})^2 * (p_1 (1-p_1)+p_2 (1-p_2))/ (p_1-p_2)^2,$$

where, $Z_{\alpha/2}$ is the critical value of the Normal distribution at $\alpha/2$ (e.g. for a confidence level of 95%, α is 0.05 and the critical value is 1.96), Z_{β} is the critical value of the Normal distribution at β (e.g. for a power of 80%, β is 0.2 and the critical value is 0.84) and p_1 and p_2 are the expected sample proportions of the two groups. Here p1=0.312 and p2=0.435. Here p1=0.312 and p2=0.435, $Z_{\alpha/2}$ = 1.96Z_{β} = 0.8416, $(Z_{\alpha/2}+Z_{\beta})^2$ = 7.84, p1 (1-p1)+p2 (1-p2) = 0.4604, $(Z_{\alpha/2}+Z_{\beta})^2 * (p_1 (1-p_1)+p_2 (1-p_2))$ = 3.60, $(p1-p2)^2$ = 0.015129, n= 3.60/0.015129= 237.95 ~ 230.

Thus, there will be need of total 230 study patients with 80% power at 95% confidence level. The number of patients in each group in the ratio 1:1 would be; 230/2 =115. Thus, the required sample size for each group will be 115. To account for the calculated sample size; 120 subjects were analysed in MS, MHO and MHNO group each in a 1:1:1 ratio.

Statistical Analysis

The quantitative data were expressed as mean ± SD. Pearson's correlation coefficient was used to test correlations between variables. Analysis of Variance Tests (ANOVA) and chi-square tests of independence were used for continuous and categorical variables, respectively. Logistic regression analysis was performed, adjusting for age, gender, WC, hypertension, FBS, LDL, HDL, and TG. A p-value <0.05 was considered to be statistically significant.

RESULTS

120 MHO, 120 MS and 120 MHNO subjects were included in the study. The MHO group was younger (34.46 ± 18.54) as compared to MS group (52.20 ± 16.58) and control group (42.35 ± 14.5), and proportion of females were more in MHO group (66 %). The male to female ratio in MHO group was 1:1.22. Studies have supported the view that MHO usually has a female preponderance. [7,8] MHO individuals were younger than the referent population. All the traditional variables and anthropometric determinants of metabolic syndrome (WC, SBP, DBP) and the parameters of metabolic syndrome (HDL, FBS, TG) differed significantly across the groups. Metabolic syndrome had the higher risk values followed by MHO and lastly the control group. The subclinical risk parameter hs – CRP, showed similar trends across the groups which were statistically significant (p<0.05).

Descriptive Statistics

Mean hs-CRP level in MS subjects was 5.22 ± 1.88, in MHO subjects it was and in control subjects it was 4.45 ± 1.46. By using one-way ANOVA statistically significant variation was found in mean hs-CRP level among three groups of subjects (F=75.86, p=0.0001). On comparing mean hs-CRP level in three groups using Multiple Comparison: Tukey Test statistically significant difference was found between MS and MHO subjects (p=0.002) and between MHO and control subjects (p=0.0001). [Table 2].

When proportion and Odd's ratios for hs-CRP across weight and metabolic risk factor-based phenotype was assessed, the proportion of abnormal hs-CRP in MHO was 68.33%. The adjusted odd's (AOR) of abnormal hs-CRP in MHO was 1.9 times that of MHNO subjects. In males it was 1.5 and in females it was 1.6 times more than MHNO subjects.

Characteristics	MS	MHO	Control	p
N	**120**	**120**	**120**	
Age (yrs.)	52.20 ± 16.58 (20-75)	34.46 ± 18.54 (18-66)	42.35 ± 14.50 (18-70)	0.0001,S
Gender				
Male	60	54 (45%)	60	0.011,S
Female	60	66 (55%)	60	
M:F Ratio	1:1	1:1.22	1:1	
BMI	30.72 ± 4.60 20.60-42.10)	28.45 ± 4.20 (25-42.50)	20.46 ± 1.54 (15-24.65)	0.0001,S
Waist Circumference				
Overall	102.00 ± 14.18 (74-130)	93.14 ± 15.48 (74-126)	76.76 ± 6.40 (68-90)	0.0001,S
Males	96.70 ± 10.43 (74-130)	94.45 ± 16.26 (74-126)	74.78 ± 8.62 (68-90)	0.0001,S
Females	89.31 ± 10.81 (64-120)	90.46 ± 9.75 (70-120)	77 ± 6.78 (68-88)	0.0001,S
BP				
SBP	136 ± 12.40 (110-178)	126.41 ± 10.66 (100-162)	121.55 ± 10.20 (100-140)	0.0001,S
DBP	90.66 ± 10.45 (70-110)	86.66 ± 6.72 (70-104)	72.56 ± 8.66 (60-90)	0.0001,S
FBS				
FBS	95.56 ± 16.81 (60-135)	92.56 ± 16.56 (59-240)	84.66 ± 12.25 (38-100)	0.0001,S
HDL				
Overall	33 ± 7.56 (26-64)	34.75 ± 12.21 (14-74)	40.60 ± 9.40 (20-55)	0.004, S
Males	32.44 ± 10.02 (26-64)	33.82 ± 11.41 (14-65)	37.46 ± 7.04 (18-55)	0.006,S
Females	34.48 ± 8.46 (24-55)	35.62 ± 10.65 (20-74)	44.88 ± 10.56 (27-50)	0.001,S
Triglyceride				
TG	180.80 ± 80.55 (66-580)	130.44 ± 40.22 (58-278)	122.36 ± 36.21 (51-360)	0.0001,S
Hs-CRP				
hs CRP	5.22 ± 1.88 (1.20-8.60)	4.45 ± 1.46 (0.80-9.50)	1.84 ± 0.77 (1.00-3.20)	0.0001,S

