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Original Article

Internal Medicine Section

Subclinical Risk Markers for Cardiovascular Disease (CVD) in Metabolically Healthy Obese (MHO) Subjects

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ABSTRACT

Introduction: Metabolically Healthy Obesity/Metabolic Healthy Obesity (MHO) is an enigma in scientific medical literature. Debate is still on regarding the safety status of MHO phenotype. The general consensus states that it is a condition with obesity but lacking metabolic abnormalities such as dyslipidemia, impaired glucose tolerance, or Metabolic Syndrome (MS). MHO population has less visceral adipose tissue, and a decreased inflammatory profile as compared to MS.

Aim: To assess subclinical cardiovascular risk markers like Carotid Intima-Media Thickness (CIMT), Non Alcoholic Fatty Liver Disease (NAFLD) and high sensitivity C-reactive Protein (hs-CRP) level in MHO subjects.

Materials and Methods: This cross-sectional study was done in a tertiary care hospital conducted for a period of three years from January 2016 to January 2019. After obtaining institutional ethical clearance, this cross-sectional study was conducted on 222 MHO subjects, 65 MS and 81 Metabolic Healthy Non Obese (MHNO) subjects. Anthropometric data was obtained. Metabolic parameters like hs-CRP, CIMT and NAFLD status were 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; 4.01±1.68 versus control group; 2.16±0.56 ($p<0.0001$). Using Pearson's correlation coefficient, significant positive correlation was found between the sub clinical CVD risk markers with other anthropometric and metabolic parameters. In multiple regression analysis body mass index Waist Circumference (WC), NAFLD and abnormal CIMT were significantly associated with elevated hs-CRP. The mean CIMT in MHO was; 0.74±0.17 versus control group; 0.65±0.14 ($p<0.0001$). In multiple regression analysis NAFLD and hs-CRP were significantly associated with CIMT values. Prevalence of NAFLD in MHO was 59.01%. In multiple regression analysis WC, CIMT and hsCRP were significantly associated with NAFLD. Adjusted Odd's Ratio (AOR) for high hs-CRP, NAFLD, and abnormal CIMT in MHO as compared to MHNO was 1.98, 1.81, 1.61 respectively.

Conclusion: MHO phenotype is associated with higher prevalence of fatty liver, increased hs-CRP levels and abnormal CIMT as compared to MHNO phenotype. This indicates 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 form of health education, life style modifications to avoid future cardiovascular morbidities. MHO phenotype with evidence of subclinical vascular inflammation should not be considered a benign condition.

Keywords: Carotid intima-media thickness, High sensitivity C-reactive protein, Metabolic syndrome, Metabolic healthy non obese, Non alcoholic fatty liver disease, Phenotype

INTRODUCTION

MHO is an emerging concept which hypothesise an individual to be phenotypically obese but devoid of metabolic abnormalities. Studies have claimed that MHO individuals usually have a reduced inflammatory profile when compared to MS [1,2]. The estimated prevalence of MHO varies from 6 to 75%, [3,4] and some studies has shown that 10 to 25% of obese individuals are metabolically healthy. It is usually common in females and its prevalence decreases with age [5].

The term "MHO", safeguards obesity as there is absence of any cardiometabolic risks in this phenotype. Studies are providing evidence that MHO individuals have increased risk of developing type 2 diabetes and cardiovascular events when compared with MHNO indivduals, but these risks are low as compared to MS [6,7]. Studies have established that some subclinical cardiovascular inflammatory risk markers like CIMT, hs-CRP and NAFLD, if present, can predict future cardiovascular events with fair predictability [8-11].

Very limited research work has been done till date focusing different parameters of cardiovascular risk profiles apart from dyslipidemia and diabetes in MHO populations. Still there is lack of substantial evidence about the existence of other cardiovascular risk factors like CIMT, NAFLD and inflammatory markers like CRP status in MHO. This study will add to the existing data; simultaneously assessing subclinical cardiovascular risk markers, like, abnormal CIMT, NAFLD and hs-CRP levels and their association with MHO population. This study was carried out with the aim to assess subclinical cardiovascular risk markers like CIMT, NAFLD and hs-CRP level in MHO population and to compare these variables with subjects of MS and MHNO group as control.

MATERIALS AND METHODS

This cross-sectional study with comparison group entitled "Subclinical risk markers for CVD in MHO subjects" was carried out over a period of three years (January 2016 to January 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 sex, age, race, 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 [12].