Table 1. Baseline Characteristics of Study Participants

Group	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
MS	120	5.22	1.88	0.17	3.98	6.81	1.20	8.60
MHO	120	4.45	1.46	0.14	3.50	5.68	0.80	9.50
Control	120	1.84	0.77	0.05	1.24	2.32	1.00	3.20

Table 2. Comparison of hs-CRP in the Three Groups

Source of Variation	Sum of Squares	df	Mean Square	F	p-value
Between Groups	336.40	2	170.05	75.86	0.0001,S
Within Groups	820.44	357	2.24		
Total	**1156.84**	**359**			

Table 3. One-Way ANOVA

Group		Mean Difference (I-J)	Std. Error	p	95% Confidence Interval	
					Lower Bound	Upper Bound
MS	MHO	0.67	0.19	0.002,S	0.21	1.12
MHO	Control	1.64	0.19	0.0001,S	1.18	2.09

Table 4. Multiple Comparison- Tukey Test

Parameters	MHO (n=120)	Control (n=120)	p	Odd's Ratio	95% CI for OR
BMI (Kg/m^2)					
Normal (<25)	0	120	0.0001,S	0.000017	0.0000033-0.00087
Obese (≥25)	120	0			
Waist Circumference (Male)					
Normal (<90 cm)	20	56	0.0001,S	0.022	0.004-0.10
Abnormal (≥90 cm)	34	4			
Waist Circumference (Female)					
Normal (<80 cm)	24	56	0.0001,S	0.007	0.00043-0.1215
Abnormal (≥80 cm)	42	06			
Systolic Blood Pressure (mmHg)					
Normal (<130 mmHg)	86	84	0.88,NS	0.92	0.52-1.61
Abnormal (≥130 mmHg)	34	36			
Diastolic Blood Pressure (mmHg)					
Normal (<85 mmHg)	108	114	0.19,NS	0.43	0.14-1.28
Abnormal (≥85 mmHg)	10	6			
Fasting Blood Sugar (mg%)					
Normal (<100 mg/dL)	102	117	0.0001,S	0.084	0.019-0.37
Abnormal (≥100 mg/dL)	18	3			
HDL-Male					
Normal (≥40 mg/dL)	24	38	0.70,NS	0.85	0.39-1.81
Abnormal (<40 mg/dL)	30	22			
HDL-Female					
Normal (≥50 mg/dL)	18	16	0.41,NS	0.70	0.31-1.58
Abnormal (<50 mg/dL)	48	44			
Triglycerides					
Normal (<150 mg/dL)	102	111	0.21,NS	0.55	0.24-1.25
Abnormal (≥150 mg/dL)	18	09			
hs-CRP (mg/dL)					
Normal (<3)	36	108	0.0001,S	0.056	0.028-0.11
Abnormal (≥3)	84	12			

Table 5. Comparison of Parameters in MHO and Control Group

	Mean	Std. Deviation	N	Correlation 'r'	p-value
hs-CRP	4.45	1.46	120	-	-
BMI	28.45	4.20	120	0.572	0.0001,**S**
WC	93.14	15.48	120	0.432	0.0001,**S**
FBS	92.56	16.56	120	0.114	0.214,**NS**
SBP	126.41	10.66	120	0.054	0.560,**NS**
DBP	86.66	6.72	120	0.006	0.945,**NS**
HDL	34.75	12.21	120	0.165	0.072,**NS**
TG	130.44	40.22	120	0.063	0.493,**NS**

Table 6. Correlation between hs-CRP and Other Metabolic Variables in MHO Group. Pearson's Correlation Coefficient

By using Pearson's Correlation Coefficient significant positive correlation was found between hs-CRP BMI, WC.

	Proportion of Elevated hs-CRP (≥3 mg/L)								
	Overall			Males			Females		
	n	UOR	AOR	N	UOR	AOR	n	UOR	AOR
Control	12 (10 %)	1	1	4 (4 %)	1	1	8 (6 %)	1	1
MHO	84 (70 %)	1.51 (1.01-2.18)	1.96 (1.29-3.12)	30 (25%)	2.15 (1.31-3.12)	1.57 (1.19-2.95)	54 (43.33%)	1.19 (0.46-2.11)	1.6 (0.49-2.93)
MS	88 (73.33%)	3.12 (1.71-3.51)	2.30 (1.91-3.41)	44 (36.5%)	2.90 (1.91-3.12)	2.13 (1.51-2.92)	44 (36.5%)	2.81 (2.11-3.63)	2.91 (2.11-4.11)

Table 7. Proportion and Odds Ratios for hs-CRP across Weight and Metabolic Risk Factors Based on Phenotype

DISCUSSION

MS had the highest risk values followed by MHO and lastly the control group. The subclinical marker hs-CRP showed similar trends across the groups which were statistically significant ($p<0.05$). As these findings suggest, though MHO individuals had less than three metabolic risk parameters and decreased levels of all these risk markers for developing cardiovascular disease when compared with MS, still they had significantly higher values of these variable than controls. This also suggests that MHO may have an increased risk of progressing to MS in future. Studies have confirmed that MHO usually progresses to MS in future being a snap shot of an abnormal pre-metabolic state.[16,15] Justin B. Echouffo-Tcheugui et al. Examined Framingham Offspring Cohort, 4,291 participants who came for the examination cycles 2 to 7 and found out that the obesity sub-phenotypes progressed over time and MHO was the most short-term phenotype and a higher composite metabolic-BMI score was associated with a higher risk of a variety of clinical outcomes (diabetes, hypertension, cardiovascular events, and death) and high prevalence of subclinical cardiovascular disease cross-sectionally. An integrated assessment which accounted for shifts in the status of obesity sub-phenotypes over time were strongly associated with prevalent subclinical cardiovascular disease and clinical outcome incidence.[15]

It is needless to deny MHO as a pre-metabolic state and it would progress to overt MS with its consequent CVD risks in future. This study shows that hs-CRP in MHO and in the control-group was statistically significant and there was significant difference within and between groups suggesting that MHO portray trends of abnormal subclinical inflammation. The mean hs CRP in MS was 5.22 ± 1.88, in MHO was 4.45 ± 1.46 and in the control group it was 1.84±0.77. The value was statistically significant across all the three groups. In one-way ANOVA there was significant difference within and between groups. Post hoc analysis with Tukey test showed MHO group had significantly increased value than control group. By using multiple regression analysis BMI, WC, were significantly associated with elevated hs-CRP [Table. 2]. An increased WC denotes visceral obesity which contributes to inflammation, insulin resistance, and fat deposition in liver. MHO population is vulnerable for all these abnormalities compared to MHNO individuals.[17]

In a study by Shaharyar S et al., the prevalence of abnormal hs-CRP values in MHO was 22% [18]. The overall AOR of high hs-CRP was 2.45 (males 2.51, females 3.59). The conclusion of this study was similar to the current study suggesting MHO as a non-healthy entity. In van Wijk DF et al., study there was a higher multivariable-adjusted hazard ratio for CHD in MHO subjects with CRP levels >2 mg/L. [19] The higher CRP levels were associated with a CHD risk. Iglesias Molli AE; in their study found that hs-CRP was significantly high in MHO than normal controls similar to the current study.[20] In our study proportion and Odd's ratios for hs-CRP across weight and metabolic risk factor based phenotype was assessed, the proportion of abnormal hs-CRP in MHO was 68.33%, adjusted odd's (AOR) of abnormal hs-CRP in MHO was 1.9 times that of MHNO subjects. Bennett NR et al., analysed 342 men and 404 women with MHO.[21] Approximately 15% of the participants had high risk hs-CRP (>3 mg/L), in logistic regression models high WC was associated with significantly higher odds of high hs-CRP (OR 7.8, 95% CI 4.8-12.9, $p<0.001$) in MHO subjects.[21] An Indian study carried out by Acharya S et al; MHO population had increased mean HS-CRP levels (4.01 ± 1.68) as compared to normal controls (2.16 ± 0.56). Adjusted odd's ratio for high hs-CRP in MHO was 1.58 in males and 1.65 in females.[22]

Limitations

This study is cross-sectional in design so it only throws light on associations of high risk subclinical pro-inflammatory markers with MHO phenotype and wouldn't prove the causation. This study defined MHO using a single criteria (NCEP ATP III).

CONCLUSIONS

Both MHO phenotype and MS are associated with higher affliction of inflammation when compared to MHNO subjects. This study proves that at any instance, asymptomatic MHO population have abnormal subclinical cardiovascular risk markers in a significantly increased proportion than a metabolic healthy non obese individual as abdominal obesity if accompanying with MHO further adds to the inflammatory cascade and risk of CVD. Time has come that we question the innocuous nature of MHO and its nomenclature should be changed to "Pre-Metabolic Syndrome" in the era of evidence-based medicine.

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