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 [13].

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 [12,14].

In this study MHNO controls were defined as: BMI ≤25 Kg/m^2 with less than 3 MS variables [15].

After taking due consent from the participants, Serum hs-CRP, CA-IMT, and USG to detect fatty liver was done.

Anthropometric data including weight, height, BMI, WC was measured by standard methods [16]. Blood Pressures (BP) was measured as per standard protocol [17]. 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 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 [18].

Ultrasonography (USG) for NAFLD

All patients underwent USG of the abdomen to detect fatty changes in the liver, performed by a single experienced radiologist. It was performed using a high resolution B-mode ultrasonography system Prosound Alpha 7 with curved linear arrays mid-frequency probe of 3-5 MHz.

Diagnosis of NAFLD was made by the presence of an increase echogenicity of liver as compared to the kidneys [19].

Measurement of Carotid Intimal Media Thickness (CIMT)

Cases were examined in the supine position, the neck was oriented in 45 degree, and B-mode ultrasound images obtained as per guidelines by one examiner who was unaware of participant's clinical characteristics. Common Carotid Artery (CCA) was scanned using Aloka prosound in B-mode at Acharya Vinoba Bhave Rural Hospital (AVBRH). IMT thickness was measured as per protocol. Two measurements were taken from each side and averaged; then, the mean CIMT was calculated as the average of measurements obtained from both CCAs [20]. As per the latest ESH/ESC hypertension guidelines (2013), carotid IMT >0.9 mm has been taken as a marker of asymptomatic organ damage [21,22].

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

Total number of participants in group MS were 65, in MHO group were 222 and in control group number of participants were 81.

The MHO group was younger (36.64±14.82) as compared to MS group (45.18±15.88) and control group (37.79±13.63), and prevalence of females were more in MHO group (54.95%). Using One-way ANOVA; All the variables differed significantly across the groups. The male to female ratio in MHO group was 1:1.2. All the variables and anthropometric determinants of metabolic syndrome (WC, SBP, DBP) and the parameters of metabolic syndrome (FBS, TG) differed significantly across the groups [Table/Fig-1].

By using Pearson's Correlation Coefficient significant positive correlation was found between CIMT and BMI, WC, FBS, SBP, TG, NAFLD and hs-CRP [Table/Fig-2]. By using Multiple regression analysis NAFLD and hs-CRP were significantly associated with CIMT [Table/Fig-3]. By using Pearson's Correlation Coefficient significant positive correlation was found between hs-CRP level and BMI, WC, FBS, SBP, DBP, TG, NAFLD and CIMT [Table/Fig-4]. By using Multiple regression analysis BMI, WC, NAFLD and CIMT were significantly associated with high hs-CRP levels [Table/Fig-5].

By using Pearson's Correlation Coefficient significant positive correlation was found between NAFLD and BMI, WC, FBS, SBP DBP, TG, CIMT and hs-CRP [Table/Fig-6]. By using Multiple regression analysis WC, CIMT and hs-CRP were significantly associated with NAFLD [Table/Fig-7].

Prevalence of high hs-CRP in metabolic syndrome group was 76.92%. The adjusted odd's ratio (AOR: adjusted with WC, HDL, FBS, TG) was (2.41; CI 1.92-3.51) compared to MHNO population. Prevalence of high hs-CRP in MHO group was 65.32%. AOR was (1.98; CI 1.29-3.12) compared to MHNW population. In MHO females the AOR was 1.65 as compared to MHNO. The prevalence of NAFLD in MHO group was 59.01%. In metabolic syndrome group the overall AOR was 2.21(1.21-2.51). In MHO group the overall AOR for NAFLD as compared to MHNO group was 1.81 (CI: 1.11-2.13). Prevalence of abnormal CIMT in MHO group was 24.32% in MHO group as compared to control 3.70%. The adjusted odd's ratio (AOR: adjusted with WC, HDL, FBS, TG) of abnormal CIMT in overall MHO subjects was around 1.6 (95% CI 1.12-1.91), in males it was 1.06 (95% CI 0.82-1.51), and in females it was 1.76 (95% CI 0.41-2.12) as compared to normal control [Table/Fig-8].

DISCUSSION

MS had the higher risk values followed by MHO and lastly the control group. The subclinical risk parameters like hs-CRP, CIMT and NAFLD 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 [23,24]. 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.

Carotid Intima Media Thickness (CIMT) and MHO

By using multiple regression analysis, NAFLD and hs-CRP were significantly associated with CIMT values in MHO group [Table/Fig-3]. As hs-CRP is also a risk marker of vascular inflammation and NAFLD suggests the altered milieu of adipose tissue metabolism, both contribute to elevated CIMT irrespective of the presence or absence of other abnormal metabolic parameters.

Jung CH et al., studied the degree of subclinical coronary

Characteristics	MS	MHO	Control	p-value
n	65	222	81	
Age (yrs)	45.18±15.88 (21-75)	36.64±14.82 (17-82)	37.79±13.63 (20-70)	0.0001,S
Gender				
Male	30 (46.15%)	100 (45.05%)	52 (64.20%)	0.010,S
Female	35 (53.85%)	122 (54.95%)	29 (35.80%)	
M:F Ratio	1:1.6	1:1.22	1.79:1	
BMI	28.35±5.33 (18.40-43.20)	29.64±3.07 (25-43.70)	21.72±2.05 (16.98-24.72)	0.0001,S
Waist circumference				
Overall	92.73±11.84 (64-120)	89.78±9.84 (70-123)	76.53±5.72 (68-95)	0.0001,S
Males	94.26±10.92 (76-120)	90.75±10.25 (74-123)	78.13±5.79 (68-95)	0.0001,S
Females	91.42±12.58 (64-120)	88.98±9.46 (70-120)	73.65±4.35 (68-86)	0.0001,S
SBP	133.07±16.91 (100-180)	126.28±9.83 (98-180)	120.41±11.70 (100-180)	0.0001,S
DBP	82.86±7.49 (70-96)	77.62±6.83 (60-100)	74.09±6.78 (60-90)	0.0001,S
FBS	101.01±16.36 (67-145)	90.23±15.42 (59-260)	82.46±10.43 (38-100)	0.0001,S
HDL				
Overall	35.66±6.84 (21-50)	37.45±10.95 (19-73)	38.14±7.47 (18-60)	0.280,NS
Males	35.50±7.06 (24-50)	37.48±9.63 (19-65)	36.94±7.00 (18-52)	0.540,NS
Females	35.80±6.75 (21-50)	37.43±11.96 (20-73)	40.31±7.91 (27-60)	0.235,NS
TG	184.29±98.54 (63-596)	132.02±39.04 (58-286)	127.11±45.05 (51-408)	0.0001,S
hs-CRP	4.88±2.26 (1.30-9.20)	4.01±1.68 (0.90-9.80)	2.16±0.56 (1.20-4.30)	0.0001,S
CIMT	0.84±0.27 (0.40-1.70)	0.74±0.17 (0.25-1.20)	0.65±0.14 (0.35-1.40)	0.0001,S
NAFLD grading				
Grade 0	26 (40%)	91 (41%)	72 (88.9%)	0.0001,S
Grade 1	24 (36.9%)	84 (37.8%)	9 (11.1%)	
Grade 2	14 (21.5%)	45 (20.3%)	0 (0%)	
Grade 3	1 (1.5%)	2 (0.9%)	0 (0%)	

[Table/Fig-1]: Baseline characteristics of study participants. One-way ANOVA

	Mean	Std. Deviation	N	Correlation 'r'	p-value
CIMT	0.74	0.17	222	-	-
BMI	29.64	3.07	222	0.309	0.0001,S
WC	89.78	9.84	222	0.281	0.0001,S
FBS	90.23	15.43	222	0.146	0.029,S
SBP	126.28	9.83	222	0.141	0.036,S
DBP	77.62	6.83	222	0.074	0.272,NS
HDL	37.45	10.95	222	0.094	0.164,NS
TG	132.02	39.04	222	0.172	0.010,S
NAFLD	0.81	0.78	222	0.517	0.0001,S
hsCRP	4.01	1.68	222	0.411	0.0001,S

[Table/Fig-2]: Correlation between CIMT and other metabolic variables in MHO group.
Pearson's Correlation Coefficient

	Mean	Std. Deviation	N	Correlation 'r'	p-value
hsCRP	4.01	1.68	222	-	-
BMI	29.64	3.07	222	0.555	0.0001,S
WC	89.78	9.84	222	0.502	0.0001,S
FBS	90.23	15.43	222	0.193	0.004,S
SBP	126.28	9.83	222	0.170	0.011,S
DBP	77.62	6.83	222	0.222	0.001,S
HDL	37.45	10.95	222	0.068	0.310,NS
TG	132.02	39.04	222	0.147	0.028,S
NAFLD	0.81	0.78	222	0.560	0.0001,S
CIMT	0.74	0.17	222	0.411	0.0001,S

[Table/Fig-4]: Correlation between hs-CRP and other metabolic variables in MHO group.
Pearson's Correlation Coefficient

Parameters	Unstandardised coefficients		Standardised coefficients	t	p-value	95.0% confidence interval for B	
	B	Std. error	Beta			Lower bound	Upper bound
CIMT	0.501	0.191					
BMI	0.003	0.004	0.050	0.632	0.528,NS	-0.006	0.012
WC	-0.001	0.001	-0.030	0.386	0.700,NS	-0.003	0.002
FBS	0.001	0.001	0.053	0.878	0.381,NS	-0.001	0.002
SBP	0.001	0.001	0.062	0.881	0.379,NS	-0.001	0.004
DBP	-0.002	0.002	-0.083	1.187	0.236,NS	-0.006	0.001
HDL	0.000	0.001	0.018	0.287	0.775,NS	-0.002	0.002
TG	0.000	0.000	0.049	0.799	0.425,NS	0.000	0.001
NAFLD	0.088	0.016	0.399	5.410	0.0001,S	0.056	0.120
hsCRP	0.017	0.008	0.164	2.110	0.036,S	0.001	0.033

[Table/Fig-3]: Multiple regression between CIMT and other metabolic variables in MHO group.

Parameters	Unstandardised coefficients		Standardised coefficients	t	p-value	95.0% confidence interval for B	
	B	Std. error	Beta			Lower bound	Upper bound
hsCRP	-6.623	1.588					
BMI	0.157	0.036	0.286	4.320	0.0001,S	0.085	0.228
WC	0.024	0.012	0.141	2.068	0.040,S	0.001	0.047
FBS	0.006	0.006	0.052	0.984	0.326,NS	-0.006	0.017
SBP	0.001	0.011	0.008	0.137	0.891,NS	-0.019	0.022
DBP	0.023	0.015	0.095	1.563	0.120,NS	-0.006	0.053
HDL	-0.007	0.008	-0.047	0.877	0.381,NS	-0.023	0.009
TG	0.002	0.002	0.035	0.665	0.507,NS	-0.003	0.006
NAFLD	0.583	0.142	0.271	4.109	0.0001,S	0.303	0.862
CIMT	1.223	0.579	0.125	2.110	0.036,S	0.080	2.365

[Table/Fig-5]: Multiple regression between hs-CRP and other metabolic variables in MHO group.

	Mean	Std. Deviation	N	Correlation 'r'	p-value
NAFLD	0.81	0.78	222	-	-
BMI	29.64	3.07	222	0.440	0.0001,S
WC	89.78	9.84	222	0.472	0.0001,S
FBS	90.23	15.43	222	0.179	0.008,S
SBP	126.28	9.83	222	0.198	0.003,S
DBP	77.62	6.83	222	0.194	0.004,S
HDL	37.45	10.95	222	0.111	0.099,NS
TG	132.02	39.04	222	0.210	0.002,S
CIMT	0.74	0.17	222	0.517	0.0001,S
hsCRP	4.01	1.68	222	0.560	0.0001,S

[Table/Fig-6]: Correlation between NAFLD and other metabolic variables in MHO group. Pearson's Correlation Coefficient

Parameters	Unstandardised coefficients		Standardised coefficients	t	p-value	95.0% confidence interval for B	
	B	Std. error	Beta			Lower bound	Upper bound
NAFLD	-3.813	0.724					
BMI	0.010	0.018	0.040	0.572	0.568,NS	-0.025	0.045
WC	0.016	0.005	0.202	2.990	0.003,S	0.005	0.027
FBS	0.002	0.003	0.039	0.729	0.467,NS	-0.003	0.007
SBP	0.004	0.005	0.052	0.842	0.401,NS	-0.006	0.014
DBP	0.005	0.007	0.047	0.773	0.441,NS	-0.008	0.019
HDL	-0.001	0.004	-0.012	0.229	0.819,NS	-0.008	0.007
TG	0.002	0.001	0.096	1.814	0.071,NS	0.000	0.004
CIMT	1.384	0.256	0.304	5.410	0.0001,S	0.880	1.889
hsCRP	0.127	0.031	0.272	4.109	0.0001,S	0.066	0.187

[Table/Fig-7]: Multiple regression between NAFLD and other metabolic variables in MHO group.

	Prevalence of elevated hs-CRP								
	Overall			Males			Females		
	n	UOR	AOR	n	UOR	AOR	n	UOR	AOR
Control	5 (6.17%)	1	1	2 (2.47%)	1	1	3 (3.70%)	1	1
MHO	145 (65.32%)	1.49 (1.01-2.12)	1.98 (1.29-3.12)	66 (29.73%)	2.13 (1.39-3.11)	1.58 (1.21-2.92)	79 (35.59%)	1.21 (0.48-2.12)	1.65 (0.51-2.91)
MS	50 (76.92%)	3.11 (1.76-3.53)	2.41 (1.92-3.51)	23 (35.38%)	2.91 (1.91-3.12)	2.12 (1.56-2.96)	27 (41.54%)	2.86 (2.15-3.61)	3.11 (2.13-4.12)
	Prevalence of fatty liver								
	Overall			Males			Females		
	n	UOR	AOR	n	UOR	AOR	n	UOR	AOR
Control	9 (11.11%)	1	1	7 (8.64%)	1	1	2 (2.47%)	1	1
MHO	131 (59.01%)	1.21 (0.96-1.51)	1.81 (1.11-2.13)	64 (28.83%)	1.92 (1.31-2.12)	1.36 (1.01-2.11)	67 (30.18%)	0.91 (0.41-1.86)	1.65 (0.51-2.91)
MS	39 (60%)	2.51 (1.21-2.91)	2.21 (1.21-2.51)	21 (32.31%)	2.61 (1.81-2.91)	2.01 (1.21-2.81)	18 (27.69%)	2.21 (1.81-2.56)	2.65 (2.11-3.11)
	Prevalence of CIMT								
	Overall			Males			Females		
	n	UOR	AOR	n	UOR	AOR	n	UOR	AOR
Control	3 (3.70%)	1	1	3 (3.70%)	1	1	0(%)	1	1
MHO	54 (24.32%)	1.30 (0.81-1.66)	1.61 (1.12-1.91)	23 (10.36%)	1.81 (1.12-2.56)	1.06 (0.82-1.51)	31 (13.96%)	0.96 (0.36-1.91)	1.76 (0.41-2.12)
MS	29 (44.62%)	2.11 (1.01-2.56)	2.01 (1.01-2.51)	14 (21.54%)	2.21 (1.31-2.92)	1.81 (1.01-2.16)	15 (23.08%)	2.01 (1.51-2.22)	2.56 (2.01-3.59)

[Table/Fig-8]: Prevalence and Odd' ratios for vascular inflammation, NAFLD, and CIMT across weight and metabolic risk factor based phenotypes.
UOR: Unadjusted odd's ratio (95% confidence interval);
AOR; Adjusted odd's ratio (95% confidence interval) adjusted for age, gender, FBS, HDL, TG
n(%): Represents number and percentage of subjects with outcome of interest (elevated hs-CRP ≥3 mg/dL, hepatic steatosis, CIMT ≥0.9 mm)
All data has associated p<0.05 unless otherwise noted

atherosclerosis in asymptomatic Korean population categorising them into different phenotypes [25]. The study concluded that, MHO subjects have substantial subclinical coronary atherosclerotic burden. Zhao M et al., in their study assessed CIMT in MHO children and adolescent population [26]. In comparison with metabolically healthy normal weight, Odds Ratios (ORs) for high CIMT were 3.91 (2.46-6.21) for MHO, concluding that CIMT was higher for both MHO and metabolically healthy overweight compared with metabolically healthy normal weight. Jae SY et al., accessed cardiorespiratory fitness association between MHO phenotype and CIMT [27]. Compared with metabolically healthy normal weight, MHO was associated with a higher prevalence of subclinical carotid atherosclerosis (odds ratio, 1.39; 95% CI, 1.12-1.72). Metabolically healthy obesity was associated with a higher prevalence of subclinical carotid atherosclerosis.

Roberson LL et al., examined four studies reporting a mean difference in Common Carotid Artery Intima Media Thickness (CCA-IMT) between MHO and MHNW individuals, of which two studies reported significantly higher levels in the MHO [7].

High Sensitive CRP (hs-CRP) and MHO

In this study, the mean hs-CRP in MHO was 4.01±1.68 and in the control group it was 2.16±0.56 (p=0.0001), suggesting that MHO portray trends of abnormal subclinical inflammation.

By using Multiple regression analysis BMI, WC, NAFLD and CIMT were significantly associated with elevated hs-CRP [Table/Fig-5]. 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.

In a study by Shaharyar S et al., the prevalence of abnormal hs-CRP values in MHO was 22% [28]. 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 [29]. 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 [30]. Bennett NR et al., analysed 342 men and 404 women with MHO [31]. Approximately 15% of the participants had high risk hsCRP (>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.

Non Alcoholic Fatty Liver Disease (NAFLD) and MHO

In this study, out of 222 MHO subjects 84 (37.8%) had grade 1

NAFLD, 45 (20.3%) had grade 2 NAFLD, and 2 (0.9%) had grade 3 NAFLD overall prevalence was 59.01%. In males the prevalence was 28.83% and in females it was 30.18%.

In Shaharyar S et al., study the prevalence of NAFLD in MHO was 40% [28]. The overall AOR of high NAFLD in MHO was 5.08. Heianza Y et al., in their study found that the prevalence of NAFLD in MHO was around 47.8% [32]. This may explain the increased risk of insulin resistance contributed by hepatic fat, there by risk of development of diabetes among the MHO phenotypes.

Chang Y et al., in another study found that the incident rate of NAFLD was 29.7 per 1,000 person-years in MHO [33]. The multivariable adjusted hazard ratio for the development of NAFLD in overweight and obese with normal-weight participants were 2.15 (95% CI; 2.06-2.26) and 3.55 (95% CI; 3.37-3.74), respectively. Overweight and obesity were strongly and progressively associated with an increased incidence of NAFLD.

Jung CH et al., investigated the effect of Fatty Liver Disease (FLD) as a risk factor for development of incident type 2 diabetes in Metabolically Healthy Obesity MHO [34]. MHO subjects with high fatty liver index had an elevated risk of incident type 2 diabetes (multivariate-adjusted HR, 1.99 (95% CI 1.36-2.92). Haskins IN et al., in their study determined the prevalence and characteristics of NAFLD in individuals with MHO [35]. In the MHO group, 23% had lobular inflammation, 8.5% had hepatocyte ballooning, 8.2% had steatohepatitis, and 4.4% had liver fibrosis. They concluded that NAFLD though asymptomatic is highly prevalent in MHO. Zhang H et al., in their study examined 485 obese adults with magnetic resonance spectroscopy [36]. MHO individuals were 1.9 times more likely to have metabolic syndrome per 1 SD increase in IHTG content. The risk for high CIMT increased 29% per 1 SD change in IHTG content in MHO group.

Gutierrez Y et al., evaluated liver fibrosis in patients with NAFLD, in MHO and Metabolically Unhealthy Obese (MUHO) [37]. MHO patients showed a significantly lower prevalence of advanced liver fibrosis than MUHO on transient elastography, but they still had NAFLD as a risk factor.

The present study showed that MHO groups have a higher prevalence of elevated hs-CRP levels, abnormal CIMT and NAFLD as compared to MHNO group. The inference of the study directs towards the subclinical vascular inflammatory triggers of obesity per se. Obesity in absence of metabolic risk factors is not entirely benign and is associated with subclinical vascular inflammation that can predispose to future development of MS and incident CVD.

Adipose tissue is highly metabolic and produces inflammatory cytokines. The pro-inflammatory markers present in MHO individuals are Complement C3, Alpha necrosis factor, CRP, Interleukin 6, leptin, resistin, TNF-a, IL-6, IL-18 [38]. These adipokines contribute to the metabolic disturbances and CVD morbitities associated with obesity. Obesity results in a pro-inflammatory metabolic state and may explain the higher prevalence of elevated inflammatory markers like hs-CRP, higher CIMT and NAFLD in our MHO subjects [39].

The present study is agreement, in that MHO subjects have increased levels of the abnormal anthropometric and metabolic variables as compared to MHNO individuals. Subclinical vascular inflammatory markers are elevated in MHO making them vulnerable for development of MS, CVD and type II diabetes in future.

LIMITATION

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).

CONCLUSION

There is no paucity of data that emphasises that MHO is actually not a "healthy" phenotype. This study indicates that both MHO phenotype and MS are associated with higher burden of inflammation when compared to MHNO subjects. It is high time; we question the benignity of MHO. Rather as a warning awareness, MHO should be replaced by the term "Premetabolic syndrome" in the era of evidence based medicine.

